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(54) Titre : COMPOSITIONS PHARMACEUTIQUES OU ALIMENTAIRES A BASE D'ACIDES GRAS A CHAINE COURTE
 ET DE SUCRES COMPLEXES UTILISEES EN CAS DE TROUBLES INTESTINAUX
 (54) Title: PHARMACEUTICAL OR DIETARY COMPOSITIONS BASED ON SHORT-CHAIN FATTY ACIDS AND
 COMPLEX SUGARS, FOR INTESTINAL DISORDERS

(57) **Abrégé/Abstract:**

Pharmaceutical and/or dietary compositions for supplying energy and eutrophication factors to the large intestine to improve its functionality and prevent the appearance of pathological conditions are described. The pharmaceutical and/or dietary compositions described are composed of one or more short-chain monocarboxylic acids or their salts, esters and/or amides, mixed with one or more soluble dietary fibres or complex sugars. These compositions are formulated by known techniques suitable for transporting the active ingredients into the colonic section of the intestine.



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(54) Title: PHARMACEUTICAL OR DIETARY COMPOSITIONS BASED ON SHORT-CHAIN FATTY ACIDS AND COMPLEX SUGARS, FOR INTESTINAL DISORDERS

(57) Abstract: Pharmaceutical and/or dietary compositions for supplying energy and eutrophication factors to the large intestine to improve its functionality and prevent the appearance of pathological conditions are described. The pharmaceutical and/or dietary compositions described are composed of one or more short-chain monocarboxylic acids or their salts, esters and/or amides, mixed with one or more soluble dietary fibres or complex sugars. These compositions are formulated by known techniques suitable for transporting the active ingredients into the colonic section of the intestine.

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"PHARMACEUTICAL OR DIETARY COMPOSITIONS BASED ON SHORT-CHAIN FATTY ACIDS AND COMPLEX SUGARS, FOR INTESTINAL DISORDERS"

Short-chain fatty acids (SCFA) are linear or branched C₁-C₅ monocarboxylic organic acids such as acetic, propionic, butyric, and isovaleric acids.

They are produced by the fermentation of undigested sugars and of dietary fibres within the large intestine by means of the bacterial flora of the intestine.

The production of short-chain fatty acids takes place along the entire large intestine with a gradient which decreases from the ileocaecal valve to the rectum. At the moment at which these short-chain fatty acids come into contact with the cells of the mucous membrane of the colon, they are rapidly captured within the cells where they are metabolized to acetyl-CoA, which is a fundamental factor of energy metabolism. Of the four short-chain fatty acids mentioned above, butyric acid is considered the most important source of energy for the colocytes since it is responsible for about 70% of their oxygen consumption. About 70-90% of all of the butyric acid produced in the colon is metabolized by the colocytes (Velazquez O.C. *et al*, Dietary Fiber in Health and Disease, Plenum Press, N.Y., 1977, 123-134; Wachtershauser A. *et al.*, Eur. J. Nutr., 2000, 39, 164-171).

Short-chain fatty acids are considered to be the main source of energy for the cells of the mucous membrane of the colon and also to be fundamental factors in the control of the growth of the mucous membrane itself. In fact a lack or substantial reduction thereof is often correlated with many functional disorders or organic pathological conditions such as, for example, disorders due to altered intestinal regularity, inflammatory intestinal conditions, ulcerative colitis,

Crohn's disease, colonic neoplasia, etc. SCFAs and butyric acid or its salts in particular also intervene in the regulation of the proliferation of any colonic epithelial cells, not only favouring processes of re-epithelialization of the normal mucous membrane, but also inhibiting the proliferation of tumour cells, particularly by inhibition of the synthesis of the DNA of the tumour cell and by re-establishment of its natural apoptosis (Wachtershauser A. *et al*, Eur. J. Nutr., 2000, 39, 164-171).

Bearing in mind the key role played by butyric acid in the regulation of these extremely important biological activities of the colon, its administration, in conditions of absolute or relative deficit, represents an action of fundamental importance.

