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(54) Title: COMPOSITIONS FOR DELIVERY OF AN ADSORBENT

(57) Abstract: The invention relates to compositions and solid dosage forms for the site-specific delivery of an adsorbent into the gastrointestinal tract of a subject.

COMPOSITIONS FOR DELIVERY OF AN ADSORBENT

FIELD OF THE INVENTION

The invention relates to compositions and solid dosage forms for the delivery of an adsorbent into the gastrointestinal tract of a subject.

BACKGROUND OF THE INVENTION

When antibiotics are administered, either orally or parenterally, a significant fraction is not absorbed and reaches the gastro-intestinal tract. When those antibiotic residues reach the colon, they provoke a serious disruption of the intestinal microbiota: several bacterial populations are decimated whereas others (sometimes pathogenic and resistant to antibiotics) proliferate; this new state of the microbiota after the antibiotic-induced disruption is called dysbiosis. The intestinal microbiota balance is hence profoundly disrupted and may take weeks to months to fully recover, i.e. return to its original equilibrium. Other drugs are also known to disrupt the microbiota such as some anti-cancer chemotherapies.

Similarly to a damaged organ, a disrupted microbiota can no longer fulfil its physiological functions, leading to many adverse consequences such as altered immunity and immune response; colonization of the intestine by pathogenic bacteria such as *Clostridioides difficile (C. difficile)*; altered metabolism with increased risk of inflammation, metabolic syndrome or obesity; and colonization or emergence of antibiotic resistant bacteria or genes of resistance to antibiotics, and their dissemination.

The medical community has well acknowledged today that preserving the microbiota balance and diversity during antibiotic treatments could prevent serious medical conditions such as *C. difficile* infections and graft-versus-host-disease. Maintaining a healthy microbiota could also prevent the selection and colonization of multi-resistant bacteria, and therefore limit the emergence and spread of antimicrobial resistance and prevent subsequent life-threatening infections. Finally, it is anticipated that maintaining the microbiota equilibrium is a driver for long-term health, and could favor better outcomes and survival for cancer patients treated with cancer therapies, such as immune checkpoint inhibitors, and also patients with hematologic malignancies treated with hematopoietic stem cell transplants.

Compositions and methods were previously developed by the present Applicant to eliminate pharmaceutical agents that can induce intestinal dysbiosis, and thus, to protect the intestinal

microbiota. One approach to achieve this goal is to administer an adsorbent to eliminate such pharmaceutical agents, more specifically antibiotics, in the lower part of the intestine. More particularly, the adsorbent is released between the part of the intestine where such pharmaceutical agents are absorbed into the blood (e.g. duodenum and jejunum) and where their deleterious effect on the commensal bacteria occur (caecum and colon). These strategies were reported in WO2006122835, WO2007132022 and WO2011104275.

The present invention provides further formulations useful to release an adsorbent in a site-specific manner and prevent dysbiosis.

SUMMARY OF THE INVENTION

The present invention relates to novel compositions providing improved release of an adsorbent.

In a first aspect, the invention relates to a composition comprising an adsorbent in admixture with an excipient selected in the group consisting of crospovidone, carboxymethylcellulose (CMC) and amidated low-methoxy (aLM) pectin.

The composition of the invention may be formulated in the form of a pellet.

A second aspect of the invention relates to a solid oral dosage form comprising one or more of such pellets. According to the present invention, the pellet(s) are coated with a polymeric enteric coating suitable to release the pellet in a desired part of the intestine.

A third aspect of the invention relates to medical uses of the solid dosage form disclosed herein. In particular, the solid oral dosage form of the invention may be used in a method for the treatment (cure or prevention) of a clinical consequence (or side effect) of a dysbiosis-inducing pharmaceutical agent. In another embodiment, the dysbiosis-inducing pharmaceutical agent is an antibiotic.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graph showing the kinetics of adsorption of ciprofloxacin with different adsorbent formulations.

DETAILED DESCRIPTION OF THE INVENTION

Adsorbents

The term "adsorbent" designates any compound or material that can adsorb a substrate, typically by physico-chemical binding between the adsorbent surface and the substrate(s) to be adsorbed. Adsorbents may be specific or non-specific. Preferred adsorbents for use in the invention are pharmaceutical grade adsorbents, best suited for use in humans or animals for pharmaceutical or veterinary applications.

Examples of adsorbents suitable for use in the present invention include, without limitation, activated charcoal (also referred to as activated carbon, active charcoal, or active carbon); clays, including bentonite, kaolin, montmorrillonite, attapulgite, halloysite, laponite, and the like; silica, including colloidal silica (Ludox® AS-40 for example), mesoporous silica (MCM41), fumed silica, zeolites and the like; talc; cholesteramine and the like; polystyrene sulfonates and the like; mono and polysulfonated resins; as well as other resins such as those used for bacteriologic testing such as BACTEC® resins.

In a particular embodiment, the adsorbent is activated charcoal, more particularly an activated charcoal having a specific surface area above 600 m^2/g, in particular above 800 m^2/g, in particular above 1000 m^2/g, in particular above 1200 m^2/g, in particular above 1400 m^2/g, in particular above 1600 m^2/g, even more particularly above 1800 m^2/g. The activated charcoal may be of vegetal, mineral or synthetic origin, its surface being optionally modified by a physical or chemical treatment. In a particular embodiment, the activated charcoal is of vegetal origin. In a particular embodiment, the activated charcoal is derived from peat. In a particular embodiment, the activated charcoal is derived from coconut husks. In a particular embodiment, the activated charcoal is derived from different sources mixed together such as peat and coconut husks. In a particular embodiment, the activated charcoal is characterized by a European molasses number (of note the European molasses number is inversely related to the North American molasses number) which is preferably higher than 100, even more particularly greater than 200, even more particularly greater than 300, even more particularly greater than 400, even more particularly greater than 500, even more particularly greater than 600. In a particular embodiment, the activated charcoal has a phenazone number (measured according to the EU Pharmacopeia) greater than 10 g/100 g, even more particularly greater than 20 g/100 g, even more particularly greater than 30 g/100 g, even more particularly greater than 40 g/100 g, even more particularly greater than 50 g/100 g, even more particularly greater than 60 g/100 g. In a particular embodiment, the activated charcoal is characterized by a density between 0.05 and 0.8, even more particularly between 0.1 and 0.7, even more

particularly between 0.15 and 0.65, even more particularly between 0.2 and 0.6, even more particularly between 0.3 and 0.5.

The amount of adsorbent employed in the methods of the invention may vary depending upon the host/material being treated and the overall capacity, adsorption power and selectivity of the adsorbent. In a particular embodiment the amount of adsorbent is an amount sufficient to prevent the deleterious impact of a substance, such as an antibiotic, on the intestinal microbiota known as disruption of the gut microbiota or “dysbiosis”. In a particular embodiment, the amount of adsorbent is an amount sufficient to improve the efficacy of an immuno-oncology agent, or to improve the effectiveness of anticancer immunosurveillance in a subject.

In a particular embodiment, the composition of the invention comprises from 50 to 99% of adsorbent, by weight of the composition. In a further embodiment, the composition comprises from 75 to 90% of adsorbent, by weight of the composition.

The adsorbent for use in the present invention is formulated in a composition, such as a pharmaceutical composition, in admixture with an excipient selected in the group consisting of crospovidone, carboxymethylcellulose (CMC) and amidated low-methoxy (aLM) pectin.

Compositions with crospovidone

Crospovidone, or polyvinylpolypyrrolidone (PVPP; IUPAC name: 1-ethenylpyrrolidin-2-one) is a highly cross-linked modification of polyvinylpyrrolidone (PVP).

In a particular embodiment, the composition comprises an adsorbent in admixture with crospovidone.

In a further embodiment, the adsorbent is in admixture with crospovidone and a microcrystalline cellulose.

In yet another embodiment, the composition comprises from 1 to 10% of crospovidone, by weight of the composition. In a further embodiment, the composition comprises from 3 to 7% of crospovidone, by weight of the composition. In a specific embodiment, the composition comprises about 5% of crospovidone.

In the context of the present invention, the term "about" used with reference to a numerical value means said value ± 10%, in particular ± 5%, more particularly ± 1%.

In another particular embodiment, the composition comprises from 1 to 30% of microcrystalline cellulose, by weight of the composition. In another particular embodiment, the composition comprises from 5 to 20% of microcrystalline cellulose, by weight of the composition. In a specific embodiment, the composition comprises about 15% of microcrystalline cellulose.

In yet another embodiment, the composition comprises:

- from 75 to 90% of the adsorbent;
- from 5 to 20% of microcrystalline cellulose; and
- from 3 to 7% of crospovidone;

by weight of the composition.

In yet another specific embodiment, the composition comprises:

- about 80% of activated charcoal;
- about 15% of microcrystalline cellulose; and
- about 5% of crospovidone;

by weight of the composition.

Compositions with carboxymethylcellulose

In another particular embodiment, the composition comprises an adsorbent in admixture with CMC.

In a further particular embodiment, the CMC is sodium CMC (CMC-Na). In another embodiment, the CMC-Na is selected from high viscosity sodium CMC-Na and medium viscosity CMC-Na.

