

IMPROVEMENTS IN OR RELATING TO COMPOSITIONS

The present invention relates to pharmaceutical

5 compositions, and in particular to composition for the treatment of reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for use as a sustained releasing or targeted delivery compositions.

10 Reflux oesophagitis occurs when small amounts of gastric juice, food and/or bile acids pass into the lower part of the oesophagus and cause oesophageal inflammation accompanied by pain which may manifest itself in the form of heartburn.

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One approach to the problem of reflux oesophagitis has been to administer a preparation which on contact with gastric acid generates a carbonated gelatinous foam or raft which floats on the stomach contents. When reflux
20 occurs it is this raft which precedes the stomach contents into the oesophagus, thus protecting the mucosa from further irritation. Known preparations of this type include liquid preparations comprising sodium alginate, sodium or potassium bicarbonate and calcium carbonate.

25 Such compositions are sold under the trade marks GAVISCON and GAVISCON ADVANCE and are described in GB-A-1,524,740 and WO 95/11668.

Other such preparations are those in solid form, for
30 example in the form of powders or tablets, such as those which again are sold under the trade mark GAVISCON. Such preparations comprise alginic acid, sodium bicarbonate

and calcium carbonate. The alginic acid and the bicarbonate and carbonate react in the aqueous environment of the mouth to form an alginate foam, which is then swallowed. In the acidic stomach environment the
5 alginate is converted back into insoluble alginic acid, which then forms the raft on top of the stomach contents.

It has been found that solid compositions which foam in the mouth are difficult, and sometimes unpleasant, to
10 swallow. In order to provide a non-foaming, solid composition we have tried to replace the alginic acid by an alginate. However, we have found that such compositions have extremely poor mouth feel. The alginate is sticky and causes the composition to stick to
15 the palate, and especially to the teeth.

We have surprisingly found that the mouth feel and stickiness of such compositions can be improved by including a further component in the composition.
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Accordingly the present invention provides a solid, ingestible composition comprising:

- a. an alginate;
- b. a bicarbonate and/or carbonate; and
- 25 c. a C₂-C₅ polyol or poly(C₂-C₅ alkylene glycol) having a molecular weight of at least 6000.

The composition of the present invention has less foaming than the tablets currently sold under the trade mark
30 GAVISCON since it comprises an alginate rather than alginic acid. It also has a good mouth feel and does not

stick to the teeth as much as a composition which does not comprise a polyol or polyalkylene glycol.

The composition of the present invention comprises an
5 alginate. Any alginate may be used, but it is especially desirable to use an alkali metal salt of an alginate, such as sodium or potassium alginate. Preferably a low viscosity grade of the alginate is used. These are generally grades of alginate for which the viscosity of a
10 10% weight/volume aqueous solution, when determined on a Brookfield RVT viscometer using spindle number 3 at 20 r.p.m. at 20 °C, falls within the range of 200 to 1,500 mPa.s. An example of a suitable commercial grade of low viscosity sodium alginate is Protanal LFR 5/60,
15 obtainable from FMC BioPolymer. High viscosity grades of alginate may also be used. These are generally grades of alginate for which the viscosity of a 1% weight/volume aqueous solution, when determined on a Brookfield RVT viscometer using spindle number 3 at 20 r.p.m. at 20 °C,
20 is above 500 mPa.s. An example of a suitable commercial grade of high viscosity sodium alginate is Protanal SF200, also obtainable from FMC BioPolymer

The compositions of the present invention generally have
25 a content of alginate of from 2 to 90 wt%, preferably 5 to 50 wt%, based on the total weight of the composition.

The compositions of the present invention also comprise a
bicarbonate and/or carbonate. Examples of bicarbonates
30 are alkali metal bicarbonates such as sodium and potassium bicarbonate and alkaline earth metal

bicarbonates. One or two or more different bicarbonates may be used. Examples of carbonates are alkali metal carbonates such as sodium and potassium carbonate and alkaline earth metal carbonates such as calcium and magnesium carbonate. Further examples are aluminium carbonate and mixed alkali metal carbonates such as sodium glycine carbonate. One or two or more different carbonates may be used. Furthermore one or more bicarbonates may be used with one or more carbonates.

