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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Pharmaceutical Compositions

We, GEIGY (U.K.) LIMITED, a British Company, whose Registered Office address is Simonsway, Manchester 22, Lancashire, 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 relates to medicinal products and more particularly to pharmaceutical preparations in liquid form providing immediate and rapid release of the therapeutic agent.

Liquid pharmaceutical preparations containing combinations of ionisable therapeutic agents with ion-exchange resins are known which provide sustained medication by giving slow and even release of the therapeutic agent over a relatively long period of time, as a result of being acted upon by the normal contents of the gastro-intestinal tract. We have found that liquid pharmaceutical preparations containing 5 - (3 - dimethyl - aminopropyl) - 10,11 - dihydro - 5H - dibenz (b,f) azepine, hereinafter referred to as "imipramine base" and certain chemically similar non-ionisable polycyclic bases as hereinafter defined in combination with cation-exchange resins in the form of methacrylate polymers containing carboxyl groups and having a degree of cross-linkage of from 1% to 10% will provide immediate and rapid release of the therapeutic agent.

The term "non-ionisable polycyclic base" as used in this specification means imipramine base, chlorimipramine base, 10 - keto - imipramine base, 5 - (3 - methylaminopropyl) - 10,11 - dihydro - 5H - dibenz (b,f) azepine hereinafter referred to as "desimipramine base", and 4 - [3 - (5 - dibenzo [b,f] azepin-5 - yl) - propyl] - 1 - (2 - hydroxyethyl) - piperazine hereinafter referred to as "opipramol base".

According to the present invention there is provided a pharmaceutical preparation for oral administration comprising a suspension or dispersion, in a carrier liquid which is substantially free of ions or ionisable material, of a solid compound formed from a non-ionisable polycyclic base as hereinafter defined and a cation ion-exchange resin in the form of a methacrylate polymer containing carboxyl groups and having a degree of cross-linkage of from 1% to 10%.

Although any of the aforementioned non-ionisable polycyclic bases may be used, imipramine base is particularly preferred.

The base used in the preparation of the solid compound formed from the base and an ion-exchange resin is preferably in the form of a pharmaceutical grade free base. The base may, if desired, be set free from the corresponding salt by a conventional method such as solvent extraction after making alkaline or by passing through an anion-exchange column. The base is subsequently converted to the solid resin-drug compound by reacting with a cation-exchange resin.

The salts, from which the bases used in the present invention may be prepared, may be, for example, the hydrochlorides which are the active substances of pharmaceutical preparations, i.e. imipramine hydrochloride, chlorimipramine hydrochloride, 10 - keto - imipramine hydrochloride, desimipramine hydrochloride and opipramol dihydrochloride.

The anion-exchange resin used in the conversion of the salt to the base may be selected

[*Price 5s. 0d.*]

from a wide range of anion-exchange resins. Strong anion-exchange resins are particularly advantageous and there may be used, for instance, "DeAcidite FF (IP)" in the hydroxide form, "Amberlite IRA 400" or "Dowex 1" which are polystyrene type polymers containing quaternary ammonium groups and cross-linked with divinyl benzene. (DeAcidite, Amberlite and Dowex are Registered Trade Marks).

The cation-exchange resin used in the preparation of the resin-drug compound preferably has a degree of cross-linkage of from 2% to 6%. The particle size of the resin is preferably in the range of 1 to 150 microns, especially 5 to 80 microns. A wide range of cation-exchange resins may be used, for instance "Zeo-Karb 226" which is a polymethacrylic acid or "Amberlite IRC-50" which is a copolymer of methacrylic acid and divinyl benzene. ("Zeo-Karb is a Registered Trade Mark). The base may, for instance, be combined with the resin by agitating the resin with a solution of the base. Suitable solvents for the base include acetone/water mixtures and isopropanol/water mixtures.

The proportion of base to the resin may vary from 10% to 50% but is preferably from 20% to 30% on a dry weight to weight basis.

The base resin/drug compound is preferably in suspension in a liquid medium in which water is present as the greatest (by weight) single component. The proportion of base present in the liquid medium is preferably in the range of from 0.001 to 0.025 parts by weight per unit part by volume. Parts by weight shown herein bear the same relation to parts by volume as do kilograms to litres.

