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The present invention relates to compositions and methods for treating obesity. More particularly, the invention relates to a composition comprising a lipase inhibitor, and konjac or glucomannan.

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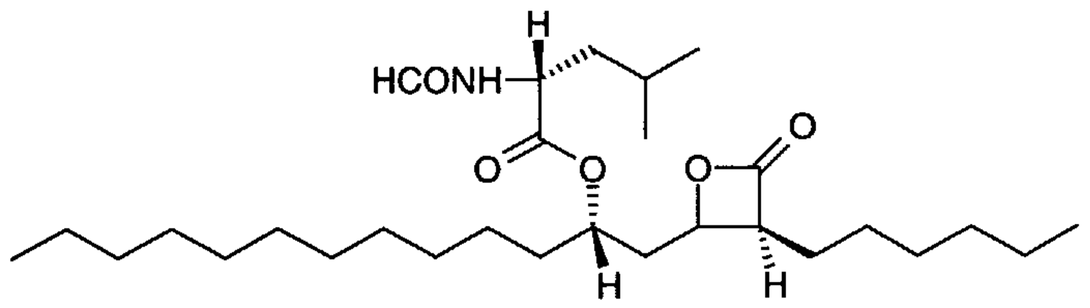
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A LIPASE INHIBITOR AND GLUCOMANNAN

(57) Abstract: The present invention relates to compositions and methods for treating obesity. More particularly, the invention relates to a composition comprising a lipase inhibitor, and konjac or glucomannan.

New Pharmaceutical Composition

The present invention relates to pharmaceutical compositions and methods for preventing and treating obesity. More particularly, the invention relates to a composition comprising a lipase inhibitor, preferably a compound of formula I (orlistat),



(I)

and glucomannan, optionally containing one or more pharmaceutically acceptable excipients.

Adverse effects which occasionally are observed in patients treated with lipase inhibitors are anal leakage of oil (oily spotting) and fecal incontinence. Oily spotting results from physical separation of some of the ingested but unabsorbed dietary fat from the bulk of the fecal mass in the colon.

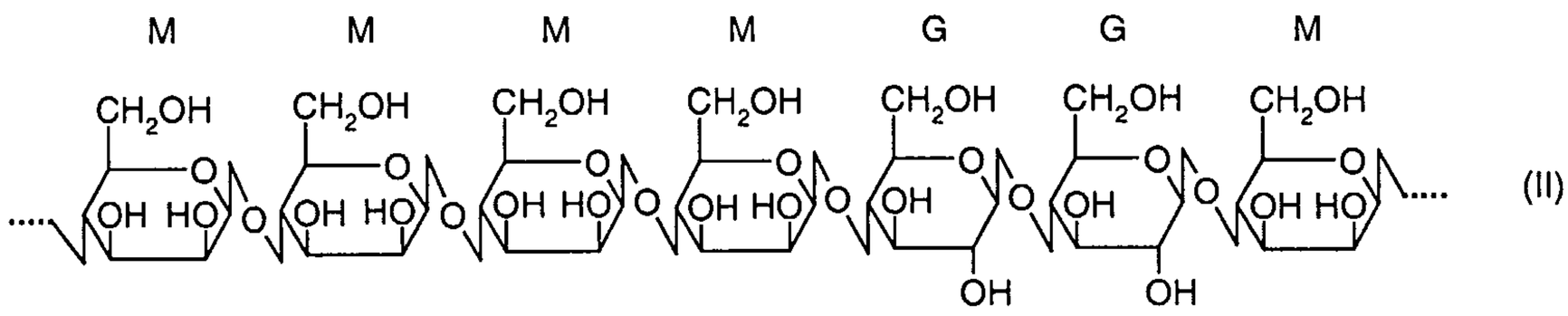
In U.S. Patent 5, 447,953 it has been shown that by combining a lipase inhibitor with substantial amounts of water insoluble crude fibers, the inhibiting effect on fat absorption can be increased. International Patent Application WO00/09123 demonstrates that by combining a lipase inhibitor such as orlistat with low amounts of chitosan or a derivative or a salt thereof, the phenomenon of anal leakage of oil can be strongly reduced.

Various approaches to control oily leakage have been discussed. Among such strategies are i) use of a surfactant to stabilize the oil/water interface in order to prevent

coalescence of the oil emulsion in the colon, ii) enhancing water viscosity in the colon to reduce both intensity and frequency of droplet-droplet interactions and by that reducing the probability of coalescence, iii) physical absorption of oil by a lipophilic compound, or iv) increasing the natural stool mass by facilitating bacterial growth in the colon. The latter approach might be achieved by either administrating prebiotic material (*e.g.*, lactobacillus) or by intake of fermentable fibers acting as substrates for bacterial growth.

Surprisingly, it has now been observed that konjac, e.g. konjac flour, and especially glucomannan are active in reducing gastro-intestinal adverse events (GI-AE) commonly observed after administration of a lipase inhibitor such as orlistat or after ingestion of artificial fat substitutes.

Konjac (*Amorphophallus konjac*) is a plant, the tuber of which is the source of a well-known foodstuff in China and Japan, namely konjac flour. This flour, comprises a highly viscous sol of glucomannan and soluble starches when reconstituted in water. The principal soluble constituent is glucomannan (formula II), a polysaccharide comprised of D-glucose and D-mannose, which is useful as an ingredient in various foodstuffs, as well as in industrial applications such as films, oil drilling fluids and paints.