10 Especially preferred combinations are sodium and/or potassium bicarbonate and calcium carbonate.

The carbonate and/or bicarbonate are present in amounts such that they provide an adequate volume of gas (carbon dioxide) to float the gel produced when the alginate contacts the gastric acid in the stomach. The rigidity and thickness of the carbonate raft will depend, for example, upon the relative amounts of carbonate and/or bicarbonate and on the grade of the alginate.

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If used alone, the bicarbonate is generally present in the compositions of the present invention in an amount of from 1.5 to 35 wt%, preferably 2 to 15 wt%, most preferably 3 to 10 wt%. If used alone, the carbonate is generally present in the compositions of the present invention in an amount of from 0.2 to 55 wt%, preferably 0.5 to 10 wt%, most preferably 1 to 4 wt%.

Preferably the bicarbonate and carbonate may also be present together in the composition, preferably from 1 to 20 wt%, for example in a total amount of from 1 to 40 wt%,

preferably 1 to 12 wt%. Approximately equal amounts of the bicarbonate and carbonate may be present in the composition. Alternatively, the composition may comprise more bicarbonate than carbonate. The weight ratio of
5 bicarbonate to carbonate in the composition may be from 1:1 to 2:1.

The compositions of the present invention also comprise a C₂-C₅ polyol or poly(C₂-C₅ alkylene glycol). Suitable
10 polyols have 2, 3, 4 or 5 carbon atoms and contain 2 or more hydroxy groups, for example 2, 3, 4 or 5 hydroxy groups. Examples of suitable compounds are ethylene glycol, propylene glycol, glycerol and erythritol.

15 The poly(C₂-C₅ alkylene glycol) is preferably a polyethylene glycol or polypropylene glycol. The polyalkylene glycol may comprise any number of alkylene glycol units, for example having a molecular weight of at least 6000. Polyalkylene glycols may be liquid or solid
20 at room temperature (20°C). It is preferred to use the solid form, particularly in the form of a free-flowing powder, for ease of handling and incorporation into the blend.

25 The polyol or poly(C₂-C₅ alkylene glycol) is generally present in the compositions of the present invention in an amount of from 1 to 50 wt%, preferably from 1 to 15 wt%, preferably 1.5 to 10 wt%, most preferably 2 to 6 wt%.

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The polyol or poly(C₂-C₅ alkylene glycol) and the alginate may, for example, be present in the composition

of the present invention in a weight ratio of from 2:1 to 1:25, preferably from 1:4 to 1:12.5.

The compositions of the present invention may also
5 comprise further, optional components.

For example, the compositions of the present invention preferably comprise a source of divalent and/or trivalent metal ions. Such ions strengthen the raft formed in the
10 stomach. Suitable metal ions are calcium and aluminium. The ions may be provided as part of the bicarbonate and/or carbonate, but may also comprise other anions if desired. For example, suitable sources of calcium ions are calcium carbonate, lactate, chloride, gluconate,
15 phosphate, hydrogen phosphate, sulfate, tartrate or citrate, and suitable sources of aluminium ions are aluminium carbonate, lactate, glycinate or phosphate, aluminium magnesium carbonate, hydroxide or magaldrate, aluminium sodium carbonate hydroxide or aluminium sodium
20 silicate. If used, the calcium ions are preferably present in an amount of from 8 to 800 parts, and the aluminium ions are preferably present in an amount of from 2 to 500 parts, per 500 parts by weight of alginate.

25 The compositions of the present invention may also comprise a preservative to prevent contamination and subsequent deterioration by micro-organisms. Examples of suitable preservatives are methyl, ethyl, propyl and butyl para-hydroxybenzoates and their salts, which are
30 preferably used in combinations, for example methyl and propyl or ethyl and butyl. The compositions of the present invention do not need to include such a preservative, but if a preservative is present it may be

used in an amount of, for example, up to 0.5 wt%, based on the total weight of the composition.

