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(54) PHARMACEUTICAL COMPOSITION

(71) We, BIOREX LABORATORIES LIMITED, a British Company, of Biorex House, Canonbury Villas, London, N1 2HB, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with an improved pharmaceutical composition in dosage unit form.

As is well known, glycrrhetinic acid and several derivatives thereof have valuable anti-inflammatory properties and can be administered topically and orally for the treatment of inflammatory conditions.

In particular, the disodium salt of glycyrrhetinic acid hemisuccinate is extensively used for the treatment of ulcerative conditions of the stomach and duodenum. This disodium salt is described and claimed in our British Patent Specification No. 843,133 and a special form of dosage unit containing this disodium salt is described and claimed in our British Patent Specification No. 1,093,286.

Oesophagitis is a common inflammatory condition of the oesphagus. There are various causes of this inflammatory condition but, broadly speaking, it involves inflammation of the mucous membranes lining the oesphagus. Although glycyrrhetinic acid and several derivatives thereof are, as mentioned above, widely used in the treatment of inflammatory conditions, they have hitherto not been extensively used for the treatment of oesophagitis because of the difficulty of ensuring a sufficiently high concentration of the active material in the oesophageal region for a sufficient period of time.

It is, therefore, an object of the present invention to provide a pharmaceutical composition in dosage unit form containing glycyrrhetinic acid and/or an anti-inflammatory active derivative thereof which can be used for the treatment of oesophagitis.

Thus, according to the present invention, there is provided a pharmaceutical composition in dosage unit form which comprises (a) glycyrrhetinic acid and/or at least one anti-inflammatory active derivative thereof, in admixture with (b) at least one non-toxic carbonate and/or bicarbonate and with (c) alginic acid and/or at least one non-toxic salt thereof and/or with at least one carboxyalkylcellulose and/or at least one non-toxic salt thereof, in the proportions hereinafter specified.

When the alginic acid and/or carboxyalkylcellulose component is dispersed in water, a colloidal solution is formed which is very stable. The presence of a carbonate or bicarbonate results in the evolution of carbon dioxide when contacted by an acidic medium, such as is found in the stomach and lower part of the oesophagus. The result is, therefore, that the colloidal solution foams up and floats on top of the contents of the stomach. As a result of the normal reflux from the stomach into the oesophagus, the lower part of the oesophagus fills with a foam which remains *in situ* for a long period of time, this having been observed in clinical trials by endoscopy. This long-lasting foam in turn ensures that the glycyrrhetinic acid and/or active derivative thereof remains in contact with the inflammatory site for a long period of time and is thus able to exert a prolonged and beneficial effect. Furthermore, the foam results in an excellent distribution of the glycyrrhetinic acid and/or derivative thereof, either in the form of a solution or of a very finely-divided dispersion, which, in turn, promotes absorption and adsorption thereof at the inflammatory site.

When the alginic acid is used in the pharmaceutical composition according to the present invention in the form of a salt, the preferred salt is the sodium or potassium salt.

The preferred carboxyalkyl celluloses used according to the present invention contain up to 3 carbon atoms in the alkyl radical, for example carboxymethyl cellulose, and the non-toxic salts thereof, for example, sodium carboxymethyl cellulose.

Any non-toxic and compatible carbonate or bicarbonate can be used, the preferred compounds being sodium carbonate, sodium bicar-

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bonate, potassium carbonate, potassium bicarbonate, calcium carbonate and magnesium carbonate.

Apart from glycyrrhetinic acid *per se*, the pharmaceutical composition according to the present invention can also contain known derivatives of glycyrrhetinic acid which inhibit damage to the mucosa of the alimentary tract. Examples of such derivatives of glycyrrhetinic acid include the esters, hemiesters and hemiester salts thereof, especially the disodium salt of glycyrrhetinic acid hemisuccinate (also known as carbenoxolone sodium) (see our British Patent Specifications Nos. 843,133; 1,022,968 and 1,032,710); the salts of glycyrrhetinic acid with non-toxic organic bases (see our British Patent Specifications Nos. 843,135 and 870,651); the salts of glycyrrhetinic acid and glycyrrhetinic acid hemiesters with bismuth, zinc or a metal of Group IIA, IIIA or VIII of the Periodic Table (see our British Patent Specification No. 950,777); the amides of glycyrrhetinic acid and of acylated glycyrrhetinic acid (see our British Patent Specifications Nos. 1,060,344 and 1,255,098), and the non-toxic metal salts of 3 - acetyl-glycyrrhetinic acid, for example aluminium 3 - acetyl - 18β - glycyrrhetinate.

The pharmaceutical composition according to the present invention is in the form of a dosage unit, preferably a tablet, which dosage unit can have a weight of, for example, from 0.20—5.0 g. and preferably of from 0.7 to 2.6 g. Each such dosage unit contains 1—100 mg. and preferably 10—50 mg. of glycyrrhetinic acid and/or at least one active derivative thereof, 1—50% by weight and preferably 10—40% by weight of alginic acid and/or of at least one non-toxic salt thereof and/or of at least one carboxyalkyl-cellulose and/or of at least one non-toxic salt thereof and 1—30% by weight and preferably 3—10% by weight of at least one non-toxic carbonate and/or bicarbonate.