M = D-Mannose, G = D-Glucose

Accordingly, the present invention refers to a composition comprising a lipase inhibitor and glucomannan.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitors of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, *J. Antibiot.*, 47(12):1369-1375 (1994)). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for

example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" also refers to 2-oxy-4H-3,1-benzoxazin-4-ones which have been described in International Patent Application WO00/40569 (Alizyme Therapeutics Ltd.), e.g. 2-decyloxy-6-methyl-4H-3,1-benzoxazin-4-one, 6-methyl-2-tetradecyloxy-4H-3,1-benzoxazin-4-one, and 2-hexadecyloxy-6-methyl-4H-3,1-benzoxazin-4-one and other oxetanones described for example in International Patent Applications WO01/32616, WO01/32669 and WO01/32670. Most preferably, the term "lipase inhibitor" refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO00/09122 and WO00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat.

Orlistat can be administered to humans in conventional oral compositions, such as tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryl sulfate, Brij* 96, or Tween* 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof; polymers like povidone and crospovidone; talc; stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating

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agents and antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively.

The term "konjac flour" refers to a hydrocolloidal polysaccharide obtained from the tubers of species of *Amorphophallus konjac*. The perennial tuber is unique to Asia and especially cultivated in Japan. Konjac flour is a high molecular weight, nonionic glucomannan consisting primarily of mannose and glucose molecules combined in a mole ratio of 1,6:1,0. It is a slightly branched polysaccharide connected by beta 1-4 linkages and has an average molecular weight ranging from 200.000 to 2.000.000 daltons. Acetyl groups along the glucomannan backbone contribute to its solubility and are located, on average, at every 9 to 19 sugar unit. Refined konjac flour is easily soluble in cold water and forms a highly viscous solution with a pH between 4,0 and 7,0. Addition of a mild alkaline solution results in the formation of a heat-stable gel that resists melting, even under extended heating conditions. The purification process for konjac flour is carried out in large-scale extraction plants. The konjac tubers are first pulverized, and then the collected glucomannan particles are polished in order to dislodge and extract noxious materials adhering to them. This process yields a refined konjac flour with high degree of purity that improves product solubility, stability and overall functionality. The particles are tasteless, odorless and white in color.

Konjac flour and glucomannan (PROPOL®, RHEOLEX®) are commercially available products (Kyoei Konnyaku, Inc., Behr, Wunderlich & Co., Provisco, FMC Biopolymers, Naturland, SiberHegner and Co. Ltd.). The preparation and use have been described e.g. in U.S. Patent Nos. 3,767,424, 3,973,007, 4,588,589, 5,486,364, 5,486,364, 5,733,593, 5,536,521, 6,126,906, etc.

The term "pharmaceutically acceptable" as used herein means that the corresponding compounds are acceptable from a toxicity viewpoint.

In more detail, the present invention relates to a pharmaceutical composition comprising a lipase inhibitor and glucomannan. Optionally this composition may contain one or more pharmaceutically acceptable excipients. The glucomannan may be provided in form of konjac. Preferably, the konjac contains at least 80 % glucomannan, more preferably at least 90 % glucomannan. The glucomannan or konjac may be provided in form of konjac powder, e.g. konjac flour. Preferably the lipase inhibitor is orlistat.

Pharmaceutical compositions incorporating both a compound of a lipase inhibitor and glucomannan are important embodiments of the present invention. Such pharmaceutical compositions comprise a therapeutically effective amount of each of the compounds. Each dosage unit can obtain the daily doses of both compounds or may contain a fraction of the daily dose, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compound. In such case the patient would daily take one of the combination dosage units, and one or more units containing only the other compound.

In a preferred embodiment of the present invention the composition comprises a) 0.1 to 20 % (w/w) lipase inhibitor, b) 10 to 75 % (w/w) konjac, and c) 0.1 to 90 % (w/w) of one or more pharmaceutically acceptable excipients. More preferably, a composition may comprise a) 0.1 to 10 % (w/w) lipase inhibitor, b) 20 to 75 % (w/w) glucomannan and c) 0.1 to 90 % (w/w) of one or more pharmaceutically acceptable excipients. Preferably, the amount of one or more pharmaceutically acceptable excipients is 5 to 50 %, more preferably 5 to 20 %. In more detail, the composition may contain a) from about 5 to about 1000 mg lipase inhibitor, e.g. orlistat, in an amount of e.g. from about 10 to about 500 mg lipase inhibitor, preferably from about 20 to about 100 mg lipase inhibitor, e.g. from about 10 to about 360 mg orlistat, more preferably from about 30 to about 120 mg orlistat, more preferably from about 40 to about 80 mg orlistat and b) from about 0.5 to about 10 g glucomannan, preferably from about 0.5 to about 8 g glucomannan, and more preferably from about 0.5 to about 6 g glucomannan.

The pharmaceutically acceptable excipients may be selected from the group consisting of fillers, surfactants, disintegrants, binders, lubricants, flowability enhancers, sweeteners, and colorants, e.g. a composition may comprise of a) about 5 to about 1000 mg lipase inhibitor; b) about 0.5 to about 10 g glucomannan; and optionally pharmaceutically acceptable excipients selected from the group of about 0.1 to about 10 g fillers, about 0.05 to about 5.0 g surfactants, about 0.05 to about 2.0 g disintegrants, about 0.02 to about 5.0 g binder, about 0.001 to about 1.0 g lubricants, about 0.1 to about 5.0 g flowability enhancers , about 0.01 to about 4.0 g sweeteners, and about 0.001 to about 0.5 g colorants.

The pharmaceutically acceptable excipients may be selected from the group consisting of fillers, e.g. sugars and/or sugar alcohols, e.g. lactose, sorbitol, mannitol, maltodextrin, etc.; surfactants, e.g. sodium lauryl sulfate, TPGS, Brij 96 or Tween 80; disintegrants, e.g. sodium starch glycolate, maize starch or derivatives thereof; binder, e.g. povidone, crosspovidone, polyvinylalcohols, hydroxypropylmethylcellulose; lubricants,

e.g. stearic acid or its salts; flowability enhancers, e.g. silicium dioxide; sweeteners, e.g. aspartame; and/or colorants, e.g. β-carotene.