The compositions of the present invention may also
5 comprise one or more colourings, sweetenings, flavourings, pH adjusting ingredients and fillers. When the compositions of the present invention are intended for use as sustained releasing compositions they will also comprise at least one active ingredient suitable for
10 specific delivery to the stomach, such as a drug. Examples of suitable drugs are analgesics (e.g. sucetaminophen, ibuprofen, naproxen, diclofenac, ketoprofen, choline salicylate, benzydamine, buprenorphine, hydrocortisone, betamethasone);
15 decongestants (e.g. pseudoephedrine, phenylephrine, oxymetazoline, xylometazoline); cough suppressants (e.g. dextromethorphan, codeine, pholcodine); expectorants (e.g. guaiphenesin, n-acetylcysteine, bromhexine); antiseptics (e.g. triclosan, chloroxylenol,
20 amylmetacresol, hexylresorcinol, dichlorobenzyl alcohol, benzyl alcohol); cardiovascular agents (e.g. glyceryl trinitrate); local anaesthetics (e.g. benzocaine, lignocaine); antacid agents (e.g. calcium carbonate, sodium bicarbonate, magnesium trisilicate, aluminium
25 hydroxide, magaldrate,); antiulcer agents (e.g. carbenoxolone, sucralfate, cimetidine, ranitidine, nizatidine, famotidine, omeprazole, pantoprazole); antihistamines (e.g. loratidine, terfenadine, diphenhydramine, chlorphenhydramine, triprolidine,
30 acrivastine); antinausea agents (e.g. prochlorperazine, sumatriptan); bowel regulatory agents (e.g. diphenoxylate, loperamide, sennosides); antifungal agents

(e.g. clotrimazole); antimicrobial agents and antibiotics (e.g. fusafungine, tyrothricin).

It is also possible for the compositions of the present invention to comprise alginic acid, although this is not preferred since it could cause undesirable foaming in the mouth.

The compositions of the present invention may be in any solid form. For example they may be in the form of a tablet, such as a chewable tablet. They may also be in the form of a chewable gum, a confectionary such as a fudge or boiled sweet or in the form of particles or granules, for example free-flowing or packed in a capsule, for example a soft or hard gel capsule.

The composition of the present invention may be used in a method of treatment of the human or animal body by therapy, especially use in the treatment of reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for use as a sustained releasing or targeted delivery composition.

The composition of the present invention may be used in the manufacture of a medicament for the treatment of reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for use as a sustained releasing or targeted delivery composition.

The composition of the present invention may be used in a method of treating reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for sustained releasing or targeting a delivery composition, which comprises

orally administering to a subject in need thereof or liable to need an effective amount of the composition.

The composition is generally administered in an amount of
5 from 100 to 2000 mg alginate per dose.

The compositions of the present invention may be prepared by simply mixing the ingredients. It is especially preferred to mix the ingredients together in particulate
10 form and then granulate or agglomerate the particles using a suitable granulating agent such as water, a C₂ to C₄ alcohol such as ethanol or isopropanol, or a mixture thereof. This is especially suitable when the PEG used is naturally a solid. It is also possible to granulate
15 the remaining ingredients with PEG as a granulating agent when it is in liquid form. Additional granulating binders may also be used, for example povidone, a cellulose derivative such as HPMC or starch paste. A preferred starch paste uses water as the granulating
20 solvent, and povidone is generally used with an ethanol or isopropanol solvent. We have surprisingly found that when a wet granulation is carried out, the amount of polyol or polyalkylene glycol can be reduced while retaining a satisfactory mouthfeel. A normal granulation
25 process may need a weight ratio of polyol or polyalkylene glycol to alginate of up to about 1:1. However, using a wet granulation process enables the weight ratio of polyol or polyalkylene glycol to alginate to be reduced to less than 0.25:1, especially less than 0.15:1, while
30 retaining a satisfactory mouthfeel.