In yet another particular embodiment, the composition comprises from 1 to 25% CMC, such as CMC-Na, by weight of the composition. In a further embodiment, the composition comprises from 5 to 20% CMC, such as CMC-Na, by weight of the composition. According to another particular embodiment, the composition comprises about 15% of CMC, such as CMC-Na, by weight of the composition.

In another particular embodiment, the composition optionally further comprises microcrystalline cellulose. In yet another embodiment, the composition comprises from 0 to 20% of microcrystalline cellulose, by weight of the composition. According to another embodiment, the composition comprises from 5 to 15% of microcrystalline cellulose, by weight

of the composition. In a particular embodiment, the composition comprises about 12.5% of microcrystalline cellulose, by weight of the composition. In another particular embodiment, the composition is devoid of microcrystalline cellulose.

In a particular embodiment, the composition comprises:

- from 75 to 90% of the adsorbent;
- from 1 to 25% of CMC-Na; and
- from 0 to 15% of microcrystalline cellulose;

by weight of the composition.

In a specific embodiment, the composition comprises:

- about 85% of activated charcoal; and
- about 15% of CMC-Na;

by weight of the composition.

Compositions with amidated low-methoxy pectin

In a particular embodiment, the composition comprises an adsorbent in admixture with aLM pectin.

The Applicant has previously shown that pectin-containing compositions may advantageously used to deliver an adsorbent into the colon, which contains pectinolytic enzymes that can thus release the adsorbent content of such compositions. Unexpectedly, it is herein shown that specific grades of pectin, namely aLM pectin, provide improved properties to such compositions.

The degree of methylation (DM) is defined as the percentage of carbonyl groups esterified with methanol. If more than 50% of the carboxyl groups are methylated the pectins are called high-methoxy pectins (HM), and less than that degree of methylation are called low methoxy (LM) pectins.

In a particular embodiment, the composition comprises from 2 to 22% of aLM pectin, by weight of the composition. In yet another particular embodiment, the composition comprises from 8 to 16% of aLM pectin, by weight of the composition. In a further embodiment, the composition comprises about 12% of aLM pectin, by weight of the composition.

In addition, the composition comprises a divalent cation used to crosslink the pectin. Representative divalent cations include, without limitation, calcium and zinc, in particular calcium. The divalent cations may be incorporated into the composition by addition of a divalent cation salt, such as calcium chloride. In a particular embodiment, the composition is prepared by addition of calcium chloride in an amount comprised from 0.5 to 4.5%, by weight of the composition, such as from 1 to 2%. In yet another embodiment, the composition comprises about 1.5% of calcium chloride, by weight of the composition.

The composition may further comprise other components, such as an acid, in particular an organic acid, more particularly citric acid. In this embodiment, citric acid may be comprised in the composition in an amount from 0.5 to 4.5%, by weight of the composition, such as from 1 to 2%. In yet another embodiment, the composition comprises about 1.5% of citric acid, by weight of the composition.

In a particular embodiment, the composition comprises:

- from 75 to 95% of an adsorbent;
- from 8 to 16% of an aLM pectin;
- from 1 to 2% of citric acid; and
- from 1 to 2% of calcium chloride;

by weight of the composition.

In a specific embodiment, the composition comprises:

- about 85% of activated charcoal;
- about 12% of sodium aLM pectin;
- about 1.5% of citric acid; and
- about 1.5% of calcium chloride;

by weight of the composition.

Solid dosage forms

The composition of the invention described above may be formulated in the form of a pellet. This pellet can be incorporated into a solid dosage form.

Accordingly, a second aspect of the invention relates to a solid oral dosage form comprising one or more of the pellets of the invention. According to the present invention, the pellet(s) are coated with a polymeric enteric coating suitable to release the pellet in a desired part of the intestine.

In a representative embodiment, the solid dosage form may comprise:

- a core corresponding to the pellet disclosed herein; and
- a layer of an external coating formed around the core such that said core is released in the desired part of the intestine.

In a particular embodiment, the desired part of the intestine is the lower part of the intestine.

The external coating formed around the core is selected among coatings suitable to release the core in the desired part of the intestine.

Examples of suitable coatings include pH-dependent enterosoluble polymers, azopolymers, disulphide polymers, and polysaccharides, in particular amylose, pectin (e.g. pectin crosslinked with divalent cations such as calcium pectinate or zinc pectinate), chondroitin sulphate and guar gum. Representative pH-dependent enterosoluble polymers include cellulose acetate trimellitate (CAT), cellulose acetate phthalate (CAP), acrylic polymers, methacrylic polymers, anionic copolymers based on methylacrylate, methylmethacrylate and methacrylic acid, hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers in a 1:1 molar ratio, methacrylic acid and methyl methacrylate copolymers in a 1:2 molar ratio, polyvinyl acetate phthalate (PVAP) and shellac resins. Particularly preferred polymers include shellac, anionic copolymers based on methyl acrylate, methyl methacrylate and methacrylic acid, such as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) in a 7:3:1 molar ratio, as well as methacrylic acid and methyl methacrylate copolymers in a 1:2 molar ratio. Ideally, the polymer dissolves at a pH equal to 6.0 and above, preferably 6.5 and above. Suitable coatings may also be obtained by mixing the polymers and copolymers aforementioned. In another embodiment, suitable coatings are time-dependent coatings or based on time-dependent polymers such as mixture of ethylcellulose polymers with alginate sodiums.

In a particular embodiment, the formulation comprises a further intermediate coating located between the core and the external pH-dependent layer. The intermediate coating can be formed from a variety of polymers, including pH-dependent polymers, pH-independent water soluble polymers, pH-independent insoluble polymers, and mixtures thereof. Examples of such pH-dependent polymers include shellac type polymers, anionic copolymers based on methylacrylate, methylmethacrylate and methacrylic acid, methacrylic acid and ethyl acrylate copolymers, hydroxypropyl methylcellulose phthalate (HPMCP), and

hydroxypropylmethylcellulose acetate succinate (HPMCAS). Examples of pH-independent water soluble polymers include PVP or high molecular weight cellulose polymers such as hydroxypropylmethylcellulose (HPMC) or hydroxypropylcellulose (HPC). Examples of pH-independent insoluble polymers include ethylcellulose polymers or ethyl acrylate and methyl methacrylate copolymers.

In a particular embodiment, the invention uses a formulation comprising:

- a core comprising a pellet according to the invention,
- an intermediate coating selected in the group consisting of HPMC, ethylcellulose and a mixture of methacrylic acid and ethyl acrylate copolymer such as Eudragit® L30D-55, and ethyl acrylate and methyl methacrylate copolymer such as Eudragit® NE30D (for example in a mixture weight ratio of 1:9 to 9:1, preferably of 2:8 to 3:7), and
- an external layer of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid, such as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, e.g. Eudragit® FS30D.

In a specific embodiment, the formulation comprises a core, comprising a pellet according to the invention which comprises about 85% activated charcoal, and a coating with an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid (such as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1, e.g. Eudragit® FS30D, Evonik, Darmstadt, Germany) or a mixture of methacrylic acid and ethyl acrylate copolymer (such as Eudragit® L30D55, Evonik, Darmstadt, Germany).

In a particular embodiment, the external coating comprises an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid, such as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In a further particular embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:
- from 75 to 90% of the adsorbent;
- from 5 to 20% of microcrystalline cellulose; and
- from 3 to 7% of crospovidone;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In a further particular embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:

- about 80% of activated charcoal;
- about 15% of microcrystalline cellulose; and
- about 5% of crospovidone;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In yet another embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:

- from 75 to 90% of the adsorbent;
- from 1 to 25% of CMC-Na; and
- from 0 to 15% of microcrystalline cellulose;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In yet another embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:

- about 85% of activated charcoal; and
- about 15% of CMC-Na;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In a further particular embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:

- from 75 to 95% of an adsorbent;
- from 8 to 16% of an aLM pectin;
- from 1 to 2% of citric acid; and
- from 1 to 2% of calcium chloride;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

In a further particular embodiment, the solid oral dosage form comprises:

a) a core composition in the form of a pellet comprising:

- about 85% of activated charcoal;
- about 12% of sodium aLM pectin;
- about 1.5% of citric acid; and
- about 1.5% of calcium chloride;

by weight of the core composition; and

b) an external coating comprising poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

Uses of the solid dosage forms of the invention

The solid dosage forms according to the invention can be used to treat conditions and disorders for which intestinal delivery of adsorbents is suitable.

Accordingly, the invention also relates to a solid dosage form as described above, for use as a medicament or as a medical device.

In a particular embodiment, the solid oral dosage of the invention is for use in a method for the treatment of a side effect of a dysbiosis-inducing pharmaceutical agent.

The solid dosage form according to the invention can be used to adsorb and therefore remove from the intestine any drug, metabolite or prodrug thereof, or toxin. This may be done after oral or parenteral administration of an active drug, which could be useful for limiting or decreasing adverse effects in the subject being treated the drug, metabolite or prodrug thereof reaches the lower intestine and/or colon.