In a preferred embodiment of the present invention the composition comprises a) about 0.1 to about 20 % (w/w) lipase inhibitor; b) 10 to about 75 % (w/w) glucomannan; and optionally pharmaceutically acceptable excipients selected from the group of about 0.1 to about 20 % (w/w) fillers, about 0.1 to about 10 % (w/w) surfactants, about 0.1 to about 10 % (w/w) disintegrants, about 0.1 to about 10 % (w/w) binder, about 0.1 to about 10 % (w/w) lubricants, about 0.1 to about 10 % (w/w) flowability enhancers, about 0.1 to about 10 % (w/w) sweeteners, and about 0.1 to about 5 % (w/w) colorants.

In more detail, the composition may contain a) from about 5 to about 1000 mg lipase inhibitor, e.g. orlistat, in an amount of e.g. from about 10 to about 500 mg lipase inhibitor, preferably from about 20 to about 100 mg lipase inhibitor, e.g. form about 10 to about 360 mg orlistat, more preferably from about 30 to about 120 mg orlistat, more preferably from about 40 to about 80 mg orlistat and b) from about 0.5 to about 10 g glucomannan, preferably from about 0.5 to about 8 g glucomannan, and more preferably from about 0.5 to about 6 g glucomannan.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, bars, sachets, granules, syrups and aqueous or oily suspensions. The pharmaceutically acceptable excipients (diluents and carriers) are known in the pharmacist's art. Tablets may be formed from a mixture of the active compounds with fillers, for example calcium phosphate; disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tabletting the mixture by known methods. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. For example, the tablets and capsules may conveniently each contain the amounts of lipase inhibitor and glucomannan as described above.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compounds in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing the active compounds in a suitable vegetable oil, for example arachis oil, olive

oil or myritol 318. The active compounds may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (e.g. water) before ingestion. The granules may contain disintegrants, e.g. an effervescent pair formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

In the compositions of the present invention the active compounds may, if desired, be associated with other compatible pharmacologically active ingredients. Optionally vitamin supplements may be administered with the compounds of the present invention.

Both compounds, the lipase inhibitor and glucomannan may be administered simultaneously, separately or sequentially (e.g. orlistat as described above and glucomannan in the evening). Preferably, the compounds or compositions are administered during a meal or 1 – 2 hours before or after a meal. The amount of glucomannan to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and lies within the discretion of the administering physician.

The invention also relates to the compositions as described above for use in the treatment and prevention of obesity and to a process for preparing a composition as described above, comprising mixing a lipase inhibitor with glucomannan and optionally one or more pharmaceutically acceptable excipients.

The invention also refers to a kit for treatment of obesity, said kit comprising a) a first component which is a lipase inhibitor and b) a second component which is glucomannan as defined above, e.g. in an oral unit dosage form, preferably comprising a) from 1 to 100 doses units of orlistat and b) from 1 to 100 doses units of a glucomannan.

Another embodiment of the present invention refers to a kit for treatment of obesity, said kit comprising a) a first component which is a lipase inhibitor and b) a second component which is glucomannan in oral unit dosage forms.

The present invention also relates to the use of a composition as defined above in the manufacture of medicaments useful for the treatment and prevention of obesity and to the use of a lipase inhibitor as defined above in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with glucomannan as defined above. This use of glucomannan and lipase inhibitor refers to the simultaneous, separate or sequential use for the treatment and prevention of obesity. Further the invention refers to a method of treatment of obesity in a human in need of

such treatment which comprises administration to the human of a therapeutically effective amount of a lipase inhibitor and a therapeutically effective amount of glucomannan as defined above. The method refers to the simultaneous, separate or sequential administration of the compounds. A further embodiment of the present invention is a lipase inhibitor and glucomannan or konjac as defined above as a combined preparation for simultaneous, separate or sequential use for the treatment and prevention of obesity. The invention also refers to the use of glucomannan or konjac as defined above in the manufacture of medicaments useful for the treatment and prevention of gastro-intestinal side effects selected from the group of oily spotting, fatty/oily stools, fecal urgency, increased defecation and fecal incontinence and to a method of treatment or prevention of gastro-intestinal side effects selected from the group of oily spotting, fatty/oily stools, fecal urgency, increased defecation and fecal incontinence in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of konjac or glucomannan as defined above. Further the invention refers to a lipase inhibitor and glucomannan or konjac as defined above for simultaneous, separate or sequential use for the treatment and prevention of obesity.

The invention will be better understood by reference to the following examples which illustrate but do not limit the invention described herein.

FIGURES

Figure 1 displays test emulsions of konjac after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. After a centrifugation time of $t = 300$ min, only for emulsions containing konjac in concentrations higher than 1.5% (w/w) a weak emulsification stabilization is observed.

Figure 2 shows test emulsions of konjac after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsions contained 1.0% (w/w) konjac at different pH values. After a centrifugation time of $t = 300$ min minor emulsion stabilization was observed at pH 6 and 7, respectively. For all other emulsions extensive coalescence was observed.

Figure 3: The free oil reducing effect of different types of glucomannan in % relative to controls (data as means ± SE).

EXAMPLES

Example 1: In vitro studies

Surprisingly, it has now been observed that glucomannan is active in reducing gastro-intestinal adverse events (GI-AE) commonly observed after administration of a lipase inhibitor such as orlistat.

The interaction of konjac (source of glucomannan) with oil and water was examined by an absorption test. Samples of the compound were brought into contact with either soya oil or simulated intestinal fluid (SIF, phosphate buffer without pancreatin) and incubated for 24 h at 37°C. Remaining liquid was separated from the solid material by means of centrifugation (3 x 5 min at 3100 g). Whereas in SIF significant swelling of the polymer was observed, no swelling occurred in soya oil. The SIF and soya oil absorption capacity of konjac was calculated to 4.8 g/g and 0.5 g/g, respectively. The low amount of oil binding demonstrates its poor lipophilicity.