One or more of the components may be added after granulation. In particular the polyol or polyalkylene

glycol may be added after granulation, although this is not preferred since an increased amount of this component may be required to achieve a suitable mouth feel. It is preferred to avoid the use of excessive amounts of polyol
5 or polyalkylene glycol since the amount of this component which can be ingested may be limited by regulatory authorities.

In a preferred process for preparing the composition of
10 the present invention, the alginate, carbonate and/or bicarbonate and polyol or polyalkylene glycol are granulated together, dried and screened prior to mixing in any further components. It is also possible, for example, to granulate only the alginate and the polyol or
15 polyalkylene glycol prior to adding the remaining components.

The present invention is further described in the following Examples.

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EXAMPLES

EXAMPLE 1

25 The following particulate components (each having a maximum particle size of 1mm) were mixed together in a high shear mixer for 1 minute:

30	Sodium Alginate LFR 5/60	250g
	Sodium bicarbonate	133.5g
	Calcium carbonate	80g
	PEG 20,000	30g

The mixture was then granulated in a granulator using 75ml distilled, deionised water as a granulating agent.

The granules were then dried in a fluid bed drier at 40°C
5 for 20 minutes and subsequently milled firstly through a 610µm screen and secondly through a 457µm screen using a Quadro Comill. The milled granulate was then blended with the following ingredients in a low shear tumble blender for 5 minutes:

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	Mannitol	522.75g
	Crospovidone (dispersant)	55g
	Flavour 1	5.5g
	Flavour 2	1.1g
15	Acesulfame K	5.5g
	Aspartame	1.65g

Finally, 15g magnesium stearate was added to the blender, and blending was continued for a further 2 minutes.

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The granules were then compressed into tablets each containing 250mg or 500mg sodium alginate. The tablets were found to have a smooth, slightly chewy texture with no significant toothpacking or gummy residue.

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EXAMPLE 2

250 and 500 mg tablets were prepared following the procedure of Example 1 except for using the following
30 components:

Sodium Alginate LFR 5/60	250g
Sodium bicarbonate	133.5g

	Calcium carbonate	80g
	PEG 20,000	30g
	Mannitol	516.5g
	Crospovidone	55g
5	Flavour	10g
	Aspartame	10g
	Magnesium stearate	15g

COMPARATIVE EXAMPLE 1 AND EXAMPLES 3 TO 7

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A Comparative test was carried out to illustrate the beneficial effects of a polyalkylene glycol on the mouthfeel of a composition.

15 The following compositions were prepared:

Ingredient (mg)	<u>EXAMPLES</u>					
	Comparative 1	3	4	5	6	7
Protanal LFR 5/60	520	500	500	500	500	500
NaHCO ₃	177	170	170	170	170	170
Mannitol	1178	950	600	950	1125	300
Mg-stearate	31	30	30	30	30	30
Kollidon 90F	104	-	-	-	-	-
PEG 20000	-	-	700	350	175	1000
PEG 3000	-	350	-	-	-	-
Total weight (mg)	2010	2000	2000	2000	2000	2000
PEG: Alginate	-	1:1.43	1:0.71	1:1.43	1:2.86	1:0.5
Mouthfeel	Very sticky in mouth + tooth- packing	Satisfac- tory for not sticking	Not sticking or tooth- packing. Slightly oily/creamy	Drying initially, slightly gritty. Then creamy. Not sticky	Creamy, not sticky	Quick disper- sing. Very clean in the mouth i.e. not sticky or tooth- packing

COMPARATIVE EXAMPLE 2 AND EXAMPLE 8

Tablets produced by the method set out below were then evaluated for their mouthfeel.