The endogenous production of butyric acid requires the presence of soluble dietary fibres which are fermented for this purpose by the bacterial flora of the colon. As well as being subject to fermentation by the bacterial flora and thus leading to the production of endogenous butyric acid, inulin in particular, amongst the soluble dietary fibres, is itself an important factor stimulating saprophytic bacterial growth, thus helping to promote bacterial colonization and to regulate the equilibrium of the bacterial flora of the intestine (Gibson, R.G. *et al.*, Gastroenterology, 1995, 108, 975-982; Nyman M. Br. J. Nutr. 2002, 87, s163-168).

The supplementary supply of short-chain fatty acids and of fibre can therefore be considered a constant need, even for patients who do not show clear signs of disorders or pathological conditions at intestinal level, because of ever more frequent recourse to incorrect eating habits, to inappropriate dietary regimes, and to the use of ever more refined foodstuffs

which are less and less rich in roughage and coarse fibre in particular.

In very many cases, in spite of the presence of a normal supply of fibre, the fermentation process itself may be deficient and may not lead to sufficient formation of butyric acid. This reduced or absent intestinal fermentation activity is, in most cases, caused by qualitative and quantitative modifications of the bacterial flora of the intestine which are due in turn to the ingestion of substances which inhibit the development and normal growth of the flora, such as antibacterial agents, preservatives, antibiotics, etc. As a result of this general dietary-fermentary impoverishment, the production of butyric acid may therefore be reduced to levels such as not to supply adequate energy and protection to the intestine.

The breakdown of the delicate balance of interaction between exogenous factors (dietary fibre) and endogenous factors (bacterial flora) may therefore lead to the appearance of the above-mentioned organic or functional alterations affecting the intestine and, in particular, the colon.

In the presence of a reduced or insufficient colonic endolumenal concentration of butyric acid, at the moment, the most appropriate action is therefore the supply of a sufficient quantity of exogenous butyric acid, directly into the colon.

Currently, compositions based on butyric acid alone or on its Na^+ , Ca^{++} , and Mg^{++} salts are available and the only route which can ensure that appropriate concentrations of that acid reach the interior of the colon is the rectal route which, however, since it does not enable the proximal part of the colon to be reached, limits the supply purely to the distal colon,

with the understandable and considerable inconvenience connected with this administration route.

Bearing in mind the impracticality of this latter administration route for supplementary dietary purposes and the need to limit the energy deficit and to re-establish intestinal balance, it has now surprisingly been found and constitutes the subject of the present invention that the combination of butyric acid itself, or of a salt thereof, with a soluble fibre such as, for example, inulin, in an oral formulation leads to a very significant synergic effect between the two components, leading to amplification of the effects that may be produced by the administration of the individual substances.

The combination according to the invention in fact leads to a synergy of the effects of the two substances which thus make up for the energy and protective deficit due to the lack or reduced production of endogenous butyric acid.

A subject of the present invention is therefore oral pharmaceutical or dietary compositions containing a short-chain fatty acid, in particular butyric acid, in combination with a soluble or water-dispersible dietary fibre.

In one aspect, the present invention provides an oral pharmaceutical or dietary composition containing at least one short-chain fatty acid or a salt thereof in combination with a complex sugar and/or soluble or water dispersible dietary fibre selected from the group consisting of inulin, pectin, dextrin, maltodextrin and derivatives thereof, and one or more pharmacologically acceptable excipients, wherein said composition further comprises (a) a lipophilic matrix consisting of a

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lipophilic compound with a melting point lower than 90°C and optionally an amphiphilic compound in which said short-chain fatty acid or said salt is at least partially incorporated, (b) an amphiphilic matrix, and (c) an outer hydrophilic matrix in which said lipophilic matrix and amphiphilic matrix are dispersed, and wherein said fatty acid or said salt is without a covalent bond to a carbohydrate carrier, or said complex sugar or dietary fibre.

In a further aspect, the present invention provides use of a short-chain fatty acid or a salt thereof in combination with a complex sugar and/or soluble or water dispersible dietary fibre selected from the group consisting of inulin, pectin, dextrin, maltodextrin and derivatives thereof for the preparation of a pharmaceutical or dietary composition for the treatment of intestinal disorders, inflammatory disorders, and pathological conditions of the intestinal mucous membrane and for the preventive or limiting treatment of intestinal neoplasia, wherein said composition further comprises (a) a lipophilic matrix consisting of a lipophilic compound with a melting point lower than 90°C and optionally an amphiphilic compound in which said short-chain fatty acid or said salt is at least partially incorporated, (b) an amphiphilic matrix, and (c) an outer hydrophilic matrix in which said lipophilic matrix and amphiphilic matrix are dispersed, and wherein said fatty acid or said salt is without a covalent bond to a carbohydrate carrier, or said complex sugar or dietary fibre.

