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(54) Titre : COMPOSITION PHARMACEUTIQUE COMPRENANT UN INHIBITEUR DE LIPASE ET UN ESTER D'ACIDE GRAS DE SACCHAROSE
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A LIPASE INHIBITOR AND A SUCROSE FATTY ACID ESTER

(57) **Abrégé/Abstract:**

The present invention relates to a pharmaceutical composition comprising a lipase inhibitor, preferably orlistat, having a melting point $\geq 37^{\circ}\text{C}$, a sucrose fatty acid ester wherein the sucrose fatty acid ester is a mono-, di-, tri- or tetra-ester, and optionally one or more pharmaceutically acceptable excipients.



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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A LIPASE INHIBITOR AND A SUCROSE FATTY ACID
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(57) Abstract: The present invention relates to a pharmaceutical composition comprising a lipase inhibitor, preferably orlistat, hav-
ing a melting point $\geq 37^{\circ}\text{C}$, a sucrose fatty acid ester wherein the sucrose fatty acid ester is a mono-, di-, tri- or tetra-ester, and
optionally one or more pharmaceutically acceptable excipients.



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PHARMACEUTICAL COMPOSITION COMPRISING A LIPASE INHIBITOR AND A SUCROSE FATTY
ACID ESTER

5 The present invention relates to a pharmaceutical composition comprising a lipase inhibitor, preferably orlistat, having a melting point $\geq 37^{\circ}\text{C}$, a sucrose fatty acid ester wherein the sucrose fatty acid ester is a mono-, di-, tri- or tetra-ester, and optionally one or more pharmaceutically acceptable excipients.

10 Examples of such lipase inhibitors are lipstatin and orlistat. The latter is also known as tetrahydrolipstatin or THL and is derived from a natural product excreted by *Streptomyces toxytricini*. This class of compounds was found to exhibit in vitro as well as in vivo activity against various lipases, such as lingual lipase, pancreatic lipase, gastric lipase, and carboxylester lipase. Its use for the control or prevention of obesity and hyperlipidemia is described, for instance, in US Patent 4,598,089.

15 Orlistat is currently administered at doses of 120 mg per meal and dosing is independent of the body mass of the human subject. Orlistat acts locally in the gastrointestinal (GI) tract and prevents lipase from digesting triglycerides and thus inhibits the formation of absorbable lipid degradation products. For this reason, systemic availability of the lipase inhibitors is not required and, instead, local residence in the
20 gastrointestinal tract is preferred.

Lipase inhibitor compositions currently administered inhibit around 30% of fat absorption after consumption of a mixed meal; increasing the concentrations of lipase inhibitors in the pharmaceutical composition does not increase its clinical efficacy and/or potency while the intensity of local side effects increases.

Anal leakage of oil (oily spotting) is an adverse effect, which is occasionally observed by patients treated with lipase inhibitors. This phenomenon reflects physical separation of some liquid unabsorbed dietary fat from the bulk of solids in the lower large intestine.

In US Patent No. 5,447,953 it was shown that by combining a lipase inhibitor with substantial amounts of water insoluble crude fibers, the inhibiting effect on fat absorption can be increased. In patent application WO00/09123 it has been demonstrated 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 reduced.

International Patent Application WO01/19378 discloses solid lipid formulations for lipase inhibitors useful to reduce or prevent fat excretion and unwanted formation of free oil. It has been found that a higher efficacy (high fat excretion) can be combined with a lowering of unwanted side effects, e.g. free oil. Recently it has been recognized that the efficacy of lipase inhibitors may depend strongly on the kind of the ingested food. A high efficacy have been found with meals composed of French fries, sausages and hamburgers, while lower efficacy was observed for cheese and other dairy products. Strong food dependency of the formulation efficacy is an unwanted phenomena, because either the formulation is overdosed in susceptible diets (with the consequence of free oil formation) or not active in less susceptible diets. Therefore, the decrease of the food dependency is a prerequisite to realize scenarios with a low dosage of the inhibitor, a high efficacy and less fewer side effects.

Surprisingly it has been found that a certain sucrose fatty acid ester subgroup can increase the activities of lipase inhibitors, decrease the food dependency and decreasing the formation of free oil.

FIGURES:

Fig. 1 indicates that the sucrose ester based formulations show an approximate 1.7 times higher efficacy 240 mg SUCROSEESTER P1670: 67.4 (± 5.3 %, n=5), 30 mg SUCROSEESTER P1670 66.6 (± 13 %, n=4) compared to Xenical 39.7 (± 8.1 %, n=5) in a double meal test on human volunteers.

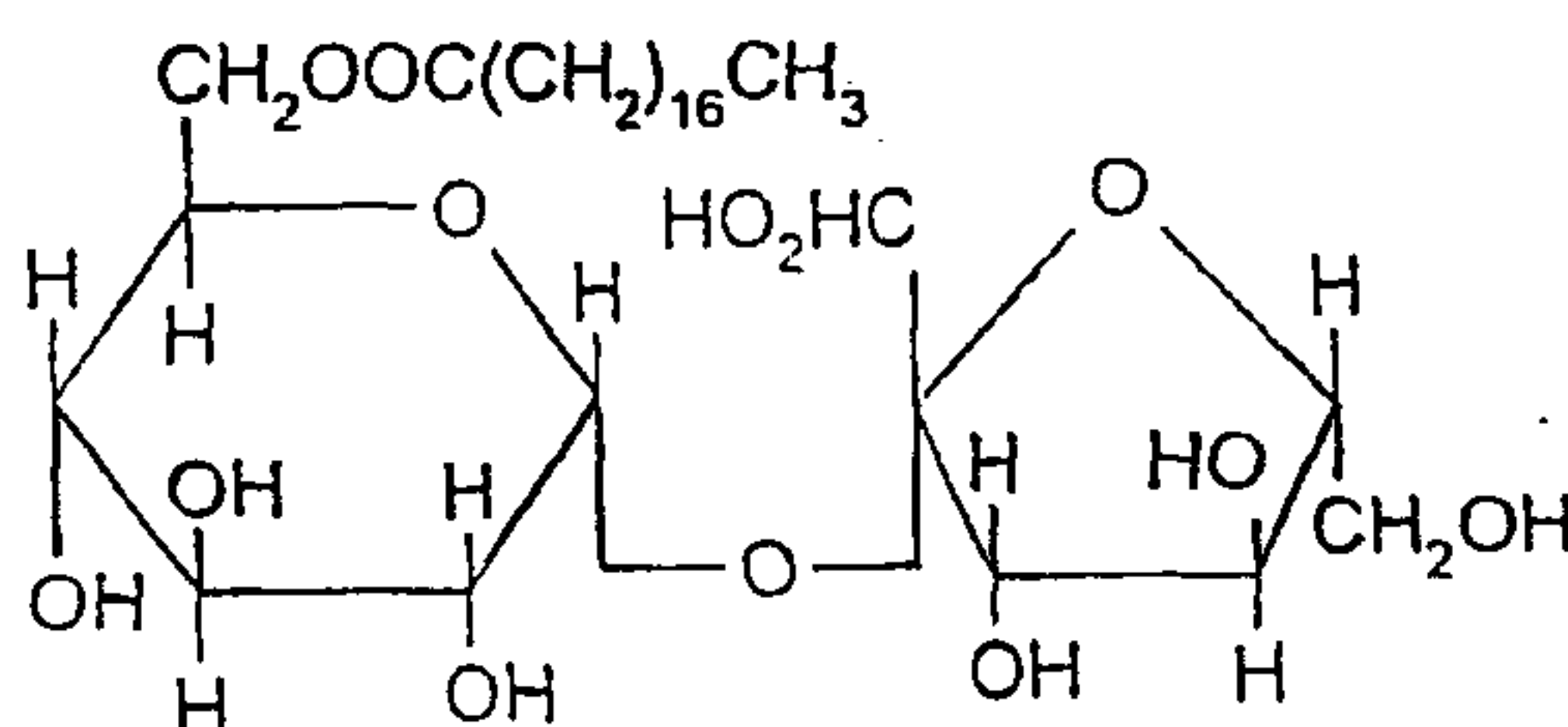
Fig. 2 indicates that the efficacy of XenicalTM in the less accessible meal was only 48.4 % compared to the accessible, while the sucrose ester formulation 30 MG SUCROSEESTER P1670 reached 73.9 % (double meal test in human volunteers).