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Ingredient	Example	
	Comparative 2	8
	mg/tablet	mg/tablet
Sodium alginate LFR5/60	250.00	250.00
Sodium bicarbonate	133.50	133.50
Calcium carbonate	80.00	80.00
Mannitol	607.75	432.75
Polyethylene Glycol 20000	0.00	175.00
Flavour 1	5.50	5.50
Flavour 2	1.10	1.10
Sweetener 1	5.50	5.50
Sweetener 2	1.65	1.65
Magnesium stearate	15.00	15.00
Tablet weight	1100mg	1100mg

Processing

Batch size produced 550g

- 10 1. Blend together ingredients except magnesium stearate for 5 minutes using a Turbula T2C tumble mixer.
2. Add the magnesium stearate and blend for a further 2 minutes.
3. Compress into tablets using the Riva Piccola tablet
- 15 press fitted with 16mm FBE punches.

Tableting of the composition of Comparative Example 2 that did not contain PEG was poor, with evidence of lamination and capping.

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The organoleptic properties of these tablets were assessed in the laboratory:

Example	Toothpacing	Mouthfeel	Taste	After taste	Overall
Example 8	Very slight	Drier, crisper. Tablet broke up quickly.	Pleasant, mint	None	OK - acceptable
Comparative 2	Worst of all batches	Drying, cloying pasty, chewy & sticky	Pleasant, mint	None	Poor - unacceptable

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To check for raft formation properties and the appearance of the rafts, four crushed tablets (total 1g sodium alginate) were mixed with 20ml of water and poured into a 250ml beaker containing 150ml 0.1M HCl at 37°C. The ability to form a coherent foamy floating gel "raft" on the surface of the acid over 30 minutes was observed.

In both cases a floating raft was rapidly formed. This was continuous across the beaker surface and was resistant to rupture. No difference was observed between the two formulations.

Addition of PEG to the composition therefore has a significant effect on the mouthfeel of the product

without affecting the ability to form a reflux-suppressing raft.

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EXAMPLE 9

Tablets containing the following components were prepared.

10	Sodium aliginate LFR5/60	250.00 mg
	Sodium bicarbonate	133.50 mg
	Calcium carbonate	80.00 mg
	Mannitol	516.50 mg
	Polyethylene Glycol 20000	30.00 mg
15	Crospovidone	55.00 mg
	Mint Flavour	10.00 mg
	Sweetener	10.00 mg
	Magnesium stearate	15.00 mg
	Tablet weight	1100 mg

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Process**1. Granulate components**

- 25 1.1 Add Sodium alginate LFR5/60, Sodium bicarbonate, Calcium carbonate, and Polyethylene Glycol 20000 to food processor Bowl (Magimix 3000 mixer fitted with large bowl).
- 30 1.2. Turn on processor and blend the powders for 2 minutes.

1.3 Granulate by spraying in water until a wet mass begins to form (approximately 70-110g water).

1.4 Dry the granules in a fluid bed drier (Aeromatic
5 Strea 1) at 40°C inlet air temperature.

1.5 screen the dried granules using Quadro Comil mill fitted with a 457µm screen.

10 1.6 sieve the granules through a 850µm sieve

2. Tableting mix

2.1 Take the granules and the appropriate amount of the
15 remaining ingredients except the magnesium stearate and tumble mix for 5 minutes.

2.2 Add the magnesium stearate and tumble mix for a further 2 minutes.

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3. Tableting

3.1 Tablet the resulting tablet blend using the Riva Piccola bench top rotary tablet press fitted with 16mm FBE punches.

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It was found that wet granulation of the components with the PEG enabled a reduced amount of PEG to be used as compared with the dry granulation of Example 8, while still retaining an acceptable mouthfeel.

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Example 10

Tablets were prepared from the following compositions, using the process described in Example 9.

5		
	Sodium alginate LFR5/60 (sorbitol free)	500.00mg
	Potassium bicarbonate, medium granular	100.00mg
	Calcium carbonate	100.00mg
	Polyethylene glycol 20,000	60.00mg
10	Mannitol	1260.00mg
	Crospovidone	110.00mg
	Mint flavour	20.00mg
	Sweetener	20.00mg
	Magnesium stearate	30.00mg
15	Total	2200.00mg

The tablets were produced to a weight of 500mg using 22mm flat bevel edge tooling.