The active components that are present in the mixture can be used in the most appropriate physical state for the production of a suitable form for administration; since

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the food supplement or the pharmaceutical composition is intended for oral administration, the preferred form is the solid form.

In order to produce these solid forms, in particular the tablet form, since butyric acid is a liquid, a solid salt of the acid such as, for example, calcium butyrate, sodium butyrate, or magnesium butyrate may be used, or the acid itself may be supported on a solid

substrate of inert material by the known spray-dry technique or by adsorption.

As solid substrates, it is possible to use the excipients that are normally used for the preparation of tablets such as, for example, gum arabic, maize starch, pre-gelatinized starch, pectin, monosaccharide and polysaccharide sugars, alginates, microcrystalline cellulose, alkyl derivatives or hydroxyalkyl derivatives of cellulose with low, medium and high viscosity, monoprotic and polyprotic mineral salts, cyclodextrin, alkylcyclodextrin, hydroxyalkylcyclodextrin, pyrrolidones or derivatives, monocarboxylic organic salts and/or esters, polycarboxylic organic salts and/or esters, inorganic substrates such as colloidal silica, talc, and organic and inorganic ion-exchange resins. In order to produce a powder from a liquid, atomization is therefore performed by the drying of a suspension of liquid butyric acid and solid substrate by the spray-dry technique, or butyric acid is adsorbed on one of the above-mentioned substrates.

In both cases, a powder containing proportional quantities of butyric acid dispersed in the solid substrate is obtained.

In a preferred embodiment, the compositions of the invention are preferably formulated in a unitary-dose form for oral administration which can reach the specific colonic section of the intestine almost intact or in a manner such that most of the active ingredients reach the colon cavity directly, thus passing through the gastric intestinal portion and the first portion of the intestinal tract.

This requirement takes account of the fact that, when butyric acid or its salts are administered orally (foods, capsules, or plain tablets) they are absorbed

very rapidly and completely by the small intestine to the extent that they do not manage to reach the colon.

This can be achieved by the use of controlled-release techniques which have their characteristic target site in the colonic section. These techniques are known in the pharmaceutical field and are normally used to formulate active substances of other types which require a specific release time and/or site such as, for example, intestinal anti-inflammatories (Brunner N. et al., Aliment.

Pharmacol. Ther. , 2003, 17, 395-402], systemic anti-inflammatories, anti-ulcerative agents, anti-microbial agents, or substances for energizing the mucous membrane.

European patent EP1183014 describes, for example, a multi-matrix controlled-release technique which is known by the trade mark MMX and is characterized by the dispersion of the active ingredient in a successive and progressive mixture of three different, interconnected matrices.

Specifically, the multi-matrix controlled-release technique of European Patent EP1183014, which is hereby admitted as prior art, is described as follows:

"[0020] The compositions of the invention can be prepared by a method comprising the following steps:

- a) the active ingredient is first inglobated by simple kneading or mixing in a matrix or coating consisting of compounds having amphiphilic properties, which will be further specified below. The active principle(s) can be mixed with the amphiphilic compounds without the aid of solvents or with small amounts of water-alcoholic solvents.
- b) The matrix obtained in a) is incorporated in a low melting lipophilic excipient or mixture of excipients, while heating to soften and/or melt the

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excipient itself, which thereby incorporates the active ingredient by simple dispersion. After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain inert matrix granules containing the active ingredient particles.

c) The inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellaable excipients. The mixture is then subjected to compression or tableting. This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

[0021] The amphiphilic compounds which can be used according to the invention comprise polar lipids of type I or II (lecithin, phosphatidylcholine, phosphatidylethanolamine), ceramides, glycol alkyl ethers such as diethylene glycol monomethyl ether (Transcutol^(R)).