The coalescence behavior of emulsions stabilized with konjac was probed using a centrifugal method. With this *in vitro* method, both concentration and pH-depended emulsion stabilities were examined. The results of these stability studies are listed in Tables 1 and 2. The use of konjac in less than 0.5 % (w/w) revealed very unstable emulsions resulting in rapid oil/water phase separation (Table 1). Even at konjac concentrations of 1.0 % (w/w), emulsions remained rather unstable and clear phase separation was obtained after 10 min centrifugation. Only emulsions containing more than 1.0 % (w/w) konjac exhibited after centrifugation times of up to $t = 300$ min medium stability with the emulsion partly broken (Figure 1).

Table 1. Stability of konjac test emulsions at various concentrations *c* and centrifugation times *t*.

	Emulsion Stability Konjac								
c (% w/w)	*t / min*								
	1	10	40	70	100	130	160	220	300
0.01	l *	l	l	l	l	l	l	l	l
0.1	l	l	l	l	l	l	l	l	l
0.5	l	l	l	l	l	l	l	l	l
1.0	m	m	l	l	l	l	l	l	l
1.5	h	m	m	m	m	m	m	m	m
2.0	h	m	m	m	m	m	m	m	m

*l = low stability: oil and water form two distinct clearly separated phases; m = medium stability: emulsion partly broken; h = high stability: no indications of coalescence, optically non-transparent, stable emulsion

Figure 1 displays test emulsions of konjac after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. After centrifugation times of $t = 300$ min, only for emulsions containing konjac in concentrations higher than 1.5% (w/w) a weak emulsification stabilization is observed.

In order to investigate emulsion stability at different pH values, test emulsions with a constant konjac concentration of $c = 1.0$ % (w/w) covering a pH range of 4 to 9 were prepared (Table 2). At both extreme pH values of 4 and 9 very poor emulsification of the test emulsions was observed, resulting in instantaneous layering of the oil phase. Whereas at pH = 8 short centrifugation times of less than 30 min also led to complete emulsion breaking, emulsions at pH = 5 revealed slightly higher stability. Here, coalescence occurred at centrifugation times higher than 60 min. The pH optimum in terms of emulsion stability was observed at slightly acidic to neutral pH values (pH 6-7).

Table 2. Stability of konjac test emulsions at various pH values and centrifugation times *t*.

pH	Emulsion Stability Konjac *t / min*				
	1	30	60	120	300
4	l *	l	l	l	l
5	m	m	m	l	l
6	m	m	m	m	m
7	m	m	m	m	m
8	m	l	l	l	l
9	l	l	l	l	l

*l = low stability: oil and water form two distinct clearly separated phases; m = medium stability: emulsion partly broken; h = high stability: no indications of coalescence, optically non-transparent, stable emulsion

Figure 2 shows test emulsions of konjac after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsions contained 1.0% (w/w) konjac at different pH values. After centrifugation for $t = 300$ min minor emulsions stabilization was observed at pH 6 and 7, respectively. For all other emulsions extensive coalescence was observed.

Solutions of konjac with concentrations of 0.01%, 0.1%, 0.5%, 1.0%, 1.5%, and 2.0% (w/w) in a simulated intestinal fluid (SIF) without pancreatin according to USP XXII, p. 1789 (pH = 7.5, potassium dihydrogenphosphate buffer) were prepared. To 18 g of such a solution 2 g of soya oil (FLUKA, 85471) was added yielding a final oil concentration with respect to the aqueous phase of 10% w/w. Soya oil was not purified and used as received. Emulsions were then prepared using a Miccra homogenization apparatus at 28.000 rpm

(level E) and a homogenization time of 1 min. As a reference, mixtures of soya oil and phosphate buffer were used without addition of surfactant. Dying of the emulsion with nile red and subsequent analysis under an optical microscope revealed that the emulsions were of the oil-in-water type. Median droplet size analysis immediately after preparation using a Galai CIS-1 apparatus yielded values of typically 20-30 µm. Glass capillaries of height ca. 95 mm and a diameter of ca. 1.7 mm (glass thickness ca. 0.8 mm) were filled up to ca. 6.5 cm with the pre-prepared emulsions by means of a syringe and centrifuged at a maximum speed of 5000 rpm (Eppendorf, Centrifuge 5403, Rotor No 16A4-44) which corresponds to a centrifugal force of 3100 g (bottom of glass capillary). In order to record the demulsification process, the centrifugation process was interrupted at defined time intervals (t = 1, 10, 40, 70, 100, 130, 160, 220, 300 min) and the capillaries placed on an optical scanner operating in transmission mode (Bio-Rad GS-700 Imaging Densitometer). The distance between the capillaries was kept constant by means of a house-made sample holder. All measurements were conducted at room temperature.

Example 2: In vivo studies I

To test substances that will ameliorate the oil-related side effects associated with orlistat treatment, an acute human model was developed.

Healthy volunteers received orlistat alone or in combination with the test substance during 3 consecutive meals (3-meal test). The modified orlistat formulations used in these 3-meal tests induce 70-80% fat excretion. A questionnaire was given to the volunteers to record side effects. The most severe oil related side effect is oily spotting (uncontrolled loss of oil). This side effect is difficult to quantify accurately in an acute model, however, in some volunteers a spontaneous separation of fat from formed stool was observed. This amount of fat, called free oil (mainly containing triglycerides) was isolated and weighted.

The amount of free oil was used as a surrogate marker for the oily spotting as this is considered necessary for the appearance of oily spotting.

