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(72) Inventors KENNETH BROWN and NEIL ARTHUR
STEVENSON



(54) A NOVEL FORM OF DISODIUM CROMOGLYCAT

(71) FISON'S LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London W1X 0AH, 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:—

This invention relates to disodium cromoglycate in a novel form and to a novel pharmaceutical formulation containing disodium cromoglycate.

Disodium cromoglycate has for a number of years been used in admixture with lactose as a powder for the inhalation therapy of asthma. For such use the disodium cromoglycate normally contains between about 8 and 10% by weight of water; disodium cromoglycate containing this proportion of water being stable in contact with air of normally encountered humidities.

We have now found that disodium cromoglycate containing smaller proportions of water has certain advantageous properties.

Thus according to the invention there is provided disodium cromoglycate containing less than 3% by weight of water.

The disodium cromoglycate preferably contains less than 2%, and more preferably less than 1% by weight of water.

The disodium cromoglycate is preferably finely divided, e.g. having a mass median diameter of less than 20 microns, more preferably in the range 0.01 to 10 microns, and most preferably at least 50% by weight of the particles having a diameter of 2 to 5 microns.

Disodium cromoglycate according to the invention is strongly hygroscopic and precautions must therefore be taken during its preparation, storage and use to ensure (insofar as is possible) that the disodium cromoglycate does not pick up water from the environment.

Disodium cromoglycate according to the invention may be made from disodium cromoglycate containing a larger proportion of water by subjecting such disodium cromoglycate to heat, e.g. to temperatures of from about 110 to 150°C, to a vacuum, to the action of a

dessicant, or to a combination of such treatments. In particular we prefer to dry the disodium cromoglycate by subjecting it to a combination of heat and vacuum. It is normally difficult, without using exceptional and expensive techniques, to obtain disodium cromoglycate containing less than about 0.05% by weight of water, and we therefore prefer disodium cromoglycate according to the invention to contain more than 0.05% by weight of water.

Disodium cromoglycate according to the invention and of fine particle size may be made by micronising, milling or grinding coarser disodium cromoglycate of appropriate water content. However because of the hygroscopic nature of the disodium cromoglycate and because of the electrostatic effects associated with mechanical working of the dry disodium cromoglycate we prefer to remove the water after the disodium cromoglycate has been reduced to the desired particle size.

Disodium cromoglycate according to the invention finds use in pharmaceutical formulations and in particular in pressure pack formulations suitable for dispensing powdered disodium cromoglycate for inhalation.

Thus according to a further feature of the invention we provide a pharmaceutical composition comprising disodium cromoglycate, the total formulation containing less than 1.0%, preferably less than 0.5%, more preferably less than 0.2% and most preferably less than 0.1% by weight of water.

More specifically we provide a pharmaceutical composition comprising from 1 to 20% by weight of finely divided disodium cromoglycate, and a liquified propellant, the composition containing less than 4% by weight of water.

We prefer the composition to contain from 2 to 12% and more preferably from 4 to 7% by weight of disodium cromoglycate.

The composition is preferably substantially anhydrous. We have found that, in general, use of dried disodium cromoglycate in the composition enables freer and easier working of the valve, better dispersion from the valve, and

less loss of propellant when the composition has been filled into pressurised packs. We prefer the percentage of water in the formulation expressed as a percentage by weight of the disodium cromoglycate to be less than 2.

5 The liquified propellant medium, and indeed the total formulation is preferably such that the disodium cromoglycate does not dissolve therein to any substantial extent.