As such, the present invention relates to the solid dosage form as described above, for use in a method for eliminating drugs in the intestinal tract before they reach the colon or as they reach the colon, preferably before they reach the caecum or as they reach the caecum and proximal colon.

The invention further provides a method for eliminating drugs in the intestinal tract before they reach the colon or as they reach the colon, preferably before they reach the caecum or as they reach the caecum and proximal colon, comprising administering to a patient in need thereof a formulation according to the invention.

Furthermore, the invention provides a formulation as described above, for use in a method for reducing or eliminating the side effect(s) of a drug in the intestinal tract, wherein the formulation

eliminates the drug before it reaches the colon or as it reaches the colon, preferably before it reaches the caecum or as it reaches the caecum and proximal colon.

Furthermore, the invention provides a formulation as described above, for use in a method for reducing or eliminating the deleterious effect(s) of toxins in the intestinal tract, wherein the formulation eliminates the toxin in the colon.

The terms "substance", "drug", "therapeutic agent", "pharmaceutical agent" and “medical device”, and terms derived therefrom, are herein used interchangeably and refer to a compound that provides a desired biological or pharmacological effect when administered to a human or animal.

Treatment or prevention of conditions related to antibiotic administration

The dysbiosis-inducing pharmaceutical agent may be an antibiotic, and the solid dosage form of the invention being used to treat a side effect of such an antibiotic.

Such side effects include, without limitation, the development of antibiotic resistance through the emergence and dissemination of antibiotic-resistant bacteria, the development of an infection by *Clostridioides difficile* or other pathogenic bacteria, a decrease in the efficacy of an anticancer agent in a subject in need thereof, a risk of developing or aggravating graft-versus-host disease in a subject and a risk of increasing the post-transplant mortality in subjects receiving or having received a hematopoietic stem cell transplant.

The adsorbent will adsorb residual antibiotics, and the solid dosage form according to the invention can be administered in a therapeutically effective amount to a patient who has been, is being, or will be administered an antibiotic. Any antibiotic that can be adsorbed into/onto the adsorbent can be inactivated and has no antibiotic activity once fully adsorbed.

The term “antibiotic” designates any compound that is active against bacteria. Antibiotics that may be eliminated thanks to the invention include but are not limited to:

- beta-lactams including:
    - penicillins (such as penicillin G, penicillin V, ampicillin, amoxicillin, bacampicillin, carbenicillin, carbenicillin indanyl, ticarcillin, azlocillin, mezlocillin, piperacillin, and the like),
    - penicillinase-resistant penicillins (such as methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin and the like),
    - cephalosporins, such as: first generation cephalosporins (such as cefadroxil, cephalexin, cephradine, cephalothin, cephapirin, cefazolin, and the like) ; second

generation cephalosporins (such as cefaclor, cefamandole, cefonicid, cefoxitin, cefotetan, cefuroxime, cefuroxime axetil, cefinetazole, cefprozil, loracarbef, ceforanide, and the like) ; third generation cephalosporins (such as cefepime, cefoperazone, cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, cefixime, cefpodoxime, ceftibuten, and the like) ; fourth generation cephalosporins (such as cefclidine, cefepime, cefozopran, cefpirome, cefquionome and the like) ; fifth and further generation cephalosporins (such as ceftobiprole, ceftaroline, ceftolozane and the like),

- carbapenems (such as imipenem, meropenem, ertapenem, doripenem and the like)
- monobactams (such as aztreonam, and the like),
- quinolones (such as nalidixic acid) and fluoroquinolones (such as cinoxacin, ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, gatifloxacin, gelifloxacin, norfloxacin and the like),
- sulfonamides (e.g., sulfanilamide, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfacetamide, sulfamethoxydiazine and the like),
- aminoglycosides (e.g., streptomycin, gentamicin, tobramycin, amikacin, netilmicin, kanamycin, neomycins B, C and E), spectinomycin, puromycin, gentamicin, and the like),
- tetracyclines (such as tetracycline, chlortetracycline, oxytetracycline, methacycline, doxycycline, minocycline, tigecycline, eravacycline and the like),
- macrolides (such as erythromycin, azithromycin, clarithromycin, fidaxomicin, telithromycin, josamycin, oleandomycin, spiramycin, tylosin, roxithromycin, cethromycin, solithromycin, and the like),
- glycopeptides (such as vancomycin, oritavancin, telavancin, teicoplanin, dalbavancin, ramoplanin and the like),
- oxazolidinones (such as linezolid, posizolid, tedizolid, radezolid, cycloserine and the like),
- phenicols (such a chloramphenicol, tiamphenicol and the like),
- lincosamides (such as clindamycin, lincomycin and the like),
- streptogramins (such as pristinamycin, quinupristin/dalfopristin, virginiamycin and the like)
- polymyxins (such as polymyxin A, B, C, D, E1(colistin A), or E2, colistin B or C, and the like),
- diaminopyrimidines (such as trimethoprim, often used in conjunction with sulfamethoxazole, pyrazinamide, and the like),
- sulfones (such as dapsone, sulfoxone sodium, and the like),
- para-aminobenzoic acid,
- bacitracin,
- isoniazid,
- rifamycins (such as rifampicin, rifabutin, rifapentine, rifalasil, rimamixin, and the like)
- ethambutol,
- ethionamide,
- capreomycin,

- clofazimine, and
- any other antibacterial agent.

The term “antibiotic” also covers combinations of antibiotics.

The invention thus also relates to a solid dosage form as described above, for use in a method for eliminating residual antibiotics in the intestinal tract, preferably before they reach the colon or as they reach the colon. More preferably, the solid dosage form is used in a method for eliminating residual antibiotics in the intestinal tract, preferably before they reach the caecum or as they reach the caecum and proximal colon. According to the invention, the adsorbent is preferably delivered between the part of the intestine where the antibiotics are absorbed (duodenum and jejunum) and where their deleterious effect on the commensal bacteria occur (caecum and colon). The invention further relates to a method for eliminating residual antibiotics in the intestinal tract, preferably before they reach the colon or as they reach the colon, most preferably before they reach the caecum or as they reach the caecum and proximal colon comprising administering to a subject in need thereof an effective amount of the solid dosage form of the invention.

The invention further relates to a solid dosage form as described above, for use in a method for eliminating the adverse effects of antibiotic agents in the intestinal tract, in particular for eliminating the development of antibiotic resistance, antibiotic treatment-associated development of *C. difficile* (or other pathogenic bacteria), antibiotic treatment-associated fungal infections or antibiotic treatment-associated diarrhea. The invention further relates to a method for eliminating the adverse effects of antibiotic agents in the intestinal tract, comprising administering to a subject in need thereof an effective amount of the solid dosage form of the invention.

In another embodiment, the present invention provides a kit, comprising an antibiotic, and a solid dosage form of the invention. The kit may be a kit-of-parts, for simultaneous, separate or sequential use in the treatment of an infection against which the antibiotic is suitable.

Cancer treatment

The present invention relates to a solid dosage form as provided above, for use in a method for improving the therapeutic efficacy of an anticancer agent, such as an immuno-oncology agent. The invention also relates to a solid dosage form as provided above, for use in a method for treating or preventing cancer, in combination with an anticancer agent, such as an immuno-

oncology agent. The invention further relates to a solid dosage form as provided above, for use in a method for treating or preventing cancer, in combination with an anticancer agent, such as an immuno-oncology agent, thereby improving the efficacy of said anticancer agent. The invention also relates to a solid dosage form as provided above, for use in a method for treating or preventing cancer, in combination with an anticancer agent, such as an immuno-oncology agent, thereby preserving the efficacy of said anticancer agent. The invention further relates to a solid dosage form as provided above, for use in a method for treating or preventing cancer, in combination with an anticancer agent, such as an immuno-oncology agent, thereby potentiating the efficacy of said anticancer agent.

The solid dosage form may be administered at any point in the therapy, e.g. before, during and/or after the anticancer agent, such as an immuno-oncology agent. In particular, the solid dosage form may be administered as soon as the patient is diagnosed with a malignancy, even if the intent to administer an anticancer agent only constitutes a remote possibility.

Anticancer agents, also sometimes referred to as antineoplastic agents, are substances that act against cancer in a mammal, such as a human being. The term “anticancer agent” includes, without limitation, chemicals and biological agents that affect directly a cancer cell, or indirectly such as by affecting the vascularisation of the cancer cell. For example, anticancer agents include, without limitation, chemotherapeutic molecules such as cytostatic agents, cytotoxic agents and anti-angiogenesis agents, anticancer antibodies targeting cancer cells, anticancer peptides and anticancer viruses. Illustrative anticancer agents include, without limitation:

- tubulin poisons, taxanes, e.g. docetaxel, paclitaxel,
- platinum compounds, e.g. cisplatin, carboplatin, oxaliplatin,
- agents interfering with DNA replication such as DNA intercalating agents, for example anthracyclines,
- topoisomerase inhibitors such as etoposide,
- antimetabolites, e.g. methotrexate, cytarabine (ara-C), gemcitabine, 5-Fluorouracil,
- alkylators, e.g. mechlorethamine, melphalan, carmustine, ifosfamide, or cyclophosphamide,
- targeted agents, such as enzyme inhibitor, in particular kinase inhibitors, e.g. erlotinib, sorafenib, imatinib, or proteasome inhibitors such as bortezomib, Carfizomib, Ixazomib,
- monoclonal antibodies targeting the extracellular region of a growth factor receptor, such as trastuzumab, bevacizumab and cetuximab,
- immuno-oncology agents, and
- combinations thereof.