[0022] The lipophilic matrix consists of substances selected from unsaturated or hydrogenated alcohols or fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, the polyethoxylated derivatives thereof, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point

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within the range of 40 to 90°C, preferably from 60 to 70°C.

[0023] If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

[0024] An amphiphilic matrix with high content in active ingredient, typically from 5 to 95% w/w, is first prepared by dispersing the active ingredient or the mixture of active ingredients in a mixture of amphiphilic compounds, such as lecithin, other type II polar lipids, surfactants, or in diethylene glycol monoethyl ether; the resulting amphiphilic matrix is then mixed or kneaded, usually while hot, with lipophilic compounds suitable to form an inert matrix, such as saturated or unsaturated fatty acids, such as palmitic, stearic, myristic, lauric, laurylic, or oleic acids or mixtures thereof with other fatty acids with shorter chain, or salts or alcohols or derivatives of the cited fatty acids, such as mono-, di-, or triglycerids or esters with polyethylene glycols, alone or in combination with waxes, ceramides, cholesterol derivatives or other apolar lipids in various ratios so that the melting or softening points of the lipophilic compounds mixtures is within the range of 40 to 90°C, preferably from 60 to 70°C.

[0025] Alternatively, the order of formation of the inert and amphiphilic matrices can be reversed,

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incorporating the inert matrix inside the amphiphilic compounds.

[0026] The resulting inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

[0027] The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which when passing from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

[0028] Examples of hydrogels which can be used according to the invention are compounds selected from acrylic or methacrylic acid polymers or copolymers, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrans, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

[0029] In case of taste-masking formulations, the use of polyalcohols such as xylitol, maltitol and mannitol as hydrophilic compounds can also be advantageous.

[0030] The lipophilic matrix granules containing the active ingredient are mixed with the hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:50 (lipophilic matrix: hydrophilic matrix). Part of the active ingredient can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is

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dispersed both in the lipophilic and the hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitables.

[0031] The compression of the mixture of lipophilic and/or amphiphilic matrix, hydrogel-forming compound and, optionally, active ingredient not inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix. A similar result can also be obtained by coating the lipophilic matrix granules with a hydrophilic polymer coating.

[0032] The tablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of, for example, methacrylic acids polymers (Eudragit^(R)) or cellulose derivatives, such as cellulose acetophthalate.

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[0034] The compositions of the invention can further contain conventional excipients, for example bioadhesive excipients such as chitosans, polyacrylamides, natural or synthetic gums, acrylic acid polymers.

[0035] The compositions of the invention can contain more than one active ingredient, each of them being optionally contained in the hydrophilic matrix or in the inert amphiphilic matrix, and are preferably in the form of tablets, capsules or minitables.

[0036] In terms of dissolution characteristics, contact with water or aqueous fluids causes the immediate penetration of water inside the more superficial layer

of the matrix which, thanks to the presence of the aqueous solvent, swells due to the distension of the polymeric chains of the hydrogels, giving rise to a high viscosity hydrated front which prevents the further penetration of the solvent itself linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness, until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of inert matrix granules, however induces the diffusion mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

[0037] The presence of the amphiphilic matrix inside the lipophilic matrix inert allows to prevent any unevenness of the release profile of the active ingredient. The surfactants present in the amphiphilic portion promote wettability of the porous canaliculuses which cross the inert matrix preventing or reducing resistance to penetration of the solvent inside the inert matrix.

[0038] To obtain taste masking tablets, the components of the hydrophilic matrix are carefully selected to minimize the active substance release time through penetration accelerated by the canalization induced by the hydrophilic compound."

Other techniques which are theoretically suitable for the formulation of the composition of the invention are described in EP572942 and WO 00/28974.

These techniques can bring about protection of the active ingredients throughout the transit through the stomach and

during the passage through the first sections of the small intestine (the duodenum and the jejunum in particular) in order to release them directly in contact with the wall of the large intestine, precisely where their maximum concentration is required for an optimal effect.

These techniques are characterized by progressive and slow erosion of the tablet or other suitable solid form for the time necessary for the gastrointestinal

transit, ensuring optimal and uniform distribution of the active ingredients along the entire mucous membrane of the colonic section.