10 The liquified propellant is preferably a gas at room temperature (65°F) and atmospheric pressure (760 mm of mercury), i.e. it should have a boiling point below 65°F at atmospheric pressure. The liquified propellant should also be non-toxic. Among the suitable liquified propellants which may be employed are alkanes containing up to five carbon atoms, e.g. butane or pentane, or a C1 to 6 alkyl chloride, e.g. methyl, ethyl or propyl chlorides. The most

20 suitable liquified propellants are the fluorinated and fluorochlorinated C1 to 3 alkanes such as are sold under the Registered Trade Mark 'Freon'. Mixtures of the above mentioned propellants may suitably be employed. The preferred fluorinated C1 to 3 alkanes contain not

25 more than two carbon atoms and at least one fluorine atom. The preferred halogenated alkanes may be represented generally by the formula $C_mH_nCl_yF_z$, wherein m is an integer less than 3, n is an integer or zero, y is an

30 integer or zero, and z is an integer, such that $n+y+z=2m+2$. Examples of these propellants are dichlorodifluoromethane ('Freon 12'), 1,2-dichlorotetrafluoroethane ('Freon

35 114') $CClF_2$, $CClF_3$, trichloromonofluoromethane ('Freon 11'), dichloromonofluoromethane ('Freon 21'), monochlorodifluoromethane ('Freon 22'), trichlorotrifluoroethane ('Freon 113') CCl_3F , CF_3Cl , and mono-

40 chlorotrifluoromethane ('Freon 13'). Propellants with improved vapor pressure characteristics may be obtained by using certain mixtures of these compounds, e.g. 'Freon 11' with 'Freon 12', or 'Freon 12' with 'Freon

45 114'. For example, dichlorodifluoromethane, which has a vapour pressure of about 70 pounds per square inch gauge and 1,2-dichloro-1,1,2,2-tetrafluoro-ethane ('Freon 114'), with a vapour pressure of about 12 pounds per

50 square inch gauge at 70°F, may be mixed in various proportions to form a propellant having a desired intermediate vapour pressure. We prefer compositions which do not contain trichloromonofluoromethane.

55 It is desirable that the vapour pressure of the propellant employed be between 35 and 70, and preferably between 50 and 65 pounds per square inch gauge at 70°F. A one-component propellant can give a composition with

60 gauge pressures in the range of 55 to 65 pounds per square inch at 70°F, which are usable safely with metal containers. Two-component propellants, e.g. certain mixtures of 'Freon 12' and 'Freon 11', have been found

65 to give gauge pressures in the range of 20 to

40 pounds per square inch at 70°F, which are usable safely with specially reinforced glass containers.

The composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a solid anionic surface active agent selected from alkali metal, ammonium and amine salts of dialkyl sulphosuccinate, where the alkyl groups have 4—12 carbon atoms, and alkylbenzene sulphonic acid where the alkyl group has 8—14 carbon atoms. It is preferred to use the solid anionic surface active agent in the form of the sodium salt, and this comprises desirably compounds of formula $ROOCCH_2CH(SO_3Na)COOR$ where R represents butyl, iso-butyl, octyl or nonyl, or the sodium salt of dodecylbenzenesulphonic acid or of decylbenzenesulphonic acid.

The preferred solid anionic surface active agent is sodium dioctyl-sulphosuccinate.

The amount of the surface active agent required is related to the solids content of the suspension and to the particle size of the solids. In general it is only necessary to use 5—15%, and preferably 5—8%, of the solid anionic surface active agent by weight of the solids content of the suspension. We have found that, under certain conditions, use of a solid anionic surface active agent gives a better dispersion of medicament when the composition is released from a pressurised pack than does the use of a liquid non-ionic surface active agent.

When a liquid, non-ionic surface-active agent is employed it should have an hydrophile-lipophile balance (HLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface-active properties of a surface-active agent. The lower the HLB ratio, the more lipophilic is the agent, and conversely, the higher the HLB ratio, the more hydrophilic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W. C. Griffin in the Journal of the Society of Cosmetic Chemists, Vol. 1, No. 5, pages 311—326 (1949). Preferably the surface-active agent employed should have an HLB ratio of 1 to 5. It is possible to employ mixtures of surface-active agents, the mixture having an HLB ratio within the prescribed range.

Those surface-active agents which are soluble or dispersible in the propellant are effective. The more propellant-soluble surface-active agents are the most effective.

The surface-active agent should of course be non-irritating and non-toxic.

We prefer the liquid non-ionic surface-active agent to comprise from 1 to 7, and more preferably from 4 to 6%, by weight of the total composition. Such compositions tend to be more physically stable on storage.