Anthracyclines include, without limitation, doxorubicin and daunorubicin.

Topoisomerase inhibitors further include, without limitation, camptothecin, irinotecan, topotecan, and derivatives thereof.
Antimetabolites further include, without limitation, capecitabine and pemetrexed.

In a particular embodiment, the anticancer agent is an immuno-oncology agent. Immuno-oncology agents (also known as immuno-targeted agents) act against tumors, at least in part, by involving the immune system, or by an immune system-related mode of action. An immuno-oncology may more particularly act by modulating the action of immune cells.

Examples of immuno-oncology agents comprise agents that modulate immune checkpoints such as 2B4, 4-1BB (CD137), AaR, B7-H3, B7-H4, BAFFR, BTLA, CD2, CD7, CD27, CD28, CD30, CD40, CD80, CD83 ligand, CD86, CD160, CD200, CDS, CEACAM, CTLA-4, GITR, HVEM, ICAM-1, KIR, LAG-3, LAIR1, LFA-1 (CD 11 a/CD 18), LIGHT, NKG2C, NKp80, OX40, PD-1, PD-L1, PD-L2, SLAMF7, TGFRp, TIGIT, Tim3 and VISTA.

Immuno-oncology agents may be in the form of antibodies, peptides, small molecules or viruses. In a particular embodiment, the immuno-oncology agent is an antibody against PD-1, PD-L1 or PD-L2.

In a particular embodiment, the immuno-oncology agent is an inhibitor of arginase, CTLA-4, indoleamine 2,3-dioxygenase, and/or PD-1/PD-L1. In certain embodiments, the immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab, ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED 14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

More generally, an immuno-oncology agent may be any agent that may be used in the treatment of malignant diseases and that acts, at least in part, by involving the immune system, or has an immune system-related mode of action. For example, the immuno-oncology agent may be selected from, without limitation:
- an immune checkpoint inhibitor such as a PD-1 inhibitor, e.g. nivolumab or pembrolizumab;
- an immune checkpoint inhibitor such as a PDL-1 inhibitor, e.g. atezolizumab, avelumab, or durvalumab; or a CTLA-4 inhibitor, e.g. ipilimumab,
- a cancer vaccine, e.g. sipuleucel-T;
- an immunomodulator such as thalidomide, lenalidomide, pomalidomide,

- a non-specific immunotherapy, e.g. interferons, or interleukins; and
- a chimeric antigen receptor (CAR)-T cell therapy, e.g. tisagenlecleucel, or axicabtagene ciloleucel, and
- combinations thereof.

In a particular embodiment, the anticancer agent is an anti-PD-1 antibody. In a further particular embodiment, the anti-PD-1 antibody is selected from nivolumab and pembrolizumab.

In a particular embodiment of the invention, the anticancer agent is selected from Afatinib, Aflibercept, Alemtuzumab, Alitretinoin, Altretamine, Anagrelide, Arsenic trioxide, Asparaginase, Atezolizumab, Avelumab, Axitinib, Azacitidine, Bendamustine, Bevacizumab, Bexarotene, Bleomycin, Bortezomib, Bosutinib, Busulfan, Cabazitaxel, Capecitabine, Carboplatin, Carmofur, Carmustine, Cetuximab, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crizotinib, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Dasatinib, Daunorubicin, Decitabine, Denileukin diftitox, Denosumab, Docetaxel, Doxorubicin, Durvalumab, Epirubicin, Erlotinib, Estramustine, Etoposide, Everolimus, Floxuridine, Fludarabine, Fluorouracil, Fotemustine, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Hydroxycarbamide, Ibritumomab tiuxetan, Idarubicin, Ifosfamide, Imatinib, Ipilimumab, Irinotecan, Isotretinoin, Ixabepilone, Lapatinib, Lenalidomide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Nedaplatin, Nelarabine, Nilotinib, Nivolumab, Ofatumumab, Oxaliplatin, Paclitaxel, Panitumumab, Panobinostat, Pazopanib, Pembrolizumab, Pemetrexed, Pentostatin, Pertuzumab, Pomalidomide, Ponatinib, Procarbazine, Raltitrexed, Regorafenib, Rituximab, Romidepsin, Ruxolitinib, Sorafenib, Streptozotocin, Sunitinib, Tamibarotene, Tegafur, Temozolomide, Temsirolimus, Teniposide, Thalidomide, Tioguanine, Topotecan, Tositumomab, Trastuzumab, Tretinoin, Valproate, Valrubicin, Vandetanib, Vemurafenib, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine and Vorinostat.

The solid dosage form of the invention and the anticancer agent may be used to treat or prevent a cancer or multiple cancers in a subject. In certain embodiments, the cancer may be one or a variant of a cancer selected from Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Adrenocortical Carcinoma, Anal Cancer, Appendix Cancer, Atypical Teratoid/Rhabdoid Tumor, Basal Cell Carcinoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Tumor, Astrocytoma, Brain and Spinal Cord Tumor, Brain Stem Glioma, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Central Nervous System Embryonal Tumors, Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Carcinoid Tumor, Carcinoma of Unknown Primary, Central Nervous System Cancer, Cervical Cancer, Childhood Cancers,

Chordoma, Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma Ductal Carcinoma In Situ (DCIS), Embryonal Tumors, Endometrial Cancer, Ependymoblastoma, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Fibrous Histiocytoma of Bone, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Ovarian Germ Cell Tumor, Gestational Trophoblastic Tumor, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Heart Cancer, Hepatocellular Cancer, Histiocytosis, Langerhans Cell Cancer, Hodgkin Lymphoma, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors, Kaposi Sarcoma, Kidney Cancer, Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia, Lip and Oral Cavity Cancer, Liver Cancer, Lobular Carcinoma In Situ (LCIS), Lung Cancer, Lymphoma, AIDS-Related Lymphoma, Macroglobulinemia, Male Breast Cancer, Medulloblastoma, Medulloepithelioma, Melanoma, Merkel Cell Carcinoma, Malignant Mesothelioma, Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndrome, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndrome, Myelodysplastic/Myeloproliferative Neoplasm, Chronic Myelogenous Leukemia (CML), Acute Myeloid Leukemia (AML), Myeloma, Multiple Myeloma, Chronic Myeloproliferative Disorder, Nasal Cavity Cancer, Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung Cancer, Oral Cancer, Oral Cavity Cancer, Lip Cancer, Oropharyngeal Cancer, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer, Papillomatosis, Paraganglioma, Paranasal Sinus Cancer, Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pineal Parenchymal Tumors of Intermediate Differentiation, Pineoblastoma, Pituitary Tumor, Plasma Cell Neoplasm, Pleuropulmonary Blastoma, Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Clear cell renal cell carcinoma, Renal Pelvis Cancer, Ureter Cancer, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoma, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary (e.g., Metastatic), Squamous Cell Carcinoma of the Head and Neck (HNSCC), Stomach Cancer, Supratentorial Primitive Neuroectodermal Tumors, T- Cell Lymphoma, Testicular Cancer, Throat Cancer, Thymoma, Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Triple Negative Breast Cancer (T BC), Gestational Trophoblastic Tumor, Unknown Primary,

Unusual Cancer of Childhood, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Waldenstrom Macroglobulinemia, and Wilms Tumor.

In particular, the cancer may be selected from:

- tumors of epithelial origin affecting organs such as breast (breast adenocarcinoma), skin (melanoma), lung (non-small cell lung cancer and small cell lung cancer), kidney (renal cell carcinoma), pancreas (pancreatic carcinoma), bladder,
- digestive tumors such as gastro-oesohagial adenocarcinomas,
- head and neck cancers (in particular squamous tumors),
- squamous lung tumors,
- malignancies affecting blood of immune cells such as multiple myeloma, lymphoma (Hodgkin's and non-Hodgkin's of all types), leukemia among which lymphocytic leukemia (such as acute lymphoblastic leukemia (ALL), or chronic lymphocytic leukemia, (CLL)), myologenous leukemia (such as acute myolegenous leukemia (AML), and crhonic myelogenous leukemia (CML)), hairy cell leukemia, T-cell prolymphocytic leukemia, large granular lymphocytic leukemia, adut T-cell leukemia, adult T-cell lymphoma/leukemia.

In a particular embodiment, the cancer is selected from a cancer of the lung, a melanoma, a cancer of the pancreas, a cancer of the kidneys, refractory leukemia and lymphoma.