Two clinical studies have been conducted to investigate the gastro-intestinal adverse event modifying effects of numerous substances. It appears that volunteers show an individual sensitivity to the orlistat-related gastro-intestinal side effects. Therefore, each volunteer was used as his own control (treatment with orlistat alone). Volunteers showing a weak sensitivity to orlistat related side effects were excluded from the test evaluation. For

a given volunteer a substance is considered as positive when the free oil quantity is reduced by at least 50% compared to the control value (orlistat alone).

Glucomannan was tested as konjac powder. The konjac powder is obtained from the root of a tree (*Amorphophallus konjac)* and this the natural source of glucomannan. This substance was tested in the acute side effect model at the dosage of 4g / meal. Among the 5 tested volunteers 4 had a decrease by at least 50% of the free oil generated without glucomannan (see table 3). Volunteers treated with glucomannan / orlistat had no fat excretion decrease (compared to volunteers treated with orlistat alone, data not shown) suggesting no interaction of glucomannan with orlistat. No major AEs associated with the glucomannan treatment has been reported.

Table 3: Konjac (Glucomannan) results

Glucomannan (Konjac; 4g/meal)	Free oil production (g/ week)	
	orlistat	orlistat + Konjac
Test 1	11 9	8 0
Test 2	39 17 40	16 8 6
Positive / total *(50%<control)*	4 / 5	

Example 3: In vivo studies II

The results from the *in vitro* experiments were further supported by studies carried out with an *in vivo* mouse model. The experiment is based on the observation that mice under a high fat diet with orlistat or other lipase inhibitor treatment distribute the excreted free oil over their furs while grooming. Several types and formulations of glucomannan were examined for their ability to reduce or eliminate the production of free oil. The results obtained are shown in Figure 3.

Example 4: Orlistat Pharmaceutical Compositions

A)

Ingredient	Quantity mg / Capsule
orlistat	120.00
microcrystalline cellulose (AVICEL PH-101)	93.60
sodium starch glycolate (PRIMOJEL)	7.20
sodium lauryl sulfate	7.20
polyvinylpyrrolidone (Povidone K-30)	12.00
talc	0.24
Total	**240.24 mg**

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified v
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

B)

Ingredient	Quantity mg / Capsule
orlistat	60
microcrystalline cellulose	46.8
sodium starch glycolate	3.6
sodium lauryl sulfate	3.6
polyvinylpyrrolidone	6.0
talc	0.12
Total	120.12 mg

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

C)

Ingredient	Quantity mg / Capsule	
orlistat	60	120
lactose	40	80
microcrystalline cellulose	60	120
sodium lauryl sulfate	5.7	11.4
sodium starch glycolate	20	40
polyvinylpyrrolidone	10	20
talc	0.2	0.4
Total	195.9 mg	391.8 mg

Procedure:

1. Blend orlistat, lactose, microcrystalline cellulose and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

Example 5: Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Chewable tablet
glucomannan	1.5 g
sorbitol	1.1 g
lactose anhydrous	0.376 g
talc	0.16 g
sodium stearyl fumarate	0.064 g
Total	3.2 g

Procedure:

1. Blend glucomannan, sorbitol and lactose in a suitable mixer.
2. Pass the powder mixture through a sieve.
3. Add talc and sodium stearyl fumarate and mix.
4. Directly compress the powder mixture to a chewable tablet.

Example 6: Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Sachet
glucomannan	4 g
aspartame	0.5 g
beta-carotene	0.001 g
Total	4.501 g

Procedure:

1. Fill glucomannan in a suitable high shear mixer.
2. Granulate with a solution / colloidal suspension of Aspartame and beta-carotene in purified water.
3. Dry the granules at 60°C.

4. Pass the dry granulation through a sieve.
5. Fill into sachets.

Example 7: Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Chewable tablet
glucomannan	0.5 g
lactose	0.5 g
microcrystalline cellulose	1.31 g
sodium lauryl sulfate	0.09 g
sodium starch glycolate	0.3 g
polivinylpyrrolidone	0.15 g
talc	0.15 g
Total	3.0 g

Procedure:

1. Blend glucomannan, lactose, microcrystalline cellulose, sodium starch glycolate in a suitable mixer.
2. Dissolve sodium lauryl sulfate and polivinyl pyrrolidone in purified water.
3. Granulate with the liquid.
5. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form round pellets.
6. Dry the pellets at 65°C.
7. Add talc and mix
8. Compress the pellets to a chewable tablet.

Example 8: Orlistat/Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Chewable tablet
orlistat	0.06 g
glucomannan	0.75 g
lactose	0.5 g
microcrystalline cellulose	1.31 g
sodium lauryl sulfate	0.09 g
sodium starch glycolate	0.3 g
polivinylpyrrolidone	0.15 g
talc	0.15 g
Total	3.31 g

Procedure:

1. Blend orlistat, glucomannan, lactose, microcrystalline cellulose, sodium starch glycolate in a suitable mixer.
2. Dissolve sodium lauryl sulfate and polivinyl pyrrolidone in purified water.
3. Granulate with the liquid.
5. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form round pellets.
6. Dry the pellets at maximum 35°C.
9. Add talc and mix
10. Compress the pellets to a chewable tablet.

Example 9: Orlistat/Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Sachet
orlistat	0.12 g
glucomannan	4 g
saccharose	2.8 g
beta-carotene	0.001 g
silicium dioxide	0.5 g
Total	7.421 g

Procedure:

1. Blend orlistat, glucomannan, sachharose in a suitable mixer.
2. Mix in several portion with the mixture of beta-carotene and silicium dioxide.
3. Fill into sachets.