Among the liquid non-ionic surface-active

agents which may be employed are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, oleostearic and oleic acids with a aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the Registered Trade Mark 'Spans') and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides, e.g. olive oil, may be employed. The preferred liquid non-ionic surface-active agents are the oleates of sorbitan, e.g. those sold under the Registered Trade Marks 'Arlacel C' (Sorbitan sesquioleate), 'Span 80' (Sorbitan monooleate) and 'Span 85' (Sorbitan trioleate). Specific examples of other liquid non-ionic surface-active agents which may be employed are sorbitan monolaurate, polyoxyethylene sorbitol tetraoleate, polyoxyethylene sorbitol pentaoleate, and polyoxypropylene mannitol dioleate. A solid non-ionic surface active agent which may be mentioned is lecithin, e.g. soya lecithin, a vegetable lecithin extracted from soya beans, but lecithin is not preferred.

Undesirable separation of the suspension may be avoided by the introduction of a sufficient quantity of an additional auxiliary finely divided solid of density greater than that of the liquid phase. The auxiliary solid should be compatible with the other ingredients and insoluble in the propellant. For example, we may use an inorganic compound such as sodium sulfate, calcium chloride or sodium chloride. We may also use an organic material such as powdered lactose or sucrose. The auxiliary solid should of course be non-toxic and non-irritant. The particle size of the auxiliary solid should be of the same order of magnitude as the disodium cromoglycate. The auxiliary powder may also function as a desiccant as in the case of anhydrous sodium sulfate or calcium chloride. The desired proportion of the auxiliary solid can be calculated using well known techniques.

It has also been found that the inclusion of a minor amount of an alkyl halide quaternary salt of pyridine in which the alkyl has 10 or more carbon atoms, or an equivalent thereof, can help to overcome undesirable caking or deposition. Higher alkyl halide quaternary salts of substituted pyridines having one or more substituents, for example C1 to 6 alkyl, on the pyridine ring are, for the purposes of this specification, the full equivalent of higher alkyl halide quaternary salts of pyridine. Among particularly useful higher alkyl halide quaternary salts of pyridine and their equivalents are myristyl-gamma-picolinium chloride, cetyl pyridinium bromide and cetyl pyridinium chloride. Such higher alkyl halide quaternary salts of pyridine may, if desired, be used in

the form of their monohydrates. The compositions preferably contain between 0.01 and 1 percent by weight of the higher alkyl halide quaternary salt of pyridine or an equivalent thereof.

The composition may also contain a suitable desiccant independent of the auxiliary solid, e.g. up to about 100 mg of anhydrous calcium sulphate or silica gel per 10 ml of composition.

The composition may contain other medicaments in addition to the disodium cromoglycate. For example the composition may contain a bronchodilator such as ephedrine, isoprenaline or a suitable salt thereof. The composition preferably contains between 0.1 and 1.0% by weight of the bronchodilator.

The composition may also contain an antioxidant, e.g. ascorbic acid, preferably in a proportion of from 0.5 to 2.0% by weight. In addition the composition may contain a sufficient quantity of a suitable flavour. We prefer compositions which do not contain ethanol.

We prefer packages containing from 8 to 30 ml of composition, e.g. a conventional aerosol pressure pack of 10 ml. The pack preferably has a valve adapted to deliver unit dosages of composition of between 0.025 and 0.25 mls of composition. The container may also contain a ball bearing to assist in the prevention of caking within the container.

The compositions of the invention may be made by mixing the various components at a temperature and pressure at which the propellant is in the liquid phase and the disodium cromoglycate is in the solid phase.