If desired, the pharmaceutical composition according to the present invention can also contain up to 30% by weight and preferably 5—15% by weight of at least one antacid compound, i.e. a non-toxic compound which counteracts acidity either by neutralising or buffering acidity, for example, aluminium hydroxide, aluminium phosphate, dihydroxy-aluminium aminoacetate, magnesium hydroxide or magnesium trisilicate.

Furthermore, the pharmaceutical composition according to the present invention can contain conventional solid pharmaceutical diluents or carriers, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acid, gelatine, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). If desired, the composition can also comprise at least one flavouring and/or sweetening agent and can also contain or be coated with a colouring material.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

Tablet formulation	
carbenoxolone sodium	20 mg.
mannitol	400 mg.
alginic acid	200 mg.
sodium alginate	200 mg.
aluminium hydroxide, dried gel	80 mg.
sodium bicarbonate	70 mg.
magnesium trisilicate	20 mg.
magnesium stearate	12 mg.
gum acacia	35 mg.
peppermint oil	2 mg.
	1039 mg.

Example 2

Tablet formulation	
18β-glycyrrhetinic acid	10 mg.
mannitol	150 mg.
sucrose	150 mg.
alginic acid	150 mg.
sodium alginate	150 mg.
aluminium hydroxide, dried gel	80 mg.
sodium bicarbonate	70 mg.
magnesium trisilicate	20 mg.
magnesium stearate	10 mg.
gum acacia	30 mg.
peppermint oil	2 mg.
	822 mg.

Example 3

Tablet formulation	
carbenoxolone sodium	20 mg.
mannitol	400 mg.
carboxymethyl-cellulose	200 mg.
aluminium hydroxide, dried gel	80 mg.
sodium bicarbonate	70 mg.
magnesium trisilicate	20 mg.
magnesium stearate	12 mg.
gum acacia	35 mg.
peppermint oil	1 mg.
	838 mg.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition in dosage unit form comprising (a) 1—100 mg. of glycyrrhetinic acid and/or of at least one anti-inflammatory active derivative thereof, in admixture with (b) 1—50% by weight of alginic acid and/or of at least one non-toxic salt thereof and/or of at least one carboxyalkyl-cellulose and/or of at least one non-toxic salt thereof, (c) 1—30% by weight of at least one non-toxic carbonate and/or bicarbon-

bonate, potassium carbonate, potassium bicarbonate, calcium carbonate and magnesium carbonate.

Apart from glycyrrhetinic acid *per se*, the pharmaceutical composition according to the present invention can also contain known derivatives of glycyrrhetinic acid which inhibit damage to the mucosa of the alimentary tract. Examples of such derivatives of glycyrrhetinic acid include the esters, hemiesters and hemiester salts thereof, especially the disodium salt of glycyrrhetinic acid hemisuccinate (also known as carbenoxolone sodium) (see our British Patent Specifications Nos. 843,133; 1,022,968 and 1,032,710); the salts of glycyrrhetinic acid with non-toxic organic bases (see our British Patent Specifications Nos. 843,135 and 870,651); the salts of glycyrrhetinic acid and glycyrrhetinic acid hemiesters with bismuth, zinc or a metal of Group IIA, IIIA or VIII of the Periodic Table (see our British Patent Specification No. 950,777); the amides of glycyrrhetinic acid and of acylated glycyrrhetinic acid (see our British Patent Specifications Nos. 1,060,344 and 1,255,098), and the non-toxic metal salts of 3 - acetyl-glycyrrhetinic acid, for example aluminium 3 - acetyl - 18β - glycyrrhetinate.

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ate and (d) 0—30% by weight of at least one antacid compound.

2. A pharmaceutical composition according to claim 1, wherein said dosage unit has a weight of 0.20—5.0 g.

3. A pharmaceutical composition according to claim 2, wherein said dosage unit has a weight of 0.7—2.6 g.

4. A pharmaceutical composition according to any of the preceding claims, wherein the glycyrrhetinic acid and/or derivative thereof (a) is present in an amount of from 10—50 mg.

5. A pharmaceutical composition according to any of the preceding claims, wherein the alginic acid and/or carbalkoxy-cellulose component (b) is present in an amount of from 10—40% by weight.

6. A pharmaceutical composition according to any of the preceding claims, wherein the carbonate and/or bicarbonate component (c) is present in an amount of from 3—10% by weight.

7. A pharmaceutical composition according to any of the preceding claims, wherein the antacid compound (d) is present in an amount of from 5—15% by weight.

8. A pharmaceutical composition according to any of the preceding claims, wherein the glycyrrhetinic acid derivative is the disodium salt of glycyrrhetinic acid hemisuccinate.

9. A pharmaceutical composition according to any of the preceding claims, which additionally comprises at least one pharmaceutical diluent or carrier and/or at laest one flavouring agent and/or at least one sweetening agent and/or at least one colouring material.

10. A pharmaceutical composition according to claim 1, substantially as hereinbefore described and exemplified.

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