It has thus been possible to provide a local topical treatment, utilizing to the maximum the energizing and protective capacities of butyric acid, which can thus act directly on the specific section of the mucous membrane of the colon, in combination with those of inulin which is thus brought into contact with the bacteria which can ferment it directly and produce further quantities of short-chain fatty acid.

On the basis of the foregoing, a further subject of the present invention is therefore controlled-release, gastro-resistant, oral pharmaceutical or dietary compositions containing a mixture of short-chain fatty acid and soluble fibre, which can pass through the entire gastric section and the first intestinal section without disintegrating and can release the active ingredients directly at colonic level.

The following examples are included to illustrate the invention further without being limiting thereof.

Examples

Example 1

3.075 kg of calcium butyrate (equal to 2.5 kg of butyric acid) was mixed with 1 kg of maize starch, 2.5 kg of inulin, 50 g of stearic acid, and 50 g of soya lecithin and mixed with water to a pasty consistency. The paste was then divided into granules by passing it through a drum granulator and, after the addition of 4 kg of maltodextrin, 1.975 kg of microcrystalline cellulose, 1 kg of medium viscosity sodium carboxymethyl cellulose, 200 g of colloidal silica, and 150 mg of magnesium stearate, was subjected to compression to a unit weight of 1400 mg/tablet

(equivalent to a content per unit of 250 mg of butyric acid and 250 mg of inulin for each core).

The cores were then film-coated with an alcoholic suspension usable for depositing, per unit, on the cores, 20 mg of lac, 10 mg of talc, 6 mg of titanium dioxide, and 4 mg of triethyl citrate. The tablets thus produced were found to be capable of resisting disintegration in 0.1 N hydrochloric acid (simulating the gastric contents) for 1 hour or more and of progressively releasing the active ingredients contained, after an initial lag time, over the next 8 hours, in a buffered pH 7.4 solvent simulating the fluid that is present at intestinal level.

Example 2

3.075 kg of calcium butyrate (equal to 2.5 kg of butyric acid) was mixed with 2.5 kg of inulin, with 300g of sodium starch glycolate, 50 g of soya lecithin, and 950 g of microcrystalline cellulose, and mixed with 100 g of beeswax which had been heated to melting point, and then with water, to a pasty consistency. The paste was then divided into granules by passing it through a drum granulator and, after the addition of 4 kg of maltodextrin, 1.975 kg of dibasic calcium phosphate, 1 kg of medium-viscosity sodium carboxymethyl cellulose, 200 g of colloidal silica, and 150 mg of magnesium stearate, was subjected to compression to a unit weight equivalent to a content of 250 mg of butyric acid and 250 mg of inulin for each core.

The cores were then film-coated with an alcoholic solution of methacrylic acid and methacrylic esters, talc, triethyl citrate, and iron oxide which was able to deposit about 40 mg of coating per unit on the cores.

The tablets thus produced were found to be capable of resisting disintegration in 0.1 N hydrochloric acid (simulating the gastric contents) for 1 hour or more and of progressively releasing the active ingredients contained, after an initial lag time, over the next 8 hours, in a buffered pH 7.4 solvent simulating the fluid that is present at intestinal level.

Example 3

2.5 kg of maltodextrin was added to and dispersed in 2.5 kg of butyric acid; the suspension, optionally diluted with water to the ideal consistency, was dried by atomization or spray-drying and a powder containing about 50% of butyric acid was obtained; 50 g of soya lecithin, 80 g of beeswax, and 950 g of lactose were added to this powder and mixed to a pasty consistency with a binding solution produced by dispersing 150 g of low-viscosity sodium carboxymethyl cellulose in 5 litres of water. The paste was then divided into granules by passing it through a drum granulator and, after the addition of 1.2 kg of microcrystalline cellulose, 0.6 kg of hydroxymethyl cellulose, 150 g of colloidal silica and 100 g of magnesium stearate, was subjected to compression to a unit weight equivalent to a content of 250 mg of butyric acid and 250 mg of inulin for each core.

The cores were then film-coated with an alcoholic solution of methacrylic acid and methacrylic esters, talc, triethyl citrate and iron oxide so as to deposit about 30 mg of coating per unit on the cores.

The tablets thus produced were found to be capable of resisting disintegration in 0.1N hydrochloric acid (simulating the gastric contents) for 1 hour or more and of progressively releasing the active ingredients contained, after an initial lag time, over the next 8

hours, in a buffered pH 7.4 solvent simulating the fluid that is present at intestinal level.