In certain embodiments, the method of the invention may further comprise administering one or more additional therapeutic agents conjointly with the anticancer agent. Representative therapeutic agents that may be conjointly administered with the anticancer agent include, without limitation: aminoglutethimide, amsacrine, anastrozole, asparaginase, AZD5363, Bacillus Calmette-Guerin vaccine (beg), bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, cobimetinib, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, erlotinib, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, miltefosine, mitomycin, mitotane, mitoxantrone, MK-2206, nilutamide, nocodazole, octreotide, olaparib, oxaliplatin, paclitaxel, pamidronate, pazopanib, pentostatin, perifosine, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, rucaparib,

selumetinib, sorafenib, streptozocin, sunitinib, suramin, talazoparib, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene di chloride, topotecan, trametinib, trastuzumab, tretinoin, veliparib, vinblastine, vincristine, vindesine, and vinorelbine. Other representative therapeutic agents that may be conjointly administered with the anticancer agent include, without limitation, pemetrexed.

In a particular embodiment, anticancer therapy is a combination therapy with an immuno-oncology agent and one targeted therapy. For example, the patient may be administered with an immuno-oncology agent and at least one other anticancer agent selected from BRAF and MEK inhibitors.

In a particular embodiment, anticancer therapy is a combination therapy with an immuno-oncology agent and at least one other anticancer agent. For example, the patient may be administered with an immuno-oncology agent and at least one other anticancer agent selected from platinum salts (such as cisplatin, carboplatin and the like), pemetrexed and etoposide. For example, the at least one other anticancer agent may be:

- pemetrexed,
- pemetrexed and platinum salts,
- etoposide, or
- etoposide and platinum salts.

In another embodiment, the present invention provides a kit, comprising an anticancer agent, and a solid dosage form of the invention. In certain embodiments, the kit may be for use in treating a condition or disease as described herein.

The present invention provides a method of treating or preventing cancer, comprising conjointly administering a solid dosage form according to the invention and an anticancer agent. Thanks to the invention, administering the anticancer agent and the solid dosage form according to the invention provides improved efficacy relative to individual administration of the anticancer agent.

In certain embodiments, the anticancer agent is administered within about 5 minutes to within about 7 hours after the solid dosage form according to the invention. In a particular embodiment, the solid dosage form according to the invention is administered multiple times before the anticancer agent is administered in order to ensure that the anticancer immunosurveillance system of the patient is improved. For example, the solid dosage form according to the invention may be administered daily, one or several times a day, for several

days. For example, the solid dosage form according to the invention may be administered daily, one or several times a day, at least 2, at least 3, at least 4, at least 5, at least 6 or at least 7 days before administration of the anticancer agent.

In certain embodiments, the solid dosage form according to the invention is administered once daily, or multiple times daily such as twice daily or thrice daily, during the whole time of anticancer treatment and maintained between the different cycles of anticancer treatment.

In certain aspects, the solid dosage form according to the invention is for use in a subject who has a cancer and who is administered, will be administered or has been administered with a substance, besides the anticancer agent, that may disturb the gut microbiota of said patient. Thanks to the invention, the deleterious impact of such substances may be prevented and thus the efficacy of the anticancer agent may be improved. Therefore, the invention relates to a method for mitigating the deleterious effects a substance may have on the gut microbiota of a subject suffering from cancer, said subject being the recipient of an anticancer agent therapy, comprising administering to said subject an effective amount of a solid dosage form according to the invention.

In certain embodiments, the substance is a pharmaceutical substance administered to treat a pathological condition in the patient. Indeed, certain pharmaceutical substances may be administered in order to treat a disease, but may have a deleterious effect on the gut microbiota when they reach the lower part of the intestine. The subject is still to receive the pharmaceutical substance for benefiting its desired effects but, on the other hand, solutions to avoid its secondary effects should be provided. Illustrative substances having this behaviour include antibiotics. Antibiotics may be administered to a subject in order to treat a bacterial infection. However, since antibiotics are, by design, able to affect bacterial growth or survival, they threaten the gut microbiota balance and may induce dysbiosis when they reach the lower part of the intestine. This induced dysbiosis may in turn result in a decrease in the efficacy of an anticancer drug administered to the subject. Other illustrative pharmaceutical substances that may induce dysbiosis (also referred to as “dysbiosis-inducing pharmaceutical substances”) include, without limitation:

- chemotherapy agents, such as taxanes (e.g. docetaxel, paclitaxel), anthracyclines (e.g. doxorubicin), topoisomerase inhibitors (e.g. etoposide, irinotecan), antimetabolites (e.g. methotrexate, cytarabine, 5-fluorouracil, gemcitabine, pemetrexed), alkylating agents (e.g. melphalan), kinase inhibitors (e.g. erlotinib),
- antifungal agents, such as voroconazole, ambisome, posoconazole,
- antiviral agents, such as acyclovir, methisazone,

- anti-inflammatory agents, such as aspirin, ibuprofen; and
- proton pump inhibitors such as omeprazole, pantoprazole, esomeprazole.

Accordingly, in another aspect of the invention the solid dosage form of the invention is administered to a subject who has a cancer and who is treated, will be treated or has been administered with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic.

The solid dosage form of the invention may be administered to the subject even long before initial administration of the anticancer agent. For example, the subject may have been diagnosed with a malignancy but the treatment could not begin before several days, weeks, months or years. In this case, should the subject suffer, between these events, from a disease that would need a treatment with a dysbiosis-inducing pharmaceutical agent, such as an antibiotic, it would be advantageous to prevent gut microbiota dysbiosis by administering a solid dosage form of the invention as provided herein. Likewise, the solid dosage form of the invention may be administered to the subject even long before the start or after the end of administration of the anticancer agent. Firstly, it may unfortunately be that the subject's cancer could relapse. In this case, halting the systematic administration of a solid dosage form of the invention when the subject receives a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, could severely impair the efficacy of a future therapy with the same or another anticancer agent. Secondly, some therapies, such as gene therapies, may be efficient several years after administration, as long as the therapeutic gene is expressed. In that case, the administration of the solid dosage form of the invention would be beneficial for improving this kind of long-lasting anticancer therapies. Of course, the solid dosage form of the invention is preferably administered during the whole course of the anticancer agent therapy, when the subject is to receive a therapy with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic.

In a particular embodiment, the invention relates to a solid dosage form of the invention for improving the efficacy of an anticancer agent in a subject in need of such an anticancer agent, wherein the subject is also administered with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic.

The invention also relates to a solid dosage form of the invention for use in the prevention of the decrease of efficacy of an anticancer agent in a subject when said subject is administered with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic.

The invention also relates to a solid dosage form of the invention for use to maintain the efficacy of an anticancer agent in a subject when said subject is administered with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic.

The invention further relates to a solid dosage form of the invention for use along with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, in a subject in need of an anticancer agent therapy.

The invention further relates to a solid dosage form of the invention for use in combination with a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, in a method for the treatment or prevention of a disease that may be treated or prevented with said dysbiosis-inducing pharmaceutical substance, wherein the subject in need of said treatment is also in need of an anticancer therapy.

The invention further relates to a solid dosage form of the invention for use in a subject in need of an anticancer agent, for preventing the impact of a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, on the efficacy of said anticancer agent.

The invention further relates to a solid dosage form of the invention for use in a subject in need of an anticancer agent, for preventing the decrease in efficacy of said anticancer agent potentially induced by a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, administered to said subject to treat or prevent another pathological condition that may be treated or prevented with said dysbiosis-inducing pharmaceutical substance.

In a particular embodiment, the solid dosage form of the invention is administered to the subject almost simultaneously with a dysbiosis-inducing pharmaceutical substance, for example an antibiotic. By “almost simultaneously”, it is meant that the solid dosage form of the invention is administered shortly before, simultaneously, and/or shortly after administration of the dysbiosis-inducing pharmaceutical substance, in particular an antibiotic, preferably shortly before. In a particular embodiment, the solid dosage form of the invention is administered less than 30 minutes before or after the dysbiosis-inducing pharmaceutical substance, in particular an antibiotic, has been administered, in particular less than 20 minutes, less than 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 minutes, or less than one minute before or after the dysbiosis-inducing pharmaceutical substance, in particular an antibiotic, has been administered. In a further particular embodiment, the solid dosage form of the invention is administered at least once a day, in particular at least twice a day, more particularly three times a day or four times a day. In a further particular embodiment, the solid dosage form of the

invention is administered during the whole course of the treatment with the dysbiosis-inducing pharmaceutical substance, in particular with an antibiotic. In a variant of this embodiment, the solid dosage form of the invention may be administered a longer time than the dysbiosis-inducing pharmaceutical substance, in particular than an antibiotic, in order to ensure that any residual dysbiosis-inducing pharmaceutical substance, in particular any residual antibiotic, is eliminated. For example, the solid dosage form of the invention may still be administered at least one day after, such as two days after interruption of the administration of the dysbiosis-inducing pharmaceutical substance, in particular after the administration of an antibiotic.

In a particular embodiment, the invention relates to a solid dosage form of the invention for use in combination with an antibiotic, in particular almost simultaneously, to a subject who is in need of an anticancer agent. According to this embodiment, the solid dosage form of the invention prevents the adverse effects the antibiotic could have on the intestinal microbiota of the subject, and therefore may improve the therapeutic efficacy of the anticancer agent.