In producing the compositions and packages of the invention, a container equipped with a valve is filled with a propellant containing the finely-divided disodium cromoglycate in suspension. A container may first be charged with a weighed amount of dry disodium cromoglycate which has been ground to a predetermined particle size, or with a slurry of powder in the cooled liquid propellant. Alternatively and preferably the disodium cromoglycate and the surface-active agent are triturated or homogenized first into a uniform paste; for instance, by a ball mill. The homogenization may be carried out in the presence of a suitable liquid e.g. ethanol, to prevent agglomeration of the particles. This paste is then dispersed in the cooled liquefied propellant. This procedure fosters uniform wetting of the powder particles. A container may also be filled by introducing powder and propellant by the normal cold filling method, or a slurry of the powder in that component of the propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. On operating the valve, the powder will be dispensed in a stream of propellant, which will vaporize providing an aerosol of dry pow-

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der. Throughout the preparation of the product care is desirably exercised to minimise the absorption of moisture. This may be accomplished by operating in a dehumidified atmosphere using only dry materials and equipment. Under normal operating conditions one expects from 50 to 100 ppm of moisture to be incorporated in the composition during filling.

When it is necessary to employ an auxiliary solid or powder to prevent surface deposit or caking, it is desirably introduced into the composition at the time that powdered active solids are introduced. Alternatively, the auxiliary solid can be added to the composition after pre-wetting it with the surface-active agent or propellant.

The compositions of the invention may be used in the treatment of a number of allergic conditions in mammals, e.g. the inhalation treatment of allergic conditions of the airways, such as asthma or allergic rhinitis (hay fever). The treatment is preferably by oral or nasal inhalation and is preferably treatment of man.

Disodium cromoglycate is sometimes known as sodium cromoglycate or cromolyn sodium and is the disodium salt of 1,3-bis(2-carboxy-chromon-5-yloxy)-propan-2-ol.

The invention is illustrated, but in no way limited by the following Examples in which the parts and percentages are by weight.

Example 1.

Methods of preparation.

- (A) Dissolve the surface-active agent(s) in the trichloromonofluoromethane and add the micronised disodium cromoglycate (containing less than 1.0% by weight water). Disperse by using a high-shear mixer or a homogeniser. Cool to -50°C and add the 1,2-dichlorotetrafluoroethane and dichlorodifluoromethane also cooled to -50°C . Remix, cold fill into suitable cans, apply valves and crimp.
- (B) Cool the 1,2-dichlorotetrafluoroethane to -15°C and dissolve the surface active agent(s) in it. Add the dried micronised disodium cromoglycate and mix with a high-shear mixer. Cool to -50°C , add the dichlorodifluoromethane cooled to -50°C and remix. Cold fill into suitable cans, apply valves and crimp.

Suitable formulations are shown in Table I in which the figures represent the percentages

by weight of the various ingredients.

The formulations have been found to be stable when stored for 3 months, to have a high LD_{50} in rats and to provide satisfactory dispersions of disodium cromoglycate.

Compositions 26 and 31 are preferred.

In comparative examples compositions 6, 16, 29, 30 and 31 were made up using both dried and undried disodium cromoglycate. When dried disodium cromoglycate was used the percentage of water in the formulation expressed as a percentage by weight of disodium cromoglycate was less than 2. When undried disodium cromoglycate was used the percentage of water, expressed on the same basis, was from 4 to 7.

Example 2.

(a) Drying of micronised disodium cromoglycate.

1. Using heat alone.

1 kg of micronised disodium cromoglycate at a moisture content of 5.8% w/w was spread in layers approximately 2 cm thick, and heated for 42 hours at 120°C . After removal from the oven, cooling under conditions preventing ready access to atmospheric moisture, and mixing, the moisture content was 0.35% w/w.

2. Using desiccant alone.

10 g of micronised disodium cromoglycate at a moisture content of 6.3% w/w was spread in a thin layer and placed in an enclosed container in which was also placed fresh phosphorus pentoxide, also in a thin layer. After 7 days, the moisture content of the micronised disodium cromoglycate had fallen to 0.13% w/w.

(b) Determination of moisture content of micronised disodium cromoglycate.

The water content of disodium cromoglycate may be determined by weight loss on drying or by Karl-Fischer titration.

(c) Micronising of disodium cromoglycate.

By the term 'micronised disodium cromoglycate' we mean disodium cromoglycate that has been subjected to a process of attrition in a fluid energy mill, for example that manufactured by CHRISPRO LIMITED, 3 ST. MARGARET'S STREET, CANTERBURY, KENT, ENGLAND.