Example 10: Orlistat/Glucomannan Pharmaceutical Compositions

Composition:

Ingredient	Quantity g / Chewable tablet
orlistat	0.12 g
glucomannan	2.0 g
sodium starch glycolate	0.1 g
microcrystalline cellulose	0.2 g
sodium lauryl sulfate	0.03 g
crospovidone	0.1 g
aspartame	0.15 g
talc	0.15 g
magnesium stearate	0.03 g
Total	2.85 g

Procedure:

1. Blend orlistat, glucomannan, microcrystalline cellulose, sodium starch glycolate and crospovidone in a suitable mixer.
2. Granulate with a solution / colloidal suspension of sodium lauryl sulfate and aspartame in purified water.
3. Pass the granulate through a sieve.
4. Dry the granules at 30°C.
5. Pass the dry granules through a sieve.
6. Mix with talc and magnesium stearate.
7. Compress to chewable tablet.

CLAIMS

1. A pharmaceutical composition comprising a lipase inhibitor and glucomannan.

2. The pharmaceutical composition of claim 1, wherein the glucomannan is provided as konjac.

3. The pharmaceutical composition of claim 2, wherein the konjac contains at least 80% glucomannan.

4. The pharmaceutical composition of claim 3, wherein the konjac contains at least 90% glucomannan.

5. The pharmaceutical composition according to any one of claims 2 to 4, wherein the konjac is konjac flour.

6. The composition according to any one of claims 1 to 5, comprising a) about 5 to about 1000 mg lipase inhibitor and b) about 0.5 to about 10 g glucomannan.

7. The composition according to claim 6, comprising about 0.5 to about 8 g glucomannan.

8. The composition according to claim 7, comprising about 0.5 to about 6 g glucomannan.

9. The composition of any one of claims 1 to 8 further comprising one or more pharmaceutically acceptable excipients.

10. The composition according to any one of claims 2 to 5, wherein the composition comprises

a) 0.1 to 20% (w/w) lipase inhibitor,

b) 10 to 75% (w/w) konjac, and

c) 0.1 to 89.9% (w/w) of one or more pharmaceutically acceptable excipients.

11. The composition according to any one of claims 1 to 5, comprising

a) 0.1 to 10% (w/w) lipase inhibitor,

b) 20 to 75% (w/w) glucomannan, and

c) 0.1 to 79.9% (w/w) of one or more pharmaceutically acceptable excipients.

12. The composition according to any one of claims 9 to 11, wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of fillers, surfactants, disintegrants, binders, lubricants, flowability enhancers, sweeteners, and colorants.

13. The composition according to any one of claims 1 to 5, comprising

a) about 5 to about 1000 mg lipase inhibitor;

b) about 0.5 to about 10 g glucomannan; and

optionally pharmaceutically acceptable excipients selected from the group consisting of about 0.1 to about 10 g fillers, about 0.05 to about 5.0 g surfactants, about 0.05 to about 2.0 g disintegrants, about 0.02 to about 5.0 g binder, about 0.001 to about 1.0 g lubricants, about 0.1 to about 5.0 g flowability enhancers, about 0.01 to about 4.0 g sweeteners, and about 0.001 to about 0.5 g colorants.

14. The composition according to any one of claims 1 to 5, comprising

a) about 0.1 to about 20% (w/w) lipase inhibitor;

b) 10 to about 75% (w/w) glucomannan; and

optionally pharmaceutically acceptable excipients selected from the group consisting of about 0.1 to about 20% (w/w) fillers, about 0.1 to about 10% (w/w) surfactants, about 0.1 to about 10% (w/w) disintegrants, about 0.1 to about 10% (w/w) binder, about 0.1 to about 10% (w/w) lubricants, about 0.1 to about 10% (w/w) flowability enhancers, about 0.1 to about 10% (w/w) sweeteners, and about 0.1 to about 5% (w/w) colorants.

15. The composition according to any one of claims 1 to 14, comprising about 10 to about 500 mg lipase inhibitor.

16. The composition according any of claims 1 to 15, comprising about 20 to about 100 mg lipase inhibitor.

17. The composition according to any one of claims 1 to 14, wherein the lipase inhibitor is orlistat.

18. The composition according to claim 17, comprising about 10 to about 360 mg orlistat.

19. The composition according to claim 18, comprising about 30 to about 120 mg orlistat.

20. The composition according to claim 19, comprising about 40 to about 80 mg orlistat.

21. The composition according to claim 13, comprising about 0.5 to about 8 g glucomannan.

22. The composition according to claim 21, comprising about 0.5 to about 6 g glucomannan.

23. The composition of any one of claims 1 to 22 for use in the treatment or prevention of obesity.

24. A process for preparing the composition defined in any one of claims 1 to 8, comprising mixing the lipase inhibitor with glucomannan and optionally one or more pharmaceutically acceptable excipients.

25. A kit for the treatment of obesity, said kit comprising

a) a first component which is lipase inhibitor,

b) a second component which is glucomannan in oral unit dosage forms, and

c) instructions for using the first component and the second component in the treatment of obesity.

26. A use of the composition defined in any one of claims 1 to 22 in the manufacture of a medicament for the treatment or prevention of obesity.

27. A use of a lipase inhibitor in the manufacture of a medicament for the treatment or prevention of obesity in a patient who is also receiving treatment with glucomannan.