Thus, the invention thus also relates to a kit comprising a solid dosage form of the invention and a dysbiosis-inducing pharmaceutical substance, such as an antibiotic. The kit may be for use in the treatment or prevention of a pathological condition that may be treated or prevented with the dysbiosis-inducing pharmaceutical substance, such as an antibiotic. In a particular embodiment of the kit, the dysbiosis-inducing pharmaceutical substance is an antibiotic. The kit may further comprise instructions to implement the methods of the present invention, aiming at preventing the decrease in the efficacy of an anticancer agent. The components of the kit may be administered simultaneously, separately or sequentially. As provided above, the solid dosage form of the invention may, in particular, be administered before, during, or after the administration of the dysbiosis-inducing pharmaceutical agent, such as an antibiotic, in particular shortly before or shortly after, more particularly shortly before.

Graft versus host disease (GVHD)

The present invention also to the treatment, prevention or delaying GVHD or reduction of the severity of GVHD based on the use of a solid dosage form of the invention.

In particular, the present invention can be used to prevent the disruption of the microbiota in patients receiving an allogeneic hematopoietic stem cells transplant and prevent or delay the occurrence of or reduce the severity of GVHD.

In certain aspects, the solid dosage form of the invention according to the invention is for use in a subject who is administered, will be administered or has been administered with an agent that may disturb the gut microbiota of said subject. Thanks to the invention, the deleterious impact of such agents may be prevented. Therefore, the invention relates to a method for mitigating the deleterious effects a pharmaceutical agent may have on the gut microbiota of a subject who is or could be a recipient of an immuno-competent transplant, comprising administering to said subject an effective amount of a solid dosage form of the invention, suitable for inactivating a dysbiosis-inducing pharmaceutical agent.

The dysbiosis-inducing pharmaceutical agent may be a pharmaceutical agent administered to treat a pathological condition in the subject as described above.

The solid dosage form of the invention may be administered to the subject even long before transplantation. For example, the subject may have been selected as a transplant recipient but the treatment could not begin before several days, weeks, months or years. In this case, should the subject suffer, between these events, from a disease that would need a treatment with a dysbiosis-inducing pharmaceutical agent, such as an antibiotic, it would be advantageous to prevent gut microbiota dysbiosis by administering a solid dosage form as provided herein. Likewise, the solid dosage form of the invention may be administered to the subject even long after the day of transplantation. In particular, it may unfortunately be that the subject's transplant be rejected by the host. In this case, halting the systematic administration of a solid dosage form of the invention when the subject receives a dysbiosis-inducing pharmaceutical substance, such as an antibiotic, could severely impair the efficacy of a future transplantation.

In a particular embodiment, the solid dosage form of the invention is administered to the subject almost simultaneously with a dysbiosis-inducing pharmaceutical agent, for example an antibiotic, as defined above in the section relating to cancer treatment.

In a particular embodiment, the invention relates to a solid dosage form of the invention for use in combination with an antibiotic, in particular almost simultaneously, to a subject who is in need of a transplant. According to this embodiment, the solid dosage form of the invention prevents the adverse effects the antibiotic could have on the intestinal microbiota of the subject, and therefore may treat or prevent GVHD.

In a specific embodiment, the invention can be used appropriately in patients at risk of GVHD such as patients taking antibiotics waiting for a hematopoietic stem cell transplant (HSCT)

procedure, to prevent GVHD occurrence or reduce the severity of a GVHD episode should one episode occur despite the initial treatment with the invention.

In particular, the invention can be used in patients in wait of, or during the course of a HSCT procedure when they receive antibiotics, in particular during the neutropenia phase. The invention can also be used in these patients when they receive antibiotics before the neutropenia phase in order to maintain an optimal microbiota equilibrium. The invention can also be used in patients diagnosed with a cancer of the blood or bone-marrow when they receive antibiotics in order to maintain the microbiota in the best possible state for the longest possible time and improve the outcome of a HSCT if this procedure is deemed necessary to cure the patient.

The invention can also be used in patients having received a HSCT procedure when they receive antibiotics in order to prevent the occurrence of the GVHD syndrome or avoid the worsening of acute or chronic GVHD if the patient already suffers from the disease.
In particular embodiments, the invention can be used every time the subject takes antibiotics. The invention may also be used after the subject has received a fecal microbial transplant or a treatment with probiotics to restore his or her microbiota diversity and is at risk of GVHD.

In a particular embodiment, the subject was administered with an immunosuppressive agent, such as methotrexate, tacrolimus, everolimus, sirolimus, mycophenolate mofetil or cyclosporine A. In another particular embodiment, the subject was administered with an anti-inflammatory drug such as with a corticosteroid.

In a further particular embodiment, the subject has fever. In particular, the antibiotic to be eliminated from the intestine of the subject has been prescribed because of said fever.

In a further particular embodiment, the solid dosage form of the invention is for use in a method for preventing the alteration of the microbiota in a subject who has received, receives or will received an allogeneic transplantation.

The invention can further be used in subjects at high risk of GVHD such as subjects who had a previous episode of GVHD in the years prior to a novel antibiotic cure, a novel hospitalization or a novel immune-suppressive cure.

Thus, the invention also relates to a kit comprising a solid dosage form of the invention and a dysbiosis-inducing pharmaceutical agent, such as an antibiotic, or to a kit comprising a solid

dosage form of the invention and an antibiotic. The kit may be for use in the treatment or prevention of a pathological condition that may be treated or prevented with the dysbiosis-inducing pharmaceutical agent, such as an antibiotic. In a particular embodiment of the kit, the dysbiosis-inducing pharmaceutical agent is an antibiotic. The kit may further comprise instructions to implement the methods of the present invention, aiming at treating or preventing GVHD. The components of the kit may be administered simultaneously, separately or sequentially. As provided above, the solid dosage form of the invention may, in particular, be administered before, during, or after the administration of the dysbiosis-inducing pharmaceutical agent, such as an antibiotic, in particular shortly before or shortly after, more particularly shortly before.

EXAMPLES

Example 1: manufacturing of carrageenan-based, cellulose-based, pectin-based and PVP-based pellets

All trials were performed by extrusion-spheronization or extrusion-knife cutting at a 20 g batch size. The granulation was performed in a high shear granulator. The extrusion and the spheronization processes were performed with the Caleva Multilab equipment. The knife cutting was performed manually. A round die with 34 holes with a diameter of 0.6 mm and a thickness of 0.6 mm was used for the extrusion process. The drying process was performed in a fluid bed system Mini Glatt.

A blending/wet granulation step was performed in a blender prior to engage raw materials in the extruder. All finished products were then dried in similar process conditions allowing to obtain comparable dried finished products (loss on drying ≤ 3%).

Example 2: analytical characterization of cellulose-based, pectin-based and PVP-based pellets

Appearance

The product is visually examined against a matt white background for colour and shape and their appearance is recorded. To be compliant, the product must be under the form of dark grey to black spheroid pellets.

Adsorption capacity of ciprofloxacin

All formulations were tested for their adsorption capacity of ciprofloxacin (CIP), antibiotic used as model antibiotic. The adsorption capacity reflects the product performance, considering that the *in vivo* action of the final product is the adsorption of the residual antibiotic in the caecum. In this *in*-vitro test, the adsorption capacity is the results of the disappearance of a compound of interest, the CIP, in the media after 3 hours in defined conditions. In order to have comparable values of adsorption, all analyses were performed with a constant theoretical quantity of activated charcoal of 20 mg, involved in the test. The pellets sampling weight was consequently adapted depending on the theoretical activated charcoal content in the formulations. Main conditions are described as follows:

Parameter	**Value**
CIP concentration	500 µg/L in adsorption medium
Adsorption medium	40 mL of 50 mM sodium phosphate buffer, pH 11.5
Sampling weight of pellets	Adjusted to have 20 mg of activated charcoal per sample
Rotor speed	10 rpm
Sampling Time	180 minutes

At 3 hours, samples are taken in order to assay the remaining CIP concentration in the media. The CIP assay is performed with a reverse-phase high-performance liquid chromatography.

The main parameters are defined as follow:

Parameters	**Value**
Chromatography Column	C18 reverse-phase column
Mobile Phase	Isocratic – 80/20 v/v TFA-NH_4^+ 0.01 M at pH 2.4/ACN
Flow rate	0.6 mL/min
Retention / Analysis time	4 minutes / 8 minutes
Oven temperature	40 °C
Auto sampler temperature	5 °C
Injection volume	10 µl
Detection wavelength	278 nm
ACN: Acetonitrile, TFA: Trifluoroacetic Acid	

Results are expressed as the adsorbed ciprofloxacin quantity (in mg) per quantity of theoretical activated charcoal (in g). The specification for this test is ≥ 300 mg of adsorbed CIP/g of activated charcoal.