The liquid medium may contain adjuvants conventionally used such as sweeteners, flavours, colloid thickening agents, colours and preservatives. Examples of sweeteners that may be used include sucrose and sorbitol; examples of colloid thickening agents include methyl cellulose, tragacanth and alginates; examples of preservatives include methyl hydroxy benzoate and sorbic acid: and examples of colours include Amarant and Tartrazine.

The pharmaceutical preparations of the present invention give immediate and rapid release of the drug over a relatively short period of time.

The therapeutic agents as normally administered in the form of their hydrochloride salts are anaesthetic to the mouth but the liquid preparation of the present invention results in the obscuration of this anaethesia. The liquid preparation also obscures the bitter taste of these compounds. Further, the resin-drug compound is formed in a better yield by a quicker and easier method when using the free bases of the present invention.

The following Examples further illustrate the present invention.

EXAMPLE 1

An anion-exchange column was prepared by suspending 50.0 grams of "DeAcidite FF (IP)" anion-exchange resin, in the chloride form in 500 millilitres of distilled water and filling into a Pyrex column, ("Pyrex" is a Trade Mark), effective length 30 centimetres and 18 millimetres bore. The column was washed with 2 bed-volumes of 3% sodium hydroxide solution equal to 136 millilitres to convert the resin to the hydroxide form. The column was then washed with 2 litres of carbon dioxide-free distilled water to remove excess alkali followed by a final wash with 70% volume/volume ethanol in distilled water.

5.0 grams of imipramine hydrochloride were dissolved in 100 millilitres of 70% volume/volume ethanol in distilled water. This solution was allowed to flow slowly down the column, the flow being adjusted so that it emerged at the rate of 2 drops per second. It was then washed with 70% volume/volume ethanol in distilled water and 500 millilitres of solution and washings were collected. This volume contained all the imipramine as base. To this solution was added sufficient "Zeo-Karb 226" cation-exchange resin 200 mesh (B.S.S.) to produce a drug/resin compound containing 25% by weight drug based on the total weight of drug and resin. The resin was stirred in the solution for 1 hour to allow reaction between the solution of base and the carboxylic resin.

At the end of this time the drug-resin compound was filtered off, washed with distilled water until all solvent was removed. The compound may, if desired, be dried at a temperature not exceeding 40°C.

An imipramine Syrup was prepared by the following method:—

In a suitable container were placed 50 grams sorbitol syrup, 20 millilitres of water and to this was added 12.5 grams sucrose, 0.1 grams methyl parahydroxybenzoate and the mixture was stirred until dissolved with heating as necessary.

After cooling to 40°C., 0.8 grams powdered Tragacanth was added in small quantities at a time using a high dispersion stirrer, the stirring being continued for 2 hours. To this syrup was added 0.1 millilitres of flavouring compound and the mixture was stirred until homogeneous.

1.77 grams of the imipramine base resin/drug compound (calculated as dry weight) prepared above were added followed by sufficient water to produce 100 millilitres and the suspension was stirred until homogeneous.

EXAMPLE 2

400 grams of imipramine hydrochloride were

dissolved in 4 litres of water and adjusted to pH 8 by the addition of solid sodium bicarbonate. The liberated base was extracted by diethyl ether 600, 400 and 200 millilitres. The combined ether extracts were washed with water in 100 millilitre portions until the washings were free from chloride then dried with anhydrous sodium sulphate, filtered and the solvent removed by evaporation. The residue assayed 99.9% $C_{19}H_{24}N_2$.

250 grams of the free base were dissolved in 3.5 litres of 80% volume/volume acetone/water and stirred with the equivalent of 750 grams dry weight "Zeo-Karb 226" in the hydrogen form for 2 hours. The suspension was filtered and the residue washed with acetone and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 3

250 grams of desimipramine base were dissolved in 3.5 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 750 grams dry weight "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue was washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 4

250 grams of chlorimipramine base were dissolved in 3.5 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 750 grams dry weight of "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 5

50 grams of opipramol dihydrochloride were dissolved in 1 litre of water and made alkaline with 300 millilitres of an aqueous solution of sodium bicarbonate containing 20 grams of solid sodium bicarbonate. The base was precipitated and filtered off using a Buchner funnel. The precipitate was then dissolved in 500 millilitres of ethanol and reprecipitated by adding 2 litres of water and filtered off using a Buchner funnel. The precipitate was washed with water and dried overnight at room temperature. The residue assayed 100.1% as dihydrate $C_{23}H_{29}N_3O.2H_2O$.