Example 4

1.2 kg of pre-gelatinized starch and 2.4 kg of lactose were added to and dispersed in 2.4 kg of butyric acid; the suspension, optionally diluted with water to the ideal consistency, was dried by atomization or spray-drying and a powder containing about 40% of butyric acid was obtained; 30 g of soya lecithin, 20 g of sodium dioctylsulphosuccinate, 100 g of finely divided stearic acid, and 800 g of lactose were added to this powder and were mixed to a pasty consistency with a binding solution produced by dispersing 150 g of medium-viscosity hydroxypropylmethyl cellulose in 5 litres of water. The paste was then divided into granules by passing it through a perforated drum granulator and, after the addition of 1.2 kg of microcrystalline cellulose, a further 0.8 kg of hydroxypropylmethyl cellulose, 120 g of colloidal silica, and 100 g of magnesium stearate, was subjected to compression to a unit weight equivalent to a content of 250 mg of butyric acid and 250 mg of inulin for each core.

The cores were then film-coated with an aqueous dispersion of methacrylic acid and methacrylic esters, talc, triethyl citrate and titanium dioxide so as to deposit about 40 mg of film-forming coating per unit on the cores.

The tablets thus produced were found to be capable of resisting dissolution in 0.1N hydrochloric acid (simulating the gastric contents) for more than 1 hour and of progressively releasing the active ingredients contained, after an initial lag time, over the next 8 hours, in a buffered pH 7.4 solvent simulating the

fluid that is present at intestinal level, in accordance with the following profile:

- after 2 hours about 40% of the active ingredients
- after 4 hours about 70% of the active ingredients present,
- at 8 hours, more than 90% of the active ingredients

had been given up.

The clinical study described below was performed with the tablets thus produced.

The study was performed on 18 adult patients of both sexes, divided into three homogeneous groups each of 6 patients, who were suffering from inflammatory bowel disease (IBD) and were treated as follows:

Group 1: 250 mg butyric acid

Group 2: 250 mg inulin

Group 3: 250 mg butyric acid + 250 mg inulin

The active ingredients were transported in tablets which were indistinguishable in shape, size, weight and colour.

The treatments were administered orally daily before the main meal for a period of 4 weeks.

Before the start of the treatment (base time) and then upon completion of the 4 weeks of treatment, each patient was assessed for the presence of the symptom of diarrhoea.

This symptom was quantified, according to its intensity, on a subjective 5-point scale graduated from 0 (absence of indisposition) to 4 (indisposition of considerable gravity). The mean intensity at the base time and at the end of the period of treatment and the percentage of improvement relative to the base time were calculated for this symptom. The results obtained are given in Table 1 below:

Table 1 - Effect of daily oral treatment for 4 weeks on the symptom of IBD

Symptom	250 mg butyric acid (n = 6)	250 mg inulin (n = 6)	250 mg butyric acid + 250 mg inulin (n = 6)
<u>Diarrhoea</u>			
- base	2.7	2.9	2.8
- final	1.5	2.1	1.0
- % improvement	44	27	64

Results

The table given above shows that the administration of tablets containing the combination of butyric acid (250 mg) and inulin (250 mg) brought about a 45% improvement in the symptom compared with the administration of butyric acid (250 mg) alone. Moreover, this percentage of improvement was much greater than the improvement provided by the administration of inulin alone which, as shown in the table, was 27%, i.e. corresponding to about half of that achieved with the mixture.

It was consequently shown that the combination of butyric acid and inulin leads to a synergic effect which is clear from the improvement of at least one symptom which is characteristic of the intestinal condition IBD (inflammatory bowel disease); this improvement is greater as a percentage than that which is achieved by the administration of the individual active ingredients.