Fig. 3 displays test emulsions of Surfhope™ SE Pharma D-1811 after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsion containing 2.0% (w/w) sucrose ester remains even after a centrifugation time of $t = 300$ min stable (picture (b), right capillary). From left to right: reference (mixture soya oil/buffer); $c = 0.01\%$, $c =$
 5 0.1% ; $c = 0.5\%$; $c = 1.0\%$; $c = 1.5\%$; $c = 2.0\%$ (w/w).

Fig. 4 shows test emulsions of Surfhope™ SE Pharma D-1811 after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsions are stabilized with 1.0% (w/w) sucrose ester at different pH values. Whereas emulsions at $\text{pH} \leq 7$ clearly show phase separation after centrifugation for $t = 300$ min, emulsions at $\text{pH} > 7$ noticeably
 10 revealed less free oil.

The present invention relates to a pharmaceutical composition comprising a lipase inhibitor, preferably orlistat, having a melting point $\geq 37^\circ\text{C}$, a sucrose fatty acid ester wherein the sucrose fatty acid ester is a mono-, di-, tri- or tetra-ester, and optionally one
 15 or more pharmaceutically acceptable excipients.

Sucrose fatty acid esters are nonionic surfactants consisting of sucrose as hydrophilic moiety and one or more fatty acid moieties as lipophilic group(s). They are manufactured from purified sugar and vegetable oils. As sucrose has a total of 8 hydroxyl groups, compounds ranging from sucrose mono to octa fatty acid esters can be produced. The
 20 following formula shows as an example the chemical structure of sucrose monostearate:



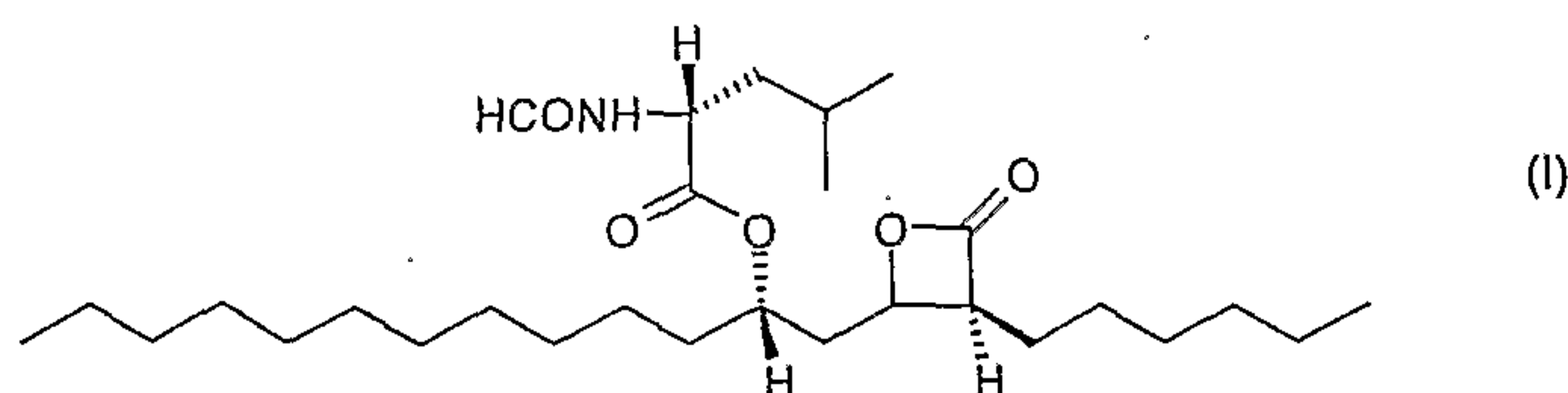
The term "sucrose fatty acid ester" comprises one single sucrose fatty acid ester as well as a mixture of two or more sucrose ester fatty acids as defined below. In a preferred embodiment of the present invention the substitution degree of sucrose ester varies
 25 between 1 and 4; e.g. mono-, di-, tri-, tetra-ester of fatty acids with sucrose. The term includes pure sucroseesters as well as mixtures of sucroseesters, wherein the sucroseester might be esterified by different fatty acids and might have several substitution degrees, e.g. mono-, di-, tri- or tetra-substituted.

Sucrose fatty acid ester and mixtures thereof and their preparation are known in the art and commercially available (Mitsubishi-Kagaku Foods Corp., Montello Inc., Multi-Kem Corp., etc.; see also Garti, N.; Clement, V.; Leser, M.; Aserin, A.; Fanun, M. Sucrose ester microemulsions. *J. Mol. Liq.* (1999), 80(2,3), 253-296; Carbohydrate-alkyl ester derivatives as biosurfactants. Allen, D.K.; Tao, B.Y., *J. Surfactants Deterg.* (1999), 2(3), 383-390.).

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 compounds commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, *J. Antibiot.* (1994), 47(12), 1369-1375). The term "lipase inhibitor" refers also to synthetic 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. In addition, 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.

In German Patent DE1965133 (Merck) some poly(styrene) derived polymers are described which exhibit direct lipase inhibition next to bile acid and triglyceride binding properties.

Orlistat is a known compound (formula I) 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, WO00/09123, WO01/19340 and
5 WO01/19378. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

In a preferred embodiment of the present invention, the sucrose ester molecules are mono-, di- or tri-ester. More preferably, the sucrose ester molecules are a mono- or di-ester and most preferably the sucrose ester are a mono-ester.

10 In a di-, tri or tetra-ester the fatty acid moieties may be identical or different (e.g. sucrosepalmitostearate), preferably identical.

The preferred ratio (w/w) between the lipase inhibitor and the sucrose fatty acid ester is as follows: The composition may comprise 0.05 mg to 20 mg sucrose fatty acid ester per 1 mg lipase inhibitor, preferably 0.1 mg to 10 mg sucrose fatty acid ester per 1 mg
15 lipase inhibitor, more preferably 0.1 to 2 mg sucrose fatty acid ester per 1 mg lipase inhibitor and most preferably 0.15 to 1 mg sucrose fatty acid ester per 1 mg lipase inhibitor.

Preferably, the lipase inhibitor is a lipophilic compound. Most preferably, the lipase inhibitor is orlistat.

20 In a further preferred embodiment of the present invention, the fatty acid moiety of the sucrose fatty acid ester is a C₈ to C₂₄ saturated or partially non-saturated fatty acid. Preferably, the fatty acid moiety of the sucrose fatty acid ester is a C₁₂ to C₁₈ saturated fatty acid, e.g. sucroselaurate, sucrosemyristate, sucrosepalmitate, sucrosetearate, sucrosearachidonate and sucrosebehanate, preferably sucroselaurate, sucrosemyristate,
25 sucrosepalmitate, sucrosetearate, more preferably sucrosepalmitate or sucrosetearate.

In a further preferred embodiment of the invention the fatty acid of the sucrose ester may be selected from C₈ to C₂₄, preferably a C₁₂ to C₁₈, mono-or polyunsaturated fatty acids, e.g. selected from the group consisting of palmitoleic acid, oleic acid, elaidic acid, erucic acid, linoleic acid, gamma-linolenic acid, alpha-linolenic acid and arachidonic acid,
30 most preferably oleic acid, i.e. sucrose fatty acid esters may be sucroseoleate.

The fatty acid moieties in a di-, tri-, or tetra-sucrose fatty acid ester may be a mixture of two or more fatty acid, e.g. sucrosepalmitostearate.