Disintegration test by adsorption of ciprofloxacin

The principle of this test is to evaluate the capacity of pellets to release activated charcoal in a specific media (phosphate buffer, pH 6.5). This test consists in measuring the disintegration profile of pellets. Pellets are immersed into a buffer which is spiked with a reference antibiotic, the CIP, to be adsorbed. The quantification of the release of activated charcoal in the buffer is performed by an indirect method based on the adsorption of CIP. The disappearance of the CIP, due to its adsorption by the activated charcoal, is measured over time by HPLC, which allows to evaluate the kinetics of the release of the activated charcoal in the media and thus the disintegration of pellets. The HPLC method to determine CIP concentration is described in the ciprofloxacin adsorption capacity test section.

The analysis of each formula is performed on a BioDis apparatus (dissolution Apparatus 3 as described in European Pharmacopeia - EP - monograph 2.9.3). Experimental conditions are summarized hereafter:

Parameter	**Value**
Dissolution media	180 mL, Phosphate buffer 50 mM, pH 6.5
CIP concentration	200 µg/mL
Pellets mass	36 mg of adsorbent
Dipping rate	5 dips/min
Screen size	40 Mesh (420 µm)
Sampling Time	T0, 5, 10, 15, 20, 30, 45 and 60 minutes
Sample preparation	Filtration with 0.45µm Nylon filters

Results of the disintegration test are expressed in cumulated quantity of adsorbed CIP (in mg).

Example 3: Manufacturing of K-carrageenan based formulations and characterization

The reference formulation made of K-carrageenan and activated charcoal was manufactured according to Example 1, by extrusion-spheronisation.

This reference formula (trials named P017 and P030) is presented in the table hereafter:

Trial number	**P017/P030 – REF**
Raw material	**Centesimal formulation (%)**
Activated Charcoal	85
K-carrageenan	15

Batches P017 and P030 were considered as the best prototypes obtained at small lab scale.

The appearance was determined as described in Example 2. The shape of obtained pellets was acceptable, with presence of rounded pellets, of dumbbell shaped pellets and some cylinders. These results showed that an optimal shape of pellets was difficult to obtain at this very low batch size whereas this formulation used to lead to rounded pellets at larger scales. Consequently, the targeted shape of new formulations was to obtain at least an equivalent appearance of those produced with k-carrageenan during batches P017 and P030.

In terms of disintegration (measured as described in Example 2), a fast disintegration with an adsorbed quantity of CIP of 8.9 mg after 5 minutes was measured, whereas the value at T60 min was equal to 12.3 mg, meaning equivalent to the T60-min reference value for this activated charcoal batch. These results confirmed that the produced pellets disintegrated as expected.

Example 4: Appearance of cellulose based formulations

As described in Example 1, the extrusion of activated charcoal formulated with cellulose-based excipients was assessed at small-scale in order to determine if the new formulations were suitable or not regarding the manufacturing process and the extrudates quality attributes. Activated charcoal was formulated with different cellulose-based excipients, especially with a mixture of pregelatinized corn starch and low-substituted hydroxypropyl cellulose (trial named P023), two grades of carboxymethyl cellulose (trials named P027 and P028), one grade of hydroxypropyl methyl cellulose (trial named P029) and a mixture of carboxymethyl cellulose and microcrystalline cellulose (trial named P046). The compositions are described as follow:

	Trial number	**P030 - REF**	**P023**	**P027**	**P028**	**P029**	**P046**
Raw material	**Grade (Supplier)**	**Centesimal formula (%)**					
Activated Charcoal		85	80	85	85	85	85
K-carrageenan		15	/	/	/	/	/
Pregelatinized corn starch	Starch 1500 (Colorcon)	/	10	/	/	/	/
Low-substituted hydroxypropyl cellulose (L-HPC, LH11)	L-HPC, LH11 (Shin-Etsu)	/	10	/	/	/	/
Carboxymethyl cellulose (CMC-Na)	Blanose 7H4XF PH (Ashland)	/	/	15	/	/	/

Carboxymethyl cellulose (CMC-Na)	Blanose 7M8SF PH (Ashland)	/	/	/	15	/	2.5
Hydroxypropyl methyl cellulose (HPMC)	Pharmacoat 603 (Shin-Etsu)	/	/	/	/	15	/
Microcrystalline cellulose (MCC)	MCC Avicel PH102 (DuPont)	/	/	/	/	/	12.5
	TOTAL	100	100	100	100	100	100

Two CMC-Na grades (Blanose 7H4XF PH and Blanose 7M8SF PH supplied by Ashland) were selected in order to assess the impact of their very different viscosity, respectively 9,000-16,800 and 375-700 mPa.s (European Pharmacopeia range at 20°C). The substitution range for both CMC-Na grades is 0.65-0.90.

In contrast, the selected HPMC grade (Pharmacoat 603 supplied by Shin-Etsu) has a substitution type in USP of 2,910 and an apparent viscosity of 2.4-3.6 mPa.s.

The MCC grade (Avicel PH102 supplied by DuPont) has a bulk density of 0.28-0.33 g/cc with a degree of polymerisation of 350.

The pregelatinized corn starch grade (Starch 1500 supplied by Colorcon) has a gelatinization level of around 20% and a mean particle size of around 65 µm. The bulk density is approx. 0.61 g/cc. The Carr's compression index for this grade is 26%.

The selected L-HPC grade (LH11, Shin-Etsu) has a polymerization degree of 730 with a hydroxy-proroxy content of 11%. Its molecular weight is 130 and the mean particle size is 55 µm. The bulk density is 0.33 g/cc with an aspect ratio of 5.0.

In terms of appearance (as determined in Example 2), the formulations trials led to very different results. Extrudates were obtained for the formulation P023, produced with Starch 1500 and L-HPC (LH11). The addition of a spheronization step did not lead to the transformation of the extrudates into pellets, but small cylinders could be obtained by manual cutting.

For the batch manufactured with HPMC (P029), sticky extrudates were obtained, making the spheronization or cutting step impossible. Therefore, the formulation with HPMC (P029) was not considered for further development steps.

Batches manufactured with CMC-Na (P027 and P028) as excipient led to better extrudates appearance. No significant differences were observed between both CMC-Na grades (P027 and P028).

The shape of pellets was further improved in trial P046, implementing a blend of MCC and CMC-Na (P046). Finished products achieved by extrusion-spheronisation were pellets presenting a shape close to the current reference (rounded pellets, dumbbells and cylinders). From all formulations performed with cellulose-derivatives excipients, the formula produced with 12.5% MCC and 2.5% CMC-Na (P046) by extrusion-spheronisation led to the best appearance.

Example 5: CIP adsorption capacity of PVP based formulations

As described in Example 1, the extrusion of activated charcoal formulated with polyvinylpyrrolidone (PVP)-based excipients was assessed at small-scale in order to determine if the new formulations were suitable or not regarding the manufacturing process and the extrudates quality attributes. Activated charcoal was formulated with different polyvinylpyrrolidone-based excipients, especially with one grade of crospovidone in association with microcrystalline cellulose (trial named P022) and one grade of polyvinylpyrrolidone with two different polymer contents (trials named P024 and P026). The compositions are described as follows:

	Trial number	**P030 - REF**	**P022**	**P024**	**P026**
Raw material	**Grade (supplier)**	**Centesimal formula (%)**			
Activated charcoal		85	80	70	85
K-carrageenan		15	/	/	/
Microcrystalline cellulose (MCC)	Avicel PH102 (DuPont)	/	15	/	/
Crospovidone	Kollidon CL-F (BASF)	/	5	/	/
Polyvinylpyrrolidone (PVP)	Kollidon K-30 (BASF)	/	/	30	15
	TOTAL	100	100	100	100

The selected MCC grade (Avicel PH102 supplied by DuPont) had a bulk density of 0.28-0.33 g/cc with a degree of polymerisation of 350. The selected crospovidone grade (Kollidon CL-F) had the following specifications:

Kollidon CL-F specifications

Swelling pressure (kPa)	Approx. 30
Time to reach 90% of the maximal swelling pressure (s)	< 15
Hydration capacity (g water/g polymer)	5.0 – 6.6
PSD > 50 µm (%)	Max 60
PSD > 20 µm (%)	Max 20
Bulk density (g/mL)	0.18 – 0.28
Tap density 500 taps (g/mL)	0.25 – 0.35
Specific surface area (N2-BET) (m^2/g)	Approx.1.5

The selected PVP grade (Kollidon K-30) grade specifications are defined as follows:

Kollidon K-30 specifications	
Nominal K value	30
Mw (g/mol)	44000 - 54000
PSD <50 µm (%)	Max 40
PSD > 250 µm (%)	Max 5
Bulk density (g/L)	400 – 600
Glass transition temperature (°C)	171

All formulations performed with PVP-based excipients led to similar product appearance (determined according to Example 2) with rigid and straight extrudates of product which were knife-cut allowing to obtain small cylinders as pellet-like products on which adsorption tests were performed.

Each formulation was then tested for its adsorption capacity of ciprofloxacin (CIP), an antibiotic used as a model antibiotic (as described in Example 2).

Adsorption capacity tests performed on formulations with PVP led to low values whatever the content of binder used in the formulation. These results were likely related to difficulties to disperse the product during the test. The strong binding effect of the PVP was thus a limit to the use of this excipient for the formulation of pellets.