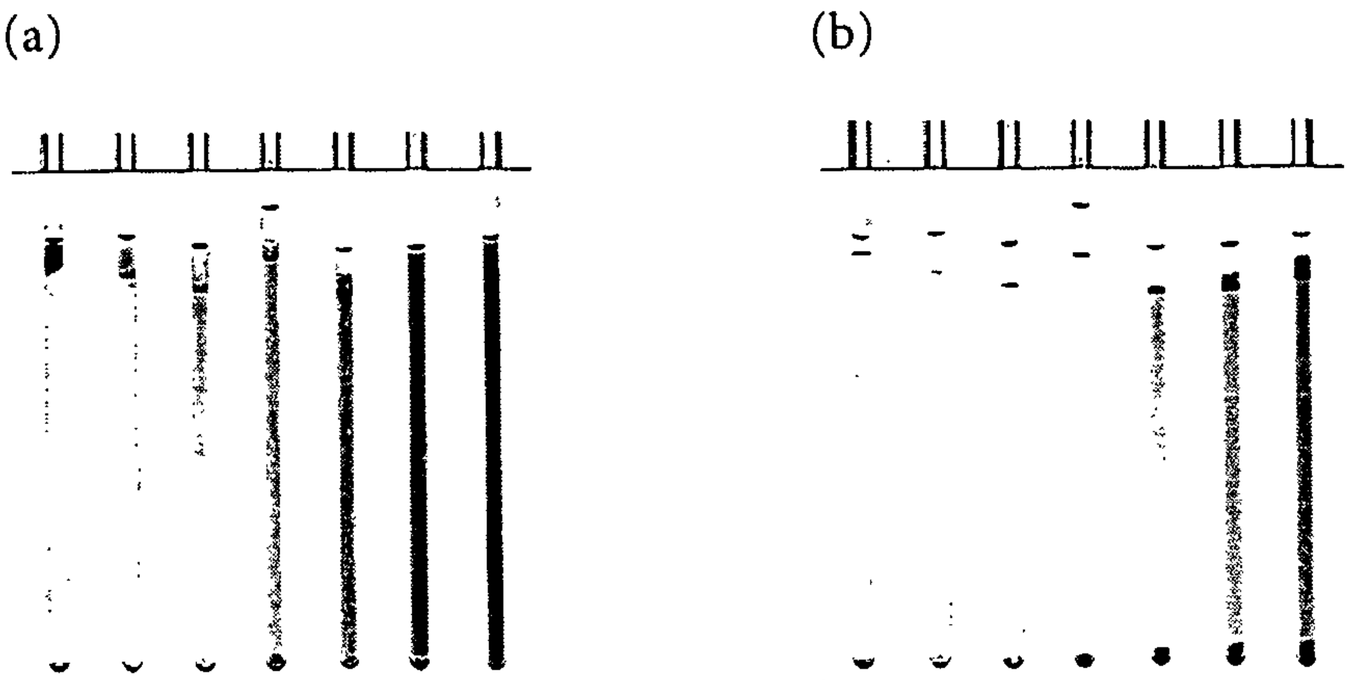
28. A use of a therapeutically effective amount of a lipase inhibitor and a therapeutically effective amount of glucomannan for the treatment or prevention of obesity in a human in need of such treatment.

29. The use according to claim 28, wherein the lipase inhibitor and the glucomannan are for simultaneous or sequential administration.

30. A use of glucomannan or konjac in the manufacture of a medicament for the treatment or prevention of a gastro-intestinal side effect caused by use of a lipase inhibitor, the gastro instestinal side effect selected from the group consisting of oily spotting, fatty/oily stools, fecal urgency, increased defecation and fecal incontinence.

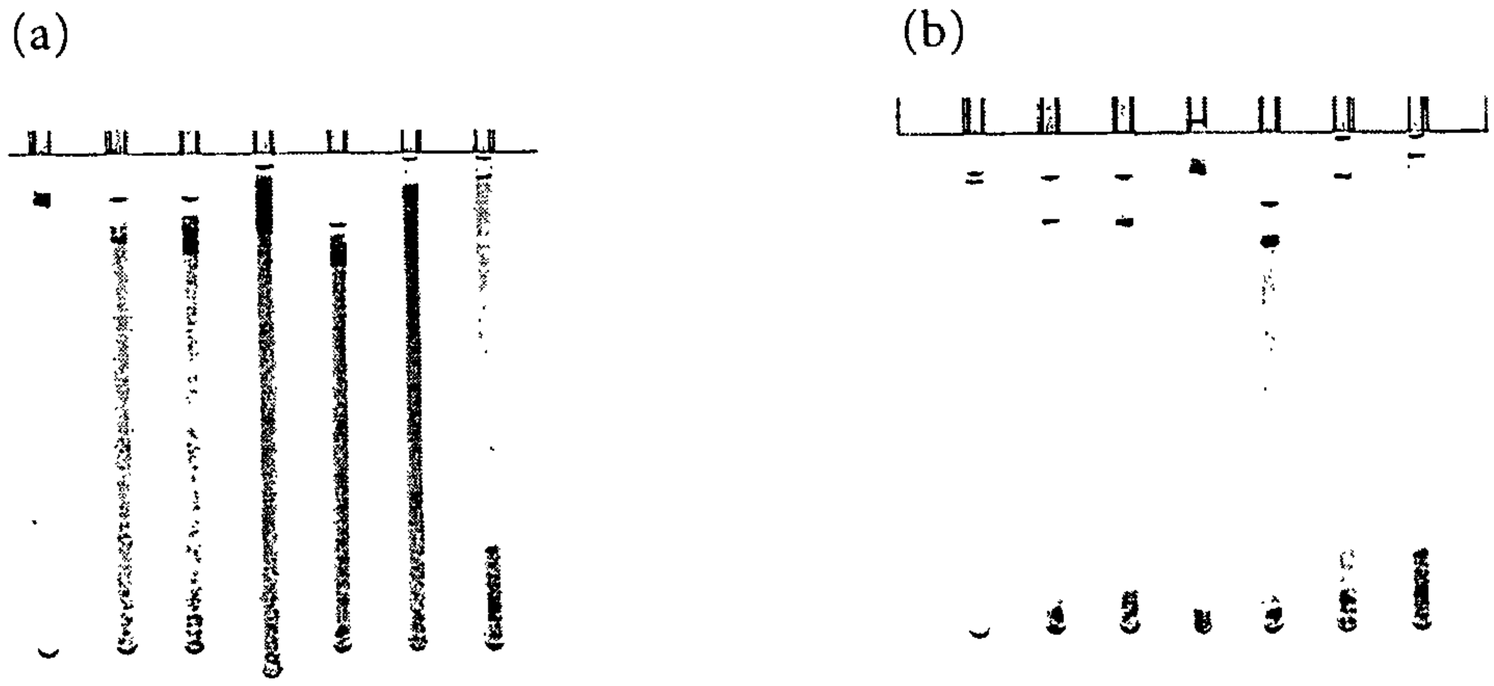
31. A use of a therapeutically effective amount of konjac or glucomannan for the treatment or prevention of a gastro-intestinal side effect caused by use of a lipase inhibitor, the gastro-intestinal side effect selected from the group consisting of oily spotting, fatty/oily stools, fecal urgency, increased defecation and fecal incontinence.