For lipase inhibitors as described above, e.g. orlistat, preferred compositions comprise 10 to 240 mg, more preferably 30 to 120 mg, e.g. 30, 40, 60, 80, 100, or 120 mg. Especially preferred compositions comprise 60 to 120 mg orlistat and 20 mg to 100 mg sucrose fatty acid ester.

- 5 For example a composition as defined above may comprise 120 mg orlistat and 60 mg sucrose ester or 120 mg orlistat and 30 mg sucrose fatty acid ester. Another composition may comprise 80 to 120 mg orlistat and 10 to 40 mg sucrose fatty acid ester or 20 to 60 mg orlistat and 5 to 15 mg sucrose fatty acid ester.

- Each dosage unit of the above pharmaceutical compositions can obtain the daily
10 doses of the pharmaceutically active compound 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. Orlistat is preferably orally administered from
15 30 to 800 mg per day in divided doses two to three times per day (see above). Other preferred daily doses may range between 120 to 360 mg, more preferred are daily doses between 180 to 270 mg and most preferably are 180 mg. Daily doses are, preferably divided and administrated twice or, particularly, three times per day. Generally, it is preferred that the lipase inhibitor has to be administered within about one or two hours of ingestion of a
20 meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity or has obtained a body mass index of 25 or greater.

- The compositions of the present invention may be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin
25 capsules, emulsions, suspensions, sachets, bars or cracker. Examples of carriers which can be used for tablets, coated tablets, dragées, hard gelatin capsules and sachets are pharmaceutically acceptable excipients like lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryl sulfate, Brij™
96, Tween™ 80; disintegrants like sodium starch glycolate, maize starch or derivatives
30 thereof; polymers like povidone, crospovidone; lubricants like talc; stearic acid or its salts and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, binding agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating 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.

Especially, the above compositions may comprise one or more pharmaceutically acceptable excipients selected from the group consisting of mannitol, lactose, HPMC, 5 lecthin, talcum, sorbitol, polyvinylpyrrolidone, polyethylenglycol, polysorbate, polyoxethylenstearate, and dimethicon, preferably lactose.

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 or sachets. The pharmaceutically acceptable excipients (diluent and 10 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 tableting the mixture by known methods. Similarly, capsules, 15 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 a pharmaceutically active compound and a sucrose ester as described above.

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

The oral dosage form may be a chewable tablet comprising 10-240 mg of orlistat, 0.5-1000 mg of sucrose fatty acid ester and further excipients such as maltodextrin, lactose or cellulose, for example 120 mg orlistat, 30 mg sucrosepalmitate e.g. Sucrosepalmitate 25 P1670, 960 mg maltodextrin, 360 mg Cellactose and 15 mg talcum.

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.

The invention also refers to a process for preparing a composition as described 30 above, comprising mixing a pharmaceutically active compound thereof with sucrose fatty acid ester and one or more pharmaceutically acceptable diluents and/or carriers.

The invention also provides the use of the above combination of compounds in the manufacture of a medicament for the treatment and prevention of obesity. Additionally, it provides the above compositions for use in the treatment and prevention of obesity.

In addition, the present invention refers to a method of treatment of obesity in a
5 human in need of such treatment which comprises administration to the human of a pharmaceutically active compound as defined above and a sucrose fatty acid ester, and optionally additional pharmaceutical acceptable excipients.

The invention also refers to the use of a composition as defined above for use in the treatment and prevention of obesity.

10 Another embodiment of the present invention refers to a process for preparing a composition as defined above, comprising mixing a pharmaceutically active compound as defined in claim 1 with sucrose ester, and optionally, more pharmaceutically acceptable diluent and/or carrier.

Further the invention refers to a kit for treatment of obesity, said kit comprising a
15 first component which is a lipase inhibitor and a second component which is sucrose fatty acid ester unit dosage forms.

Another embodiment 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 a method of treatment of obesity in a human in need of such treatment which comprises
20 administration to the human of a therapeutically effective amount of a lipase inhibitor and a sucrose ester defined above. The invention also refers to a lipase inhibitor and sucrose ester as defined above 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.

EXAMPLES

General remarks: All compounds used in the examples are commercially available.

Example 1 - Orlistat transfer into oil in vitro

Formulation	Transfer in Cream (%)		Transfer in Oliveoil (%)	
	after 10'	after 60'	after 10'	after 60'
Xenical	5	10	35	70
L-1695	55	65	55	80
P-1670	25	45	50	80
S-1670	10	25	60	90
O-1570	55	65	45	80

5

Orlistat (4mg) suspensions stabilized by sucroseesters (2mg) were transferred into 5ml of a 10% oil in water emulsion (pH value 4.5; oil components: olive oil and cream respectively). The dispersion underwent end-over end mixing for a desired period of time. The oil phase was separated by cold centrifugation and the orlistat content in the oil phase was determined by HPLC. For comparison, an adequate experiment was also performed with a suspension of XENICAL[®]. L-1695, P-1670, S-1670, O-1570 are commercial sucroseesters (Sucroselaurate, Sucrosepalmitate, Sucrosetearate, Sucroseoleate respectively) from Mitsubishi-Kagaku Foods, Japan.

The results indicate that the sucroseester have a higher efficacy of the transfer orlistat transfer into oil compared to XENICAL[®]. In addition to a general higher transfer efficacy and in contrast to XENICAL[®], orlistat is transferred into different kind of oils (cream: emulsified and casein covered oily droplets; olive oil: unprotected oil) at more comparable rates. The high food dependency of orlistat is reflected in the fact, that the transfer after 10 min into olive oil is 7 times more efficient than the transfer into cream. The sucrose ester

15

show less food dependency. Therefore, a dose reduction and decreased side effects can be expected.

Example 2: Tablet formulation

5 Chewable tablets of the following composition were made:

Composition 1	
Orlistat	120 g
Sucrosepalmite P1670	30 g
Maltodextrin	960 g
Cellactose	360 g
Talcum	15 g

Orlistat, sucrosepalmite and maltodextrin were homogeneously mixed and 350 g water were added stepwise under continuous mixing.

10 With the help of a syringe the homogeneous dispersion were spread on a sieve (mesh size 0.5 mm) in tracks. The sieve was put into a vacuum drying oven (Heraeus VT 5050 EK) which was tempered to 25 °C. Chamber pressure was lowered to 30 Torr (Leybold Heraeus TRIVAC D8B; COMAT AG DPI 700). After 5 minutes, the development of a foam structure was completed. The foam was dried in vacuum for several hours. Care was taken to control that the temperature of the foam did not exceed 35°C. The resulting foam
15 was desintegrated and sieved in order to achieve a homogenous flowable powder. Cellactose and talcum were added and homogeneously distributed by dry mixing. The resulting composition was tableted into tablets containing Orlistat 120 mg, Sucrosepalmite 30 mg, Maltodextrin 960 mg, Cellactose 360 mg, and Talcum 15 mg.

Example 3: Chewable tablet formulation

Chewable tablets of the following composition were made:

Composition 2	
Orlistat	120 g
Sucrosepalmitate P1670	240 g
Maltodextrin	750 g
Cellactose	375 g
Talcum	15 g

The tablets were made by the same procedure as described in Example 2.

5

Example 4: Chewable tablet formulation

Chewable tablets of the following composition were made:

Composition 3	
Orlistat	60 g
Sucrosepalmitate P1670	60 g
Maltodextrin	750 g
Cellactose	375 g
Talcum	15 g

The tablets were made by the same procedure as described in Example 2.

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Example 5: Chewable tablet formulation

Chewable tablets of the following composition were made:

Composition 4	
Orlistat	60 g
Sucrosetearate S1811	60 g
Maltodextrin	750 g
Cellactose	375 g
Talcum	15 g

The tablets were made by the same procedure as described in Example 2.