25 grams of opipramol base was dissolved in 0.35 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 75 grams dry weight of "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially the same as that described in Example 1.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation for oral administration comprising a suspension or dispersion, in a carrier liquid which is substantially free of ions or ionisable material, of a solid compound formed from a non-ionisable polycyclic base as hereinbefore defined and a cation-exchange resin in the form of a methacrylate polymer containing carboxyl groups and having a degree of cross-linkage of from 1% to 10%.

2. A pharmaceutical preparation as claimed in Claim 1 wherein the solid compound is obtained from a base in the form of a pharmaceutical grade free base.

3. A pharmaceutical preparation as claimed in Claim 1 or Claim 2 wherein the solid compound is obtained from a base which has been set free from the corresponding salt.

4. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the solid compound is obtained from a base which has been set free from the corresponding hydrochloride salt.

5. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the solid compound is obtained from a base which has been set free from the corresponding salt by solvent extraction after making alkaline.

6. A pharmaceutical preparation as claimed in any of Claims 1 to 4 wherein the solid compound is obtained from a base which has been set free from the corresponding salt by passing through an anion-exchange resin column.

7. A pharmaceutical preparation as claimed in Claim 6 wherein the anion-exchange resin is a polystyrene type polymer containing quaternary ammonium groups and cross-linked with divinyl benzene.

8. A pharmaceutical preparation as claimed in any of claims 1 to 7 wherein the solid compound is obtained from a cation-exchange resin having a degree of cross-linkage of from 2% to 6%.

9. A pharmaceutical preparation as claimed in any of claims 1 to 8 wherein the solid compound is obtained from a cation-exchange resin having a particle size in the range of from 1 to 150 microns.

10. A pharmaceutical preparation as claimed in Claim 9 wherein the particle size of the cation-exchange resin is in the range of from 5 to 80 microns.

11. A pharmaceutical preparation as claimed in any one of Claims 1 to 10 wherein the solid compound is obtained from a cation-exchange resin which is a polymethacrylic acid.

12. A pharmaceutical preparation as claimed in any one of Claims 1 to 10 wherein the

dissolved in 4 litres of water and adjusted to pH 8 by the addition of solid sodium bicarbonate. The liberated base was extracted by diethyl ether 600, 400 and 200 millilitres. The combined ether extracts were washed with water in 100 millilitre portions until the washings were free from chloride then dried with anhydrous sodium sulphate, filtered and the solvent removed by evaporation. The residue assayed 99.9% $C_{19}H_{24}N_2$.

250 grams of the free base were dissolved in 3.5 litres of 80% volume/volume acetone/water and stirred with the equivalent of 750 grams dry weight "Zeo-Karb 226" in the hydrogen form for 2 hours. The suspension was filtered and the residue washed with acetone and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 3

250 grams of desimipramine base were dissolved in 3.5 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 750 grams dry weight "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue was washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 4

250 grams of chlorimipramine base were dissolved in 3.5 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 750 grams dry weight of "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially similar to that described in Example 1.

EXAMPLE 5

50 grams of opipramol dihydrochloride were dissolved in 1 litre of water and made alkaline with 300 millilitres of an aqueous solution of sodium bicarbonate containing 20 grams of solid sodium bicarbonate. The base was precipitated and filtered off using a Buchner funnel. The precipitate was then dissolved in 500 millilitres of ethanol and reprecipitated by adding 2 litres of water and filtered off using a Buchner funnel. The precipitate was washed with water and dried overnight at room temperature. The residue assayed 100.1% as dihydrate $C_{23}H_{29}N_3O.2H_2O$.