As demonstrated in the table below, the formulation containing crospovidone and MCC (P022), led to a compliant adsorption capacity, comparable to the reference formulation (P030). This result was likely related to the crospovidone, used as super disintegrating agent in oral dosage form.

Trial	CIP adsorption capacity (mg of CIP / g of AC)
P030 (REF)	423
P022	373
P024	97
P026	130

Example 6: Pectin based formulations results

As described in Example 1, the extrusion of activated charcoal formulated with pectin-based excipients was assessed at small-scale in order to determine if the new formulations were suitable or not regarding the manufacturing process and the extrudates quality attributes. Activated charcoal was formulated with different pectin-based excipients, especially with 3 different grades of pectin (trials named P037, P038 and P039) whose compositions are described below:

	Trial number	P030 - REF	P037	P038	P039
Raw material	**Grade (Supplier)**	**Centesimal formula (%)**			
Activated charcoal		85	85	85	85
K-carrageenan		15	/	/	/
Pectin	Citrus USP (CP kelco)	/	10	/	/
Pectin	LM 30CS (CP kelco)	/	/	12	/
Pectin	LM 25AS (CP kelco)	/	/	/	12
Citric acid	N/A	/	2	1.5	1.5
Calcium chloride	N/A	/	3	1.5	1.5
	TOTAL	100	100	100	100

The specifications of these 3 pectin grades are described as follow:

	GENU Pectin (citrus) USP-H specifications	GENU pectin LM-HC-25 AS specifications	GENU pectin LM-HC-30 CS specifications
Visc 2% sol, 60 rpm, cps	200 – 450	N/A	N/A
Visc wet prep SPLENDID 100, cps	N/A	N/A	17000 - 23000

Degree of esterification (%)	65 – 75	20 – 26	15 - 25
Degree of amidation (%)	N/A	18 - 25	N/A
Methoxy groups (%)	6.7 – 12.0	2.0 – 4.0	2.0 – 4.0

In terms of appearance (determined according to Example 2), all trials led to acceptable product by extrusion-spheronisation, composed of a blend of rounded pellets, dumbbells and some cylinders. Considering that the appearance of the reference product manufactured with the equipment of this study was very similar, these products were considered as promising and may be likely improved by process adjustments and by using bigger process equipment. The pellets obtained from formulation P037 were slightly less rounded than other pellets from trials P038 and P039.

Each prototype was then assessed in a disintegration test, performed according to Example 2. In terms of adsorption profile, the formulations trials led to very different kinetics (figure 1):

- P037: This formulation presented first an intermediate release of product followed by a slow release. The final value of adsorbed quantity of ciprofloxacin was comparable to the reference considered as a high level of disintegration.
- P038: This formulation presented a slow level of disintegration, leading to a lower value of adsorbed ciprofloxacin as compared to the reference formulation.
- P039: the profile obtained with this formulation presented a fast disintegration kinetic which was considered as equivalent to the reference profile.

P037 and P039 prototypes were found to be close to the reference and good candidates for the preparation of a pharmaceutical composition.

CLAIMS

1. A composition comprising an adsorbent in admixture with an excipient selected in the group consisting of crospovidone, carboxymethylcellulose (CMC) and amidated low-methoxy (aLM) pectin.

2. The composition according to claim 1, wherein the adsorbent is activated charcoal.

3. The composition according to claim 1 or 2, wherein the composition comprises from 75 to 90% of the adsorbent, by weight of the composition.

4. The composition according to any one of claims 1 to 3, wherein the composition comprises from 3 to 7% of crospovidone, by weight of the composition.

5. The composition according to any one of claims 1 to 4, wherein the composition comprises:
- from 75 to 90% of the adsorbent;
- from 5 to 20% of microcrystalline cellulose; and
- from 3 to 7% of crospovidone; and

by weight of the composition.

6. The composition according to any one of claims 1 to 5, wherein the composition comprises:
- about 80% of activated charcoal;
- about 15% of microcrystalline cellulose; and
- about 5% of crospovidone;

by weight of the composition.

7. The composition according to any one of claims 1 to 3, wherein the composition comprises sodium CMC (CMC-Na).

8. The composition according to any one of claims 1 to 3 and 7, wherein the composition comprises from 1 to 25% of CMC, by weight of the composition.

9. The composition according to any one of claims 1 to 3, 7 and 8, wherein the composition comprises:
- from 75 to 90% of the adsorbent;
- from 1 to 25% of CMC-Na; and
- from 0 to 15% of microcrystalline cellulose;

by weight of the composition.

10. The composition according to any one of claims 1 to 3, and 7 to 9, wherein the composition comprises:

- about 85% of activated charcoal; and
- about 15% of CMC-Na;

by weight of the composition.

11. The composition according to any one of claims 1 to 3, comprising from 8 to 16% of aLM pectin, by weight of the composition.

12. The composition according to any one of claims 1 to 3 and 11, wherein the composition comprises:

- from 75 to 95% of an adsorbent;
- from 8 to 16% of an aLM pectin;
- from 1 to 2% of citric acid; and
- from 1 to 2% of calcium chloride;

by weight of the composition.

13. The composition according to any one of claims 1 to 3, 11 and 12, wherein the composition comprises:

- about 85% of activated charcoal;
- about 12% of sodium aLM pectin;
- about 1.5% of citric acid; and
- about 1.5% of calcium chloride;

by weight of the composition.

14. The composition according to any one of claims 1 to 13, wherein the composition is in the form of a pellet.

15. A solid oral dosage form comprising one or more pellets according to claim 14, wherein the pellet(s) are coated with a polymeric enteric coating suitable to release the pellet in a desired part of the intestine.

16. The solid oral dosage form according to claim 15, wherein said dosage form comprises:

- a core corresponding to the pellet according to claim 14; and

- a layer of an external coating formed around the core such as said core is released in the desired part of the intestine.

17. The solid oral dosage form according to claim 15 or 16, wherein the desired part of the intestine is the lower part of the intestine.

18. The solid oral dosage form according to any one of claim 17, wherein the dosage form comprises an external coating comprising an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid, such as poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1.

19. The solid oral dosage form according to any one of claims 15 to 18, for use in a method for the treatment of a side effect of a dysbiosis-inducing pharmaceutical agent.

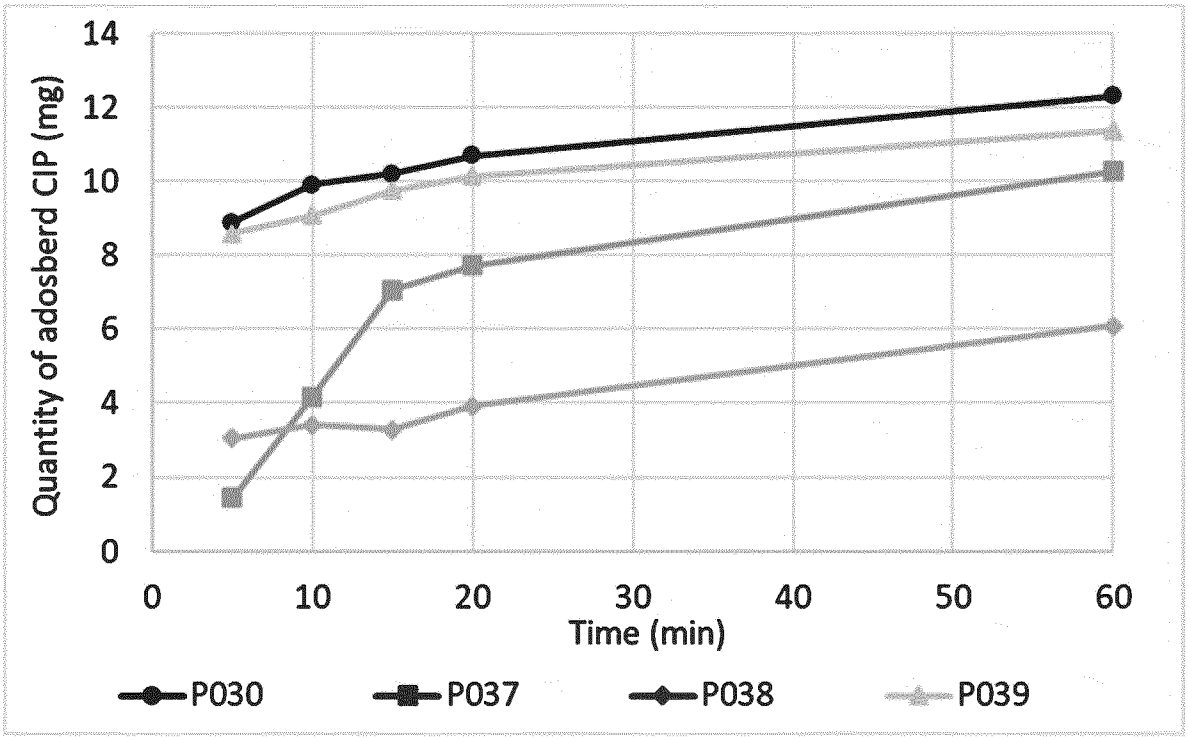
Quantity of adosberd CIP (mg)
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Time (min)
P030
P037
P038
P039

FIGURE 1