5

Example 6: Chewable tablet formulation

Chewable tablets of the following composition were made:

Composition 5	
Orlistat	60 g
Sucrosemyristate M1695	60 g
Maltodextrin	750 g
Cellactose	375 g
Talcum	15 g

The tablets were made by the same procedure as described in Example 2.

10

Example 7: Chewable tablet formulation

Chewable tablets of the following composition were made:

Composition 6	
Orlistat	60 g
Sucrosetearate S1816	60 g
Maltodextrin	750 g
Cellactose	375 g
Talcum	15 g

The tablets were made by the same procedure as described in Example 2.

5

Example 8: Pellet formulation

Composition 7	
Orlistat	240g
Sucrosepalmirate P1670	60 g
Avicel™ PH-105	35g
Sodium starch glycolate	60 g
Povidone K30	30 g

The ingredients are dry mixed together in a high speed mixer (Diosna P50). 240 g
 10 water are added stepwise and the mixing process is continued for about 5 minutes. An
 extruder is fed with this material (NICA lab E-140; screen 0.8 mm mesh size, thickness 1.0
 mm, screen surrounded by cooling device). The material is extruded to spaghettis of
 appropriate length. The temperature of the extrudate does not exceed 35°C. The extrudate
 is transferred to a spheronizer ((NICA lab S320) and spheronized for 0.5 to 3 minutes at
 15 700 rpm. The wet pellets are dried in a fluidized bed dryer (Aeromatic, MP-1) at a
 temperature of below 35°C. The dried pellets are sieved with sieve inserts of 0.5 and 1.25

mm mesh size, and under- and oversize fractions are discarded. The pellets are filled into a sachet at doses of 106 mg (corresponding to 60mg orlistat).

Example 9: Capsule formulation

- 5 The above pellets are filled into Gelatine capsules size I at a dosage of 106 mg (corresponding to 60 mg Orlistat).

Example 10: Tablet formulation

- 10 Magnesium stearate is added to the pellets described in Example 8 at a level of 1% (w/w) and homogeneously distributed by appropriate mixing. The mixture is compressed into 107 mg tablets which correspond to 60 mg Orlistat.

Example 11: In vitro efficacy

- 15 Table : Reduced food-dependent efficacy of sucrose ester based orlistat formulations in an in-vitro lipase inhibition assay with accessible and resistant fat. Xenical pellets and Tablets from Example 2 and Example 3 were investigated. Water was added to a dispersed tablet to yield a orlistat concentration of 6.64 mg/ml. The sample was stirred for 15 min and a geometric dilution series was prepared. An aliquot from each dilution step was mixed with substrate and assessed for lipase inhibition. The final emulsion contained 2.5
20 % (w/v) fat and 10 mg/ml USP pancreatin.

	<u>Hamburger/ French fries</u> IC ₅₀ (μg/ml)	<u>Cream</u> IC ₅₀ (μg/ml)	$\frac{IC_{50,Cream}}{IC_{50,Hamb.}}$
Xenical-Dispersion	2.5	46	5 %
Dispersion from Example 2 (30 mg Sucrosepalmite)	2.8	9.0	31 %
Dispersion from Example 3 (240 mg Sucrosepalmite)	1.9	5.5	34 %

5 The in-vitro lipase test mimics the gastro-intestinal fat digestion and assesses
formulation dependent inhibition of lipolysis. In this test lipase substrate (cream and
grained hamburger/ french fries, representing resistant and accessible fat, respectively) is
preincubated with a THL-formulation under simulated gastric conditions (i. e. at pH 4.5
in the presence of 20 % human gastric fluid). During this preincubation, the formulation
10 can load fat droplets with THL. Lipolysis is then started by adding artificial intestinal fluid,
containing bile salts, phospholipids and hydrolytic enzymes (pancreatin). After one hour
organic solvent is added to stop the reaction and free fatty acids are quantified. The dose-
response curve is dependent on the formulation as well as on the type of substrate
employed.

15 The IC₅₀ value is the concentration which inhibits triglyceride cleavage by 50%. A
high food dependency was observed for Xenical, the IC₅₀ increased by a factor of 20. The
in-vitro food dependency of the sucrose ester based formulations was about 6-times less
compared to Xenical.

Example 12: Efficacy in vivo

The 120 mg Orlistat tablet formulations described in Example 2 (30 mg Sucrosepalmite) and Example 3 (240 mg Sucrosepalmite), and Xenical were tested on human volunteers by means of a double-meal test, which is composed of accessible fat
5 (Lunch: Hamburger, French fries and a less accessible fat (Dinner: cheese meal). The nonabsorbed fat was determined after Bligh & Dyer (Bligh, E.G.; Dyer, W.J. *Can. J. Biochem. Physiol.* 37 (1959) 911).

The results indicate (Fig. 1) that the sucrose ester based formulations show an approximate 1.7 times higher efficacy formulation with 240 mg SUCROSEESTER P1670:
10 67.4 (± 5.3 %, n=5), formulation with 30 mg SUCROSEESTER P1670 66.6 (± 13 %, n=4) compared to Xenical 39.7 (± 8.1 %, n=5).

Example 13: Food dependency in vivo

The fatty acid specific analysis of the stool permits the selective determination of the
15 fat uptake of the lunch and dinner meal respectively. The results indicate (Fig. 2) that the efficacy of Xenical in the less accessible meal was only 48.4 % compared to the accessible, while the sucrose ester formulation 30 mg SUCROSEESTER P1670 reached 73.9 %. It can be concluded from these data that the food dependency of orlistat can be substantially minimized by sucrose ester based formulations.

20

Example 14: Side effect in vitro studies

Among various other strategies to control anal leakage, the generation of stable dietary fat emulsion in the colon is of high importance. Therefore, the emulsification properties of sucrose esters covering a wide range of hydrophile-lipophile-balance (HLB)
25 values were investigated using a centrifugal method. This in vitro method allowed both concentration and pH-depended emulsion stabilities to examine and thus to select the sucrose esters of highest potential to control side-effects. The results of the concentration depended emulsion stability studies are listed in Tables 1-3.

Table 1. Stability of Surfhope SE Pharma D-1815 test emulsions at various concentrations c and centrifugation times t .

c (% w/w)	Emulsion Stability Surfhope SE Pharma D-1815					
	t / min					
	10	70	100	160	220	300
0.01	low*	low	low	low	low	low
0.1	high	medium	medium	medium	medium	medium
0.5	high	medium	medium	medium	medium	medium
1.0	high	medium	medium	medium	medium	medium
1.5	high	medium	medium	medium	medium	medium
2.0	high	medium	medium	medium	medium	medium

*low: oil and water form two distinct clearly separated phases; medium: emulsion partly broken;

high: no indications of coalescence, optically non-transparent, stable emulsion

5

Table 2. Stability of Surfhope SE Pharma D-1811 test emulsions at various concentrations c and centrifugation times t .

c (% w/w)	Emulsion Stability Surfhope SE Pharma D-1811					
	t / min					
	10	70	100	160	220	300
0.01	low*	low	low	low	low	low
0.1	high	high	medium	medium	medium	medium
0.5	high	high	medium	medium	medium	medium
1.0	high	high	high	medium	medium	medium
1.5	high	high	high	medium	medium	medium
2.0	high	high	high	high	high	high

*low: oil and water form two distinct clearly separated phases; medium: emulsion partly broken;

high: no indications of coalescence, optically non-transparent, stable emulsion

10

Table 3. Stability of Surfhope SE Pharma D-1805 test emulsions at various concentrations c and centrifugation times t .

c (% w/w)	Emulsion Stability Surfhope SE Pharma D-1805					
	t / min					
	10	70	100	160	220	300
0.01	low*	low	low	low	low	low
0.1	low	low	low	low	low	low
0.5	medium	medium	medium	medium	medium	medium
1.0	medium	medium	medium	medium	medium	medium
1.5	high	medium	medium	medium	medium	medium
2.0	high	high	high	medium	medium	medium

*low: oil and water form two distinct clearly separated phases; medium: emulsion partly broken;

high: no indications of coalescence, optically non-transparent, stable emulsion

5 Sucrose esters such as Surfhope SE Pharma D-1811 (Table 2) with a medium HLB value of 11 proofed to be slightly superior in their ability to stabilize an emulsion with respect to Surfhope SE Pharma D-1815 (Table 1) and Surfhope SE Pharma D-1805 (Table 3), respectively. At concentrations of 2.0 % (w/w) Surfhope SE Pharma D-1811 revealed stable emulsions without any visual signs of coalescence at centrifugation times up to $t =$
 10 300 min (Figure 1). Both, Surfhope SE Pharma D-1815 and Surfhope SE Pharma D-1805 showed only slightly less stable emulsion stabilities. In addition, measurements with similarly prepared emulsions stored at room temperature for 1 week without applying any centrifugal force revealed that the conditions generated in the centrifugation experiment correlates to a normal standing period of about 2-3 days, which compares well to the
 15 average gastro-intestinal transit time in humans.