25 grams of opipramol base was dissolved in 0.35 litres of 70% volume/volume isopropanol/water and stirred with the equivalent of 75 grams dry weight of "Zeo-Karb 226" in the hydrogen form for 1 hour. The suspension was filtered and the residue washed with water and dried. A syrup was prepared from this resin-drug compound by a process essentially the same as that described in Example 1.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation for oral administration comprising a suspension or dispersion, in a carrier liquid which is substantially free of ions or ionisable material, of a solid compound formed from a non-ionisable polycyclic base as hereinbefore defined and a cation-exchange resin in the form of a methacrylate polymer containing carboxyl groups and having a degree of cross-linkage of from 1% to 10%.

2. A pharmaceutical preparation as claimed in Claim 1 wherein the solid compound is obtained from a base in the form of a pharmaceutical grade free base.

3. A pharmaceutical preparation as claimed in Claim 1 or Claim 2 wherein the solid compound is obtained from a base which has been set free from the corresponding salt.

4. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the solid compound is obtained from a base which has been set free from the corresponding hydrochloride salt.

5. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the solid compound is obtained from a base which has been set free from the corresponding salt by solvent extraction after making alkaline.

6. A pharmaceutical preparation as claimed in any of Claims 1 to 4 wherein the solid compound is obtained from a base which has been set free from the corresponding salt by passing through an anion-exchange resin column.

7. A pharmaceutical preparation as claimed in Claim 6 wherein the anion-exchange resin is a polystyrene type polymer containing quaternary ammonium groups and cross-linked with divinyl benzene.

8. A pharmaceutical preparation as claimed in any of claims 1 to 7 wherein the solid compound is obtained from a cation-exchange resin having a degree of cross-linkage of from 2% to 6%.

9. A pharmaceutical preparation as claimed in any of claims 1 to 8 wherein the solid compound is obtained from a cation-exchange resin having a particle size in the range of from 1 to 150 microns.

10. A pharmaceutical preparation as claimed in Claim 9 wherein the particle size of the cation-exchange resin is in the range of from 5 to 80 microns.

11. A pharmaceutical preparation as claimed in any one of Claims 1 to 10 wherein the solid compound is obtained from a cation-exchange resin which is a polymethacrylic acid.

12. A pharmaceutical preparation as claimed in any one of Claims 1 to 10 wherein the

solid compound is obtained from a cation-exchange resin which is a copolymer of methacrylic acid and divinyl benzene.

13. A pharmaceutical preparation as claimed in any one of the preceding claims wherein the solid compound is obtained by agitating the resin with a solution of the base.

14. A pharmaceutical preparation as claimed in Claim 13 wherein the solid compound is obtained by dissolving the base in an acetone/water mixture or an isopropanol/water mixture and agitating with the resin.

15. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the solid compound is obtained from the base and resin in a proportion of base to resin of from 10% to 50% on a dry weight to weight basis.

16. A pharmaceutical preparation as claimed in Claim 15 wherein the solid compound is obtained from the base and resin in a proportion of base to resin of from 20% to 30% on a dry weight to weight basis.

17. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the resin-drug compound is in suspension in a carrier liquid medium in which water is present as the greatest (by weight) single component.

18. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the proportion of base present in the liquid medium is in the range of from 0.001 to 0.025 parts by weight per unit part by volume.

19. A pharmaceutical preparation as claimed in any one of the preceding Claims wherein the liquid medium contains one or more sweeteners, flavours, colloid thickening agents, colours and preservatives.

20. A pharmaceutical preparation as claimed in Claim 1 when prepared in accordance with any of Examples 3 to 5.

21. A pharmaceutical preparation for oral administration comprising a suspension or dispersion, in a carrier liquid which is substantially free of ions or ionisable material, of a solid compound formed from imipramine base and a cation-exchange resin in the form of methacrylate polymer containing carboxyl groups and having a degree of cross-linkage of from 1% to 10%.

22. A pharmaceutical preparation as claimed in Claim 21 wherein the solid compound is obtained from imipramine base in the form of a pharmaceutical grade free base.

23. A pharmaceutical preparation as claimed in Claim 21 or Claim 22 wherein the solid compound is obtained from imipramine base which has been set free from the corresponding salt.

24. A pharmaceutical preparation as claimed in any of Claims 21 to 23 wherein the solid compound is obtained from imipramine base which has been set free from the hydrochloride