20 These tablets gave satisfactory mouthfeel and raft formation and texture were at least as good as those of Example 9.

Example 11

25 Example 10 was repeated but using the following compositions:

	Sodium Alginate LFR 5/60	250g
	Sodium bicarbonate	133.5g
30	Calcium carbonate	80g
	PEG 20,000	30g
	Mannitol	571.5g
	Mint flavour	10g

Sweetener	10g
Magnesium stearate	15g

The tablets produced were considered to have a better
 5 mouthfeel than those of Example 10, even though they did
 not contain Crospovidone.

Examples 12 to 17

10 Tablets were prepared from the following compositions:

Ingredient						
	12	13	14	15	16	17
	mg/ tablet	mg/ tablet	mg/ tablet	mg/ tablet	mg/ tablet	mg/ tablet
Sodium alginate LFR5/60	250.00	250.00	250.00	250.00	250.00	250.00
Sodium bicarbonate	50.00	250.00	50.00	133.00	133.00	50.00
Calcium carbonate	25.00	10.00	100.00	20.00	80.00	100.00
Polyethylene Glycol 20000	175.00	175.00	175.00	175.00	-	-
Polyethylene Glycol 3000	-	-	-	-	175.00	175.00
Crospovidone	1.10	1.10	1.10	1.10	1.10	1.10
Flavour	5.50	5.50	5.50	5.50	5.50	5.50
Sweetener	1.65	1.65	1.65	1.65	1.65	1.65
Magnesium stearate	15.00	15.00	15.00	15.00	15.00	15.00
Mannitol	Qs	qs	qs	qs	qs	qs
Tablet weight	1100mg	1100mg	1100mg	1100mg	1100mg	1100mg

Example 18

Tablets were prepared from the following compositions:

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Ingredient	mg/tablet
Sodium alginate	500.00
Potassium bicarbonate	100.00
Calcium carbonate	100.00
Polyethylene glycol 20,000	60.00
Mannitol	1370.00
Flavouring	20.00
Sweetener	20.00
Magnesium Stearate	30.00
Total	2200.00

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CLAIMS

1. A solid, ingestible composition comprising:
 - a. an alginate;
 - 5 b. a bicarbonate and/or carbonate; and
 - c. a C₂-C₅ polyol or poly(C₂-C₅ alkylene glycol) having a molecular weight of at least 6,000.
2. A composition according to claim 1 wherein the
10 polyalkylene glycol is polyethylene glycol (PEG).
3. A composition according to any one of the preceding claims wherein the alginate is sodium alginate.
- 15 4. A composition according to any one of the preceding claims wherein the bicarbonate is sodium bicarbonate.
5. A composition according to any one of the preceding claims wherein the carbonate is calcium carbonate.
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6. A composition according to any one of the preceding claims which is in the form of a tablet.
7. A composition as defined in any one of the preceding
25 claims for use in a method of treatment of the human or animal body by therapy.
8. A composition as defined in any one of claims 1 to 6 for use in the treatment of reflux oesophagitis,
30 gastritis, dyspepsia or peptic ulceration or for use as a sustained releasing or targeted delivery composition.

9. Use of a composition as defined in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for use as a sustained releasing or
5 targeted delivery composition.

10. Use of a composition s defined in any one of claims 1 to 6 for the treatment of reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for use as a
10 sustained releasing or targeted delivery composition.

11. A method of treating reflux oesophagitis, gastritis, dyspepsia or peptic ulceration or for sustained releasing or targeting a delivery composition, which comprises
15 orally administering to a subject in need thereof or liable to need an effective amount of a composition as defined in any one of claims 1 to 6.

12. A process for preparing a composition as defined in
20 any one of claims 1 to 6 which comprises mixing together the alginate, the bicarbonate and/or carbonate and the polyol or polyalkylene glycol.

13. A process according to claim 12 wherein the
25 components are granulated together in a wet granulation process.

14. A process according to claim 13 wherein the weight ratio of the polyol or polyalkylene glycol to the
30 alginate is less than 0.25:1.