Figure 3 displays test emulsions of Surfhope SE Pharma D-1811 after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsion containing 2.0% (w/w) sucrose ester remains even after a centrifugation time of $t = 300$ min stable (picture (b), right capillary). From left to right: reference (mixture soya oil/buffer); $c =$
 20 0.01%, $c = 0.1\%$; $c = 0.5\%$; $c = 1.0\%$; $c = 1.5\%$; $c = 2.0\%$ (w/w).

Similar emulsion stability tests were conducted using combinations of sucrose esters and hydrocolloids (e.g., xanthan gum, gellan gum, carrageenan gum), sphingomyelin, aerosil derivatives, calcium carboxymethylcellulose, chitosan, bentonites, whey protein concentrates, pectins, and poly(vinyl alcohol). Interestingly, these studies showed that 1:1
 25 combinations (w/w) of Surfhope SE Pharma D-1815 and Aerosil 200, carrageenan gum, and whey protein concentrates gave emulsions with clearly better stability than the single compounds alone, due to a yet unknown synergistic mechanism.

In order to investigate emulsion stability at various pH values, test emulsions with a surfactant concentration of $c = 1.0\%$ w/w covering the range from pH 4 to 9 were prepared (Table 4-7). At pH values > 7 all sucrose fatty acid esters investigated showed good emulsification properties. After centrifugation times of 300 min only a small free upper oil phase separated from the optically non-transparent emulsion phase. Sucrose esters with an HLB value below 11 gave only poor emulsification at pH values < 7 (Table 5-7). Surprisingly, Surfhope SE Pharma D-1815 with an HLB of 15 gave highly stable emulsions. This clearly indicates that sucrose esters with a rather high HLB value (typically around 15) provide practically pH-independent superior emulsification stabilities.

10 Table 4. Stability of Surfhope SE Pharma D-1815 test emulsions ($c = 1.0\%$ w/w) at various pH-values and centrifugation times t .

pH	Emulsion Stability Surfhope SE Pharma D-1815				
	t / min				
	1	30	60	120	300
4	high*	high	high	high	high
5	high	high	high	high	high
6	high	high	high	high	high
7	high	high	high	high	medium
8	high	high	medium	medium	medium
9	high	high	medium	medium	medium

*low: oil and water form two distinct clearly separated phases; medium: emulsion partly broken;

high: no indications of coalescence, optically non-transparent, stable emulsion

Table 5. Stability of Surfhope SE Pharma D-1811 test emulsions ($c = 1.0\%$ w/w) at various pH-values and centrifugation times t .

pH	Emulsion Stability Surfhope SE Pharma D-1811				
	t / min				
	1	30	60	120	300
4	high*	medium	medium	medium	low
5	high	medium	medium	medium	low
6	high	high	medium	medium	medium
7	high	high	medium	medium	medium
8	high	high	high	high	medium
9	high	high	high	high	medium

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

5

Table 6. Stability of Surfhope SE Pharma D-1807 test emulsions ($c = 1.0\%$ w/w) at various pH-values and centrifugation times t .

pH	Emulsion Stability Surfhope SE Pharma D-1807				
	t / min				
	1	30	60	120	300
4	high*	medium	medium	medium	low
5	high	medium	medium	medium	low
6	high	high	medium	medium	low
7	high	high	high	medium	medium
8	high	high	high	high	medium
9	high	high	high	high	medium

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

10

Table 7. Stability of Surfhope SE Pharma D-1805 test emulsions ($c = 1.0\%$ w/w) at various pH-values and centrifugation times t .

pH	Emulsion Stability Surfhope SE Pharma D-1805				
	t / min				
	1	30	60	120	300
4	low*	low	low	low	low
5	medium	medium	low	low	low
6	medium	medium	medium	medium	medium
7	high	high	medium	medium	medium
8	high	high	high	high	high
9	high	high	high	high	high

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

5 Figure 4 shows test emulsions of Surfhope SE Pharma D-1811 after centrifugation at 3100 g for $t = 1$ min (a) and $t = 300$ min (b), respectively. The emulsions are stabilized with 1.0% (w/w) sucrose ester at different pH values. Whereas emulsions at $\text{pH} \leq 7$ clearly show phase separation after centrifugation for $t = 300$ min, emulsions at $\text{pH} > 7$ noticeably revealed less free oil. From left to right: reference (mixture soya oil/buffer) at $\text{pH} = 7$; $\text{pH} =$
10 4, $\text{pH} = 5$; $\text{pH} = 6$; $\text{pH} = 7$; $\text{pH} = 8$; $\text{pH} = 9$.

In contrast, Sucrose Fatty Acid Ester S-370F revealed very bad emulsification properties. Due to the high hydrophobicity of the compound solubility in the continuous aqueous phase was very low. However, the compound is very easily soluble in soya bean
15 oil resulting in a significant increase in oil viscosity.

Example 15: Side effect in vivo studies

An in vivo mouse model was developed to investigate the ability of sucrose esters to reduce the free oil formation after Orlistat treatment. Orlistat was mixed with butter and
20 added to the feed. The concentration of Orlistat administered to the mice was $150 \mu\text{mol}$ Orlistat/kg body weight. The experiment is based on the observation that mice under a high fat diet treated with Orlistat or other lipase inhibitors distribute the excreted free oil over their furs while grooming (United States Patent, Patent Number 5.431.949). A variety of sucrose esters as mentioned above were examined for their ability to reduce or eliminate
25 the production of free oil. The results of these studies are summarized in Figure 5.

In this representation, the excretion of free oil by a control group which received Orlistat but no gastro-intestinal side effect controlling agent was taken as background level and arbitrarily set to zero. Any improvements in free oil production are given as minus per cent value relative to the background. These experiments revealed that sucrose esters such as Surfhope D-1811 or Surfhope D-1805 with a medium HLB value show the highest relative reduction in free oily excretion. In contrast, sucrose esters on either end of the HLB scale which are either very hydrophilic (Surfhope D-1815) or very lipophilic (Surfhope D-1803) show less activity.

10

Example 16: Pellet formulation compressed to chewable tablet

Composition 8	
Orlistat	240g
Sucrosepalmite P1670	60 g
Avicel PH-105	210 g
Sodium starch glycolate	60 g
Povidone K30	30 g
Stearic acid	6 g

The ingredients are dry mixed together in a high speed Aeromatic Fielder GP 1). 240 g water are added stepwise and the mixing process is continued for about 5 minutes. An extruder is fed with this material (NICA extruder ; screen 0.8 mm mesh size, thickness 1.0 mm). The material is extruded to spaghettis of appropriate length. The temperature of the extrudate does not exceed 35°C. The extrudate is transferred to a spheronizer ((NICA spheronizer) and spheronized for 0.5 to 5 minutes. The wet pellets are dried in a fluidized bed dryer (Aeromatic, MP-1) at a temperature of below 35°C. The dried pellets are sieved with sieve inserts of 0.5 and 1.25 mm mesh size, and under- and oversize fractions are discarded. Stearic acid is added and homogeneously distributed by dry mixing. The resulting mixture is compressed to chewable tablets containing Orlistat 120mg, Sucrosepalmite 30mg, Avicel 105mg, Sodium starch glycolate 30mg, Povidone 15mg and Stearic acid 3mg.