CLAIMS

1. Oral pharmaceutical or dietary composition containing at least one short-chain fatty acid or a salt thereof in combination with a complex sugar and/or soluble or water dispersible dietary fibre selected from the group consisting of inulin, pectin, dextrin, maltodextrin and derivatives thereof, and one or more pharmacologically acceptable excipients, wherein said composition further comprises (a) a lipophilic matrix consisting of a lipophilic compound with a melting point lower than 90°C and optionally an amphiphilic compound in which said short-chain fatty acid or said salt is at least partially incorporated, (b) an amphiphilic matrix, and (c) an outer hydrophilic matrix in which said lipophilic matrix and amphiphilic matrix are dispersed, and wherein said fatty acid or said salt is without a covalent bond to a carbohydrate carrier, or said complex sugar or dietary fibre.
2. Composition according to Claim 1 in which the short-chain fatty acid is a linear or branched C₁ – C₅ monocarboxylic organic acid.
3. Composition according to Claim 1 in which the short-chain fatty acid is selected from the group consisting of acetic acid, propionic acid, butyric acid, and isovaleric acid.
4. Composition according to Claim 1 in which the short-chain fatty acid is butyric acid.
5. Composition according to any one of claims 1 to 4, wherein the composition comprises 5 to 50% by weight of the short-chain fatty acid.
6. Composition according to any one of claims 1 to 5, wherein the composition comprises 10 to 30% by weight of the short-chain fatty acid.
7. Composition according to any one of claims 1 to 6, wherein the composition comprises 5 to 50% by weight of the soluble or water dispersible dietary fibre.
8. Composition according to any one of claims 1 to 7, wherein the composition comprises 10 to 30% by weight of the soluble or water dispersible dietary fibre.

9. Oral pharmaceutical or dietary composition according to any one of claims 1 to 8 in tablet, capsule, granule and/or micro-granule form.
10. Oral pharmaceutical or dietary composition according to any one of claims 1 to 9, characterized in that it is an intestinal controlled-release composition.
11. Oral pharmaceutical or dietary composition according to any one of claims 1 to 10, containing a gastro-resistant coating.
12. Use of a short-chain fatty acid or a salt thereof in combination with a complex sugar and/or soluble or water dispersible dietary fibre selected from the group consisting of inulin, pectin, dextrin, maltodextrin and derivatives thereof for the preparation of a pharmaceutical or dietary composition for the treatment of intestinal disorders, inflammatory disorders, and pathological conditions of the intestinal mucous membrane and for the preventive or limiting treatment of intestinal neoplasia, wherein said composition further comprises (a) a lipophilic matrix consisting of a lipophilic compound with a melting point lower than 90°C and optionally an amphiphilic compound in which said short-chain fatty acid or said salt is at least partially incorporated, (b) an amphiphilic matrix, and (c) an outer hydrophilic matrix in which said lipophilic matrix and amphiphilic matrix are dispersed, and wherein said fatty acid or said salt is without a covalent bond to a carbohydrate carrier, or said complex sugar or dietary fibre.
13. Use according to Claim 12 in which the short-chain fatty acid is linear or branched C₁ – C₅ monocarboxylic organic acid.
14. Use according to claim 12 or claim 13 in which the short-chain fatty acid is selected from the group consisting of acetic acid, propionic acid, butyric acid, and isovaleric acid.
15. Use according to any one of claims 12 to 14 in which the short-chain fatty acid is butyric acid.
16. Use according to any one of claims 12 to 15, wherein the composition comprises 5 to 50% in weight of the short-chain fatty acid.

17. Use according to any one of claims 12 to 16, wherein the composition comprises 10 to 30% by weight of the short-chain fatty acid.
18. Use according to any one of claims 12 to 17, wherein the composition comprises 5 to 50% by weight of the soluble or water dispersible dietary fibre.
19. Use according to any one of claims 12 to 18, wherein the composition comprises 10 to 30% by weight of the soluble or water dispersible dietary fibre.
20. Use according to any one of claims 12 to 19 in tablet, capsule, granule and/or micro-granule form.
21. Use according to any one of claims 12 to 20, characterized by intestinal controlled release.
22. Use according to any one of claims 12 to 21, including a gastro-resistant coating.
23. Composition according to any one of claims 1 to 11, wherein the composition is selected for release in the colon.
24. Use according to any one of claims 12 to 22, wherein the composition is selected for release in the colon.
25. Composition according to any one of claims 1 to 11, wherein the composition is for the treatment of inflammatory bowel disease.
26. Use according to any one of claims 12 to 22, wherein the composition is for the treatment of inflammatory bowel disease.