TABLE I

No.	Micronised disodium chromoglycate	'Span' 85	Cetyl Pyridinium Chloride	Soya Lecithin	Sodium Diocetyl Sulphosuccinate	Propellant 11	Propellant 114	Propellant 12	Method of Preparation
1	1.47	1.00	0.05	—	—	10.00	13.12	74.36	A
2	1.43	2.00	—	—	—	24.14	24.14	48.29	A
3	2.86	1.50	0.08	—	—	23.89	23.89	47.78	A
4	2.93	4.00	—	—	—	10.00	12.46	70.61	A
5	5.87	2.50	—	—	—	10.00	12.25	69.38	A
6	5.71	5.00	0.25	—	—	22.26	22.26	44.52	A
7	11.43	3.50	—	—	—	21.27	21.27	42.53	A
8	11.73	5.00	0.25	—	—	10.00	10.95	62.07	A
9	1.43	—	—	0.50	—	24.52	24.52	49.03	A
10	2.86	—	—	1.00	—	24.04	24.04	48.06	A
11	5.71	—	—	2.00	—	23.07	23.07	46.15	A
12	11.43	—	—	2.00	—	21.64	21.64	43.29	A
13	1.43	—	—	—	0.20	24.59	24.59	49.19	A
14	1.43	—	—	—	0.10	24.62	24.62	49.23	A
15	2.86	—	—	—	0.40	24.19	24.19	48.36	A
16	2.86	—	—	—	0.20	24.24	24.24	48.46	A

1,562,901

21

TABLE I (Continued)

No.	Micronised disodium cromoglycate	'Span' 85	Cetyl Pyridinium Chloride	Soya Lecithin	Sodium Dioctyl Sulphosuccinate	Propellant 11	Propellant 114	Propellant 12	Method of Preparation
17	5.71	—	—	—	0.80	23.37	23.37	46.75	A
18	5.71	—	—	—	0.40	23.47	23.47	46.95	A
19	11.43	—	—	—	1.20	21.84	21.84	43.69	A
20	11.43	—	—	—	0.60	21.99	21.99	43.99	A
21	1.44	—	—	—	0.20	—	39.34	59.02	B
22	1.44	—	—	—	0.10	—	39.38	59.08	B
23	2.88	—	—	—	0.40	—	38.69	58.08	B
24	2.88	—	—	—	0.20	—	38.77	58.15	B
25	5.77	—	—	—	0.80	—	37.37	56.06	B
26	5.77	—	—	—	0.40	—	37.53	56.30	B
27	11.54	—	—	—	1.20	—	34.91	52.35	B
28	11.54	—	—	—	0.60	—	35.15	52.71	B
29	2.86	4.00	0.20	—	—	23.24	23.24	46.46	A
30	11.43	5.00	0.25	—	—	20.83	20.83	41.66	A
31	5.71	5.00	—	—	—	22.32	22.32	44.64	A