Example 17: Two layer chewable tablet

Composition 9	
a) Orlistat	240g
b) Sucrosepalmirate P1670	60 g
c) Avicel PH-105	210 g
d) Sodium starch glycolate	60 g
e) Povidone K30	30 g
f) Stearic acid	6 g
g) Lactose monohydrate (powder)	1460 g
h) Avicel PH 102	200 g
i) Maize starch 1500	100 g
k) Sodium starch glycolate	100 g
l) Povidone 90F	60 g
m) Glyceryl benehate	60 g
n) Magnesium Stearate	20 g

- 5 Layer 1: The ingredients a) – e) are dry mixed together in a high speed Aeromatic Fielder GP 1). 240 g water are added stepwise and the mixing process is continued for about 5 minutes. An extruder is fed with this material (NICA extruder ; screen 0.8 mm mesh size, thickness 1.0 mm). The material is extruded to spaghettis of appropriate length. The temperature of the extrudate does not exceed 35°C. The extrudate is transferred to a
- 10 spheronizer ((NICA spheronizer) and spheronized for 0.5 to 5 minutes. The wet pellets are dried in a fluidized bed dryer (Aeromatic, MP-1) at a temperature of below 35°C. The dried pellets are sieved with sieve inserts of 0.5 and 1.25 mm mesh size, and under- and oversize fractions are discarded. Stearic acid is added and homogeneously distributed by dry mixing.

- 24 -

Layer 2: The excipients g) – m) are mixed together in a high speed mixer (Aeromatic Fielder GP 1) for 5 minutes, 400g water added for granulation. The wet granulate is sieved and dried in a fluidized bed dryer (Aeromatic, MP-1). The dried granulate is sieved, and homogeneously mixed with Magnesium stearate.

- 5 The resulting mixtures of layer 1 and 2 are compressed to a two layer tablet (Kilian compressing equipment) containing Orlistat 120mg, Sucrosepalmite 30mg, Avicel 105mg, Sodium starch glycolate 30mg, Povidone 15mg and Stearic acid 3mg in layer 1 and containing Lactose 730mg, Avicel 100mg, Maize starch 50mg, Sodium starch glycolate 50mg, Povidone 30mg, Glyceryl benehate 30mg and Magnesium stearate 10mg in the
10 second layer.

Example 18: Fast disintegrating chewable tablet

Composition 10	
Orlistat	48 g
Sucrosepalmite P1670	12 g
Sodium starch glycolate	48 g
PEG 6000	72 g
Xylit	122.4 g
Mannit pulvis	122.4 g
Myrj 52	12 g
Plasdone S630	24 g
Magnesium stearate	4.8 g
Talc	24 g

The ingredients (with exception of Magnesium stearate and Talc) were mixed in a high speed mixer (Aeromatic Fielder GP 1) for 5 minutes. 32g water was added for granulation.

- 15 The wet granulate was sieved (Siebschleuder Bergmeier 5.0mm) and dried in a fluidized bed dryer (Aeromatic Strea) below 37°C. The dry granulate was sieved (Fitzpatrick 1.62mm), mixed with Magnesium stearate and Talc and compressed to a chewable tablet (Korsch PH 250 tableting machine).

Example 19: Fast disintegrating chewable tablet

Composition 11	
Orlistat	48 g
Sucrosepalmitate P1670	12 g
Sodium starch glycolate	48 g
PEG 6000	72 g
Xylit	98.4 g
Mannit pulvis	98.4 g
Myrj 52	12 g
Alginic acid	32.64 g
Plasdone S630	24 g
Magnesium stearate	4.8 g
Talc	14.4 g
Calcium carbonate	15.36 g

The ingredients (with exception of Magnesium stearate, Talc and Calcium carbonate) were
5 mixed in a high speed mixer (Aeromatic Fielder GP 1) for 5 minutes. 30 g water was added
for granulation. The wet granulate was sieved (Siebschleuder Bergmeier 5.0mm) and dried
in a fluidized bed dryer (Aeromatic Strea) below 37°C. The dry granulate was sieved
(Fitzpatrick 1.62mm), homogeneously mixed with Magnesium stearate, Talc and Calcium
carbonate and compressed to a chewable tablet (Korsch PH 250 tableting machine).

CLAIMS

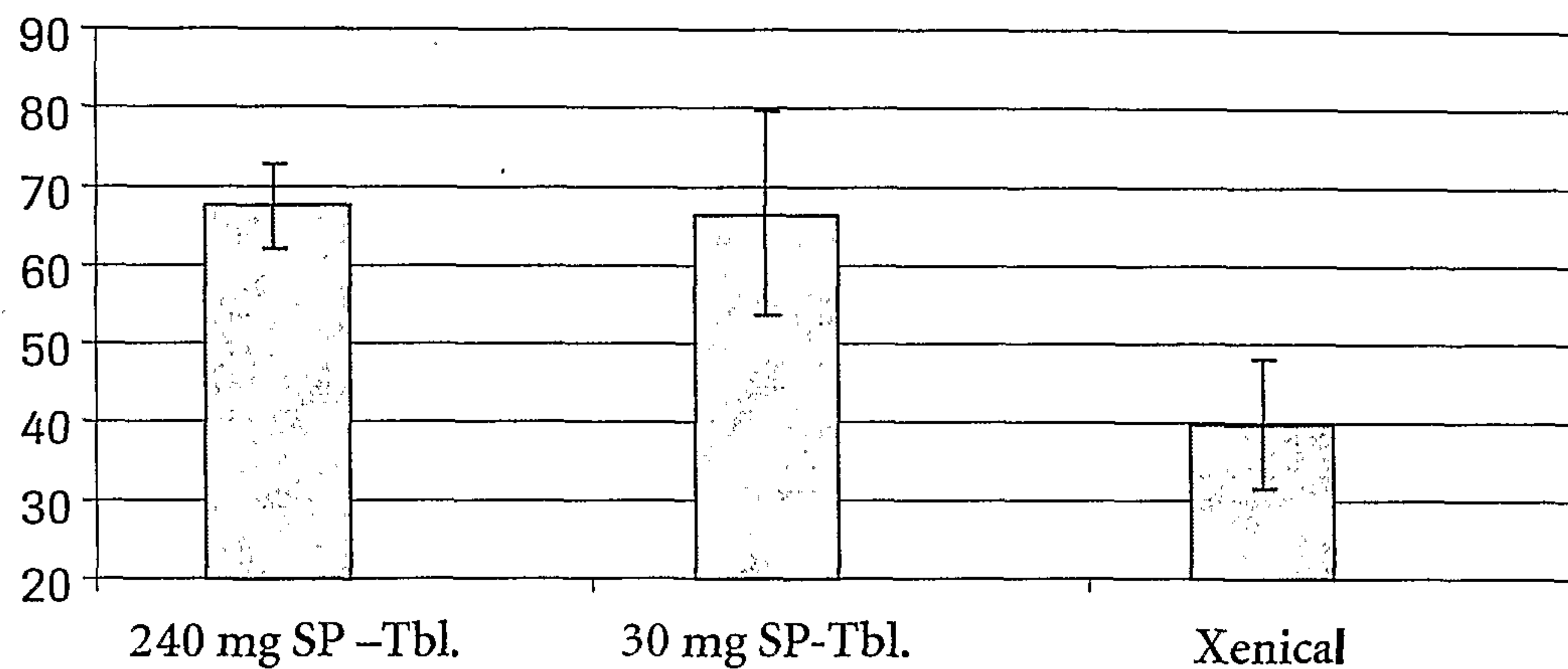
1. A pharmaceutical composition comprising a lipase inhibitor having a melting point $\geq 37^{\circ}\text{C}$, a sucrose fatty acid ester and optionally one or more pharmaceutically acceptable excipients, wherein the lipase inhibitor is orlistat and the sucrose fatty acid ester is a mono-ester selected from the group consisting of sucroselaurate, sucrosemyristate, sucrosepalmitate, sucrosetearate, sucrosearachidonate and sucrosebehanate.
2. The composition according to claim 1 comprising 0.05 mg to 20 mg of the sucrose fatty acid ester per 1 mg of the lipase inhibitor.
3. The composition according to claim 2 comprising 0.1 mg to 10 mg of the sucrose fatty acid ester per 1 mg of the lipase inhibitor.
4. The composition according to claim 3 comprising 0.1 to 2 mg of the sucrose fatty acid ester per 1 mg of the lipase inhibitor.
5. The composition according to claim 4 comprising 0.15 to 1 mg of the sucrose fatty acid ester per 1 mg of the lipase inhibitor.
6. The composition according to any one of claims 1-5, wherein the fatty acid ester is selected from the group consisting of sucroselaurate, sucrosemyristate, sucrosepalmitate, and sucrosetearate.
7. The composition according to claim 6 wherein the fatty acid ester is sucrosepalmitate.
8. The composition according to claim 6 wherein the fatty acid ester is sucrosetearate.