FIG. 1



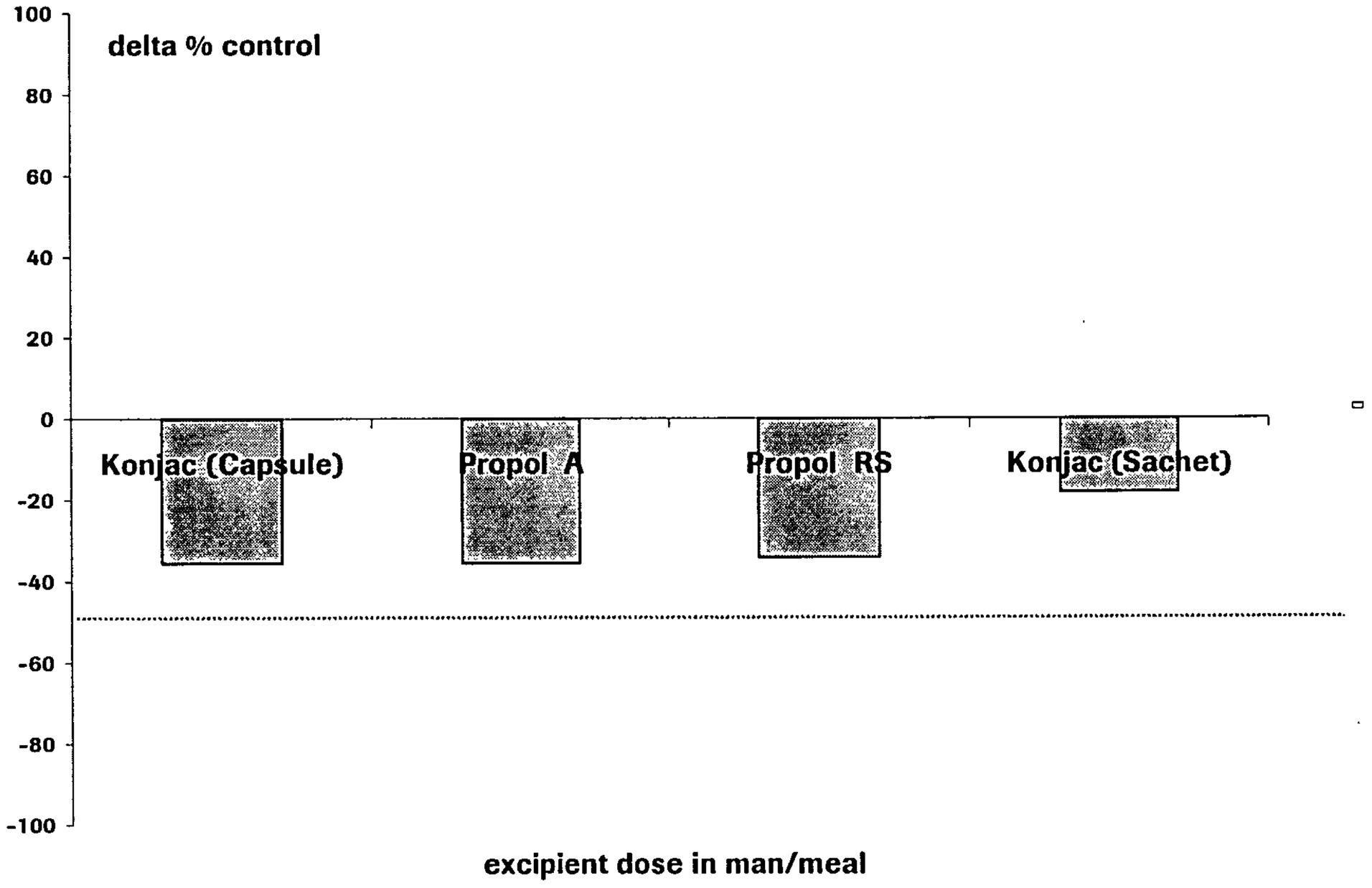
Both $t = 1$ min (a) and $t = 300$ min (b) from left to right: reference (mixture soya oil/buffer); $c = 0.01\%$, $c = 0.1\%$; $c = 0.5\%$; $c = 1.0\%$; $c = 1.5\%$; $c = 2.0\%$ (w/w).

FIG. 2



Both $t = 1$ min (a) and $t = 300$ min (b) from left to right: reference (mixture soya oil/buffer) at pH = 7; pH = 4; pH = 5; pH = 6; pH = 7; pH = 8; pH = 9.

FIG. 3


Comparison of the oil reducing effect of different glucomannan types in % relation to controls in a mouse model
delta % control
100
80
60
40
20
0
-20
-40
-60
-80
-100
Konjac (Capsule)
Propol A
Propol RS
Konjac (Sachet)
excipient dose in man/meal