* C L M S *

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1,562,901

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WHAT WE CLAIM IS:—

1. Disodium cromoglycate containing less than 3% by weight of water.
2. Disodium cromoglycate containing less than 2% by weight of water.
3. Disodium cromoglycate containing less than 1% by weight of water.
4. Disodium cromoglycate according to any one of the preceding claims containing more than 0.05% by weight of water.
5. Disodium cromoglycate according to any one of the preceding claims and having a mass median diameter of less than 20 microns.
6. Disodium cromoglycate according to Claim 5 having a mass median diameter in the range 0.01 to 10 microns.
7. Disodium cromoglycate according to Claim 6, wherein at least 50% by weight of the particles have a diameter of 2 to 5 microns.
8. A pharmaceutical composition comprising disodium cromoglycate, the composition containing less than 1.0% by weight of water.
9. A composition according to Claim 8 containing less than 0.5% by weight of water.
10. A composition according to Claim 9 containing less than 0.2% by weight of water.
11. A composition according to Claim 10 containing less than 0.1% by weight of water.
12. A pharmaceutical composition comprising from 1 to 20% by weight of finely divided disodium cromoglycate, and a liquefied propellant, the composition containing less than 4% by weight of water.
13. A composition according to Claim 12 containing from 2 to 12% by weight of disodium cromoglycate.
14. A composition according to Claim 13 containing from 4 to 7% by weight of disodium cromoglycate.
15. A composition according to any one of Claims 12 to 14 comprising disodium cromoglycate according to any one of Claims 1 to 7.
16. A composition according to any one of Claims 13 to 16, wherein the disodium cromoglycate is not dissolved in the liquefied propellant.
17. A composition according to any one of Claims 12 to 16, wherein the liquefied propellant is an alkane containing up to five carbon atoms, or a C1 to 6 alkyl chloride.
18. A composition according to any one of Claims 12 to 16, wherein the liquefied propellant is a fluorinated or a fluorochlorinated C1 to 3 alkane.
19. A composition according to Claim 18, wherein the liquefied propellant comprises dichlorodifluoromethane, 1,2 - dichlorotetrafluoroethane, trichloromonofluoromethane or a mixture of two or more thereof.
20. A composition according to any one of Claims 12 to 19, wherein the vapour pressure of the propellant employed is between 35 and 70 pounds per square inch gauge at 70°F.
21. A composition according to any one of Claims 12 to 20 comprising a liquid or solid non-ionic surface active agent or a solid anionic surface active agent selected from alkali metal, ammonium and amine salts of dialkyl sulphosuccinate, where the alkyl groups have 4—12 carbon atoms, and alkylbenzene sulphonic acid where the alkyl group has 8—14 carbon atoms.
22. A composition according to Claim 21, wherein the surface active agent is sodium dioctyl-sulphosuccinate.
23. A composition according to Claim 21 or 22 comprising from 5 to 15% of solid anionic surface active agent by weight of the solids content of the formulation.
24. A composition according to Claim 23 comprising from 5 to 8% of solid anionic surface active agent by weight of the solids content of the formulation.
25. A composition according to Claim 21 comprising a liquid non-ionic surface active agent having a hydrophile-lipophile balance ratio of less than 10.
26. A composition according to Claim 25, wherein the surface active agent is sorbitan trioleate.
27. A composition according to Claim 25 or 26, wherein the liquid non-ionic surface active agent comprises from 1 to 7% by weight of the total composition.
28. A composition according to Claim 27, wherein the surfactant comprises from 4 to 6% by weight of the total composition.
29. A composition according to any one of Claims 12 to 28 comprising an alkyl halide quaternary salt of pyridine in which the alkyl has 10 or more carbon atoms.
30. A composition according to any one of Claims 8 to 29 containing a bronchodilator.
31. A package containing from 8 to 30 ml of a composition according to any one of Claims 12 to 30.
32. A package according to Claim 31 having a valve adapted to deliver between 0.025 and 0.25 mls of the composition.
33. Disodium cromoglycate according to Claim 1 and substantially as hereinbefore described in Example 2.
34. A composition according to Claim 12 and substantially as hereinbefore described in Example 1.
35. A method of making disodium cromoglycate according to any one of Claims 1 to 7, which comprises subjecting disodium cromoglycate containing a higher percentage of water to heat, to a vacuum, to the action of a desiccant or to a combination of such treatments.
36. A method of making a composition according to any one of Claims 12 to 30, which comprises mixing the various components at a temperature and pressure at which the propellant is in the liquid phase and the disodium cromoglycate is in the solid phase.

23



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1,562,901

8

37. A method according to Claim 36 and substantially as hereinbefore described in Example 1.
- 5 38. A composition according to Claim 12 when made by a method according to Claim 36 or 37.
39. A method according to Claim 35 and substantially as hereinbefore described in Example 2.

40. Disodium cromoglycate when made by a method according to Claim 35 or 39.

C. B. CRAIG,
Chartered Patent Agent,
Agent for the Applicants,
Per: Fisons Limited,
Fison House, Princes Street,
Ipswich, Suffolk, IP1 1QH.

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