9. The composition according to any one of claims 1 to 8 comprising 10 to 240 mg of the orlistat.
10. The composition according to claim 9 comprising 30 to 120 mg of the orlistat.
11. The composition according to claim 10 comprising 30, 40, 60, 80, 100, or 120 mg of the orlistat.
12. The composition according to any one of claims 1 to 10 comprising 60 to 120 mg of the orlistat and 20 mg to 100 mg of the sucrose fatty acid ester.
13. The composition according to any one of claims 1 to 12 comprising 120 mg of the orlistat and 30 mg of the sucrose fatty acid ester.
14. The composition according to any one of claims 1 to 12 comprising 80 to 120 mg of the orlistat and 10 to 40 mg of the sucrose fatty acid ester.
15. The composition according to any one of claims 1 to 11 comprising 20 to 60 mg of the orlistat and 5 to 15 mg of the sucrose fatty acid ester.
16. The composition according to any one of claims 1 to 15 comprising at least one pharmaceutically acceptable excipient selected from the group consisting of mannitol, lactose, HPMC, talcum, sorbitol, polyvinylpyrrolidone, lecithin, polyethyleneglycol, polysorbate, polyoxyethylenestearate, and dimethicon.
17. The composition according to claim 16 comprising lactose as the at least one pharmaceutically acceptable excipient.

18. The composition according to any one of claims 1 to 9 comprising 10 to 240 mg of the orlistat and 0.5 to 1000 mg of the sucrose fatty acid ester.
19. The composition of claim 18 comprising one or more excipients selected from the group consisting of maltodextrin, lactose and cellulose.
20. The composition according to any one of claims 1 to 19 for use in the treatment and prevention of obesity.
21. A process for preparing the composition defined in any one of claims 1 to 19, comprising mixing a lipase inhibitor with a sucrose fatty ester, and optionally, one or more pharmaceutically acceptable excipients.
22. A kit for the treatment of obesity, said kit comprising a first component which is an orlistat and a second component which is the sucrose fatty acid ester defined in claim 1 wherein the first component and the second component are in a unit dosage form.
23. A use of the composition defined in any one of claims 1 to 19 in the manufacture of a medicament for the treatment or prevention of obesity.
24. A use of the composition defined in any one of claims 1 to 19 for the treatment or prevention of obesity.
25. A combination comprising the lipase inhibitor and the sucrose fatty acid ester as defined in any one of claims 1 to 19 for the treatment or prevention of obesity.

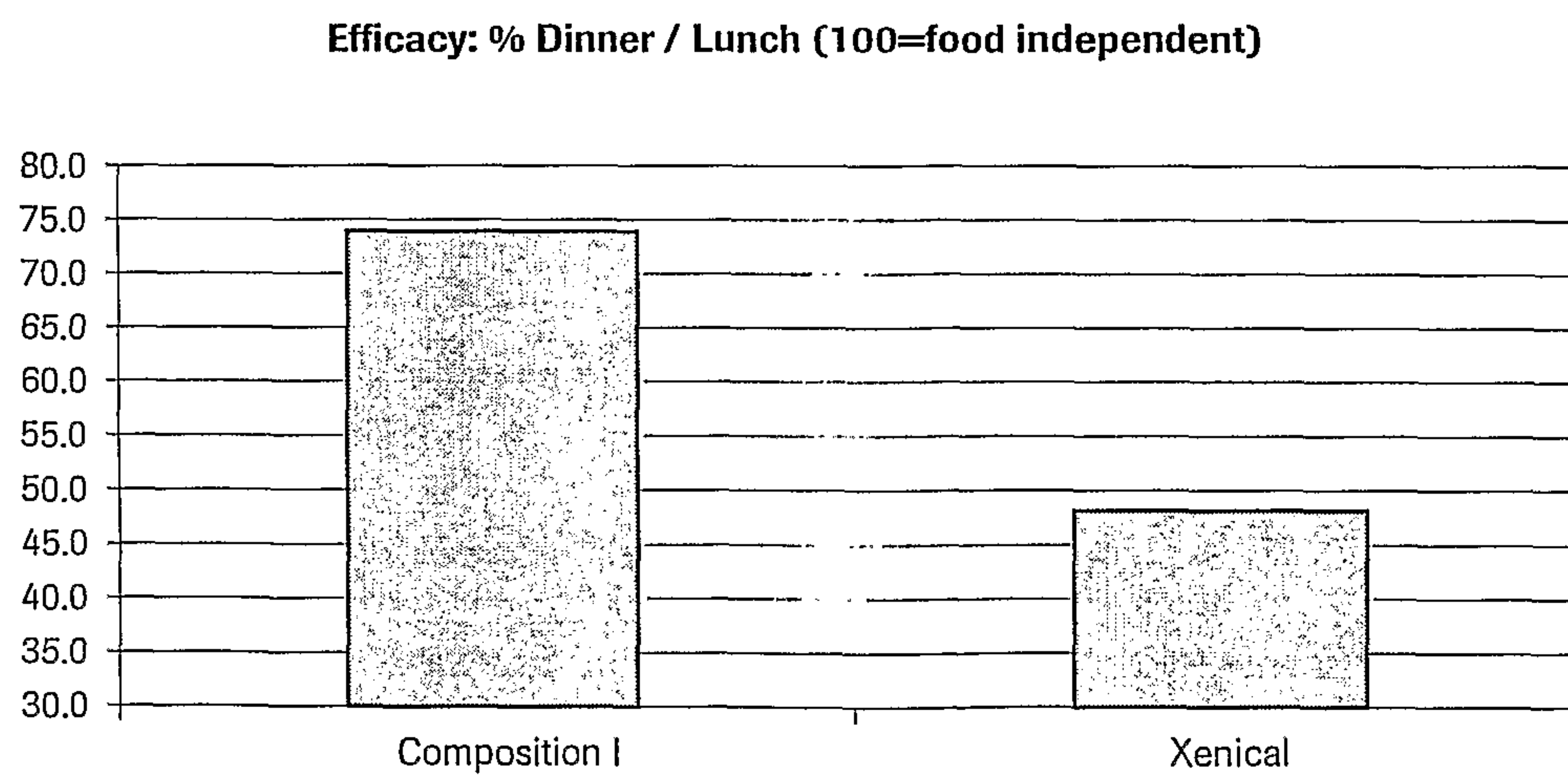
FIGURES

FIG. 1



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FIG. 2



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FIG. 3

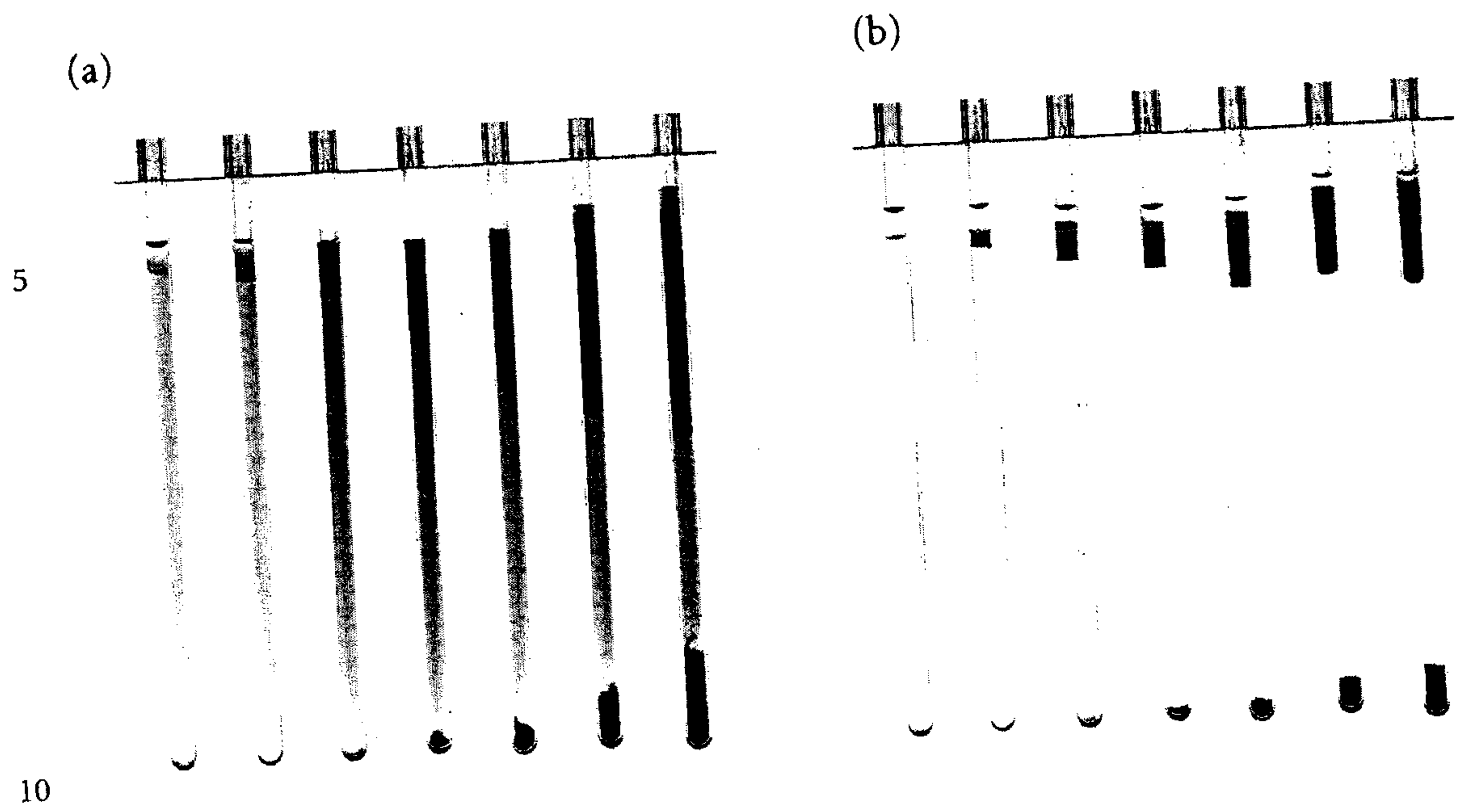


Fig. 4

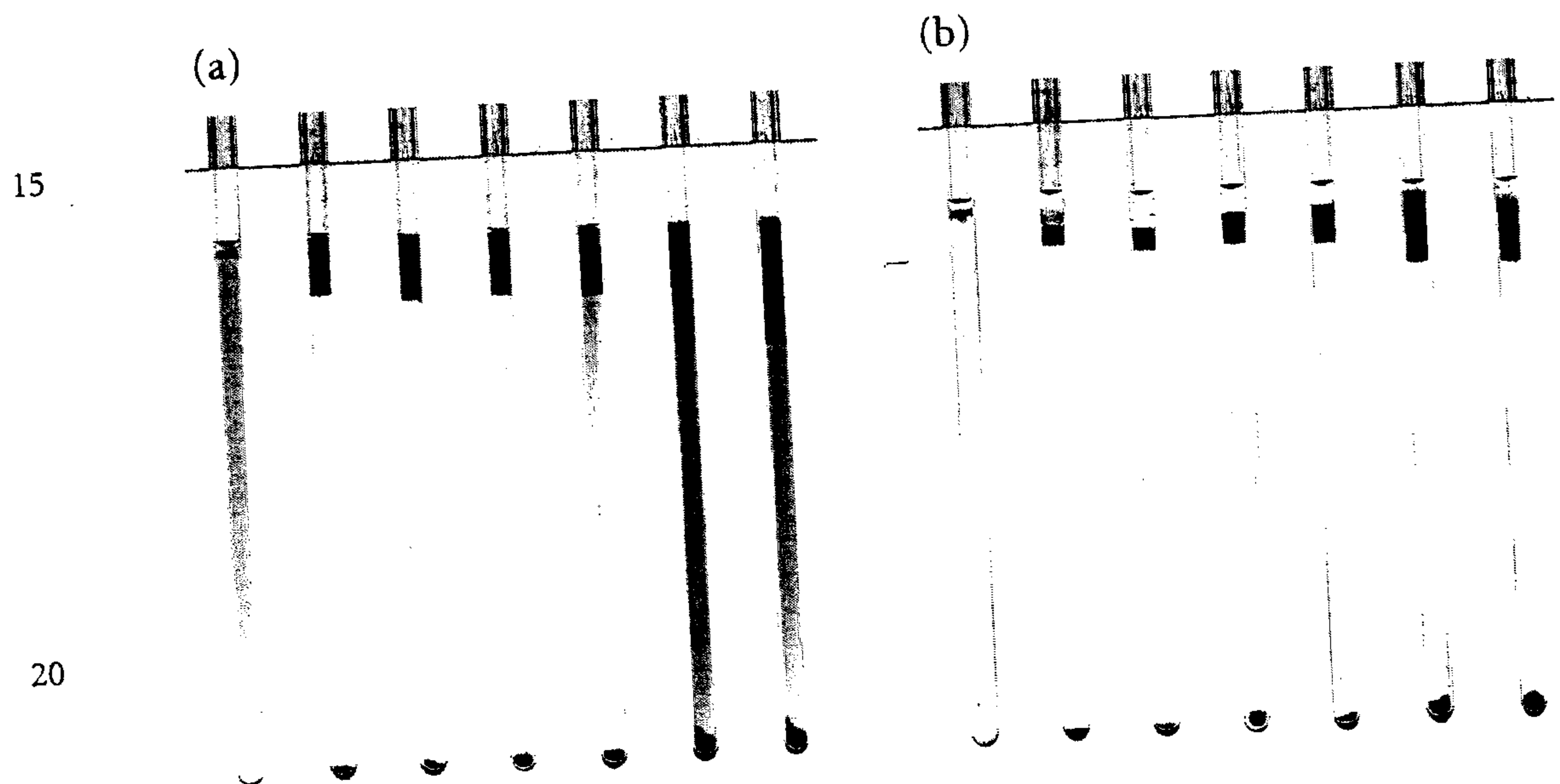


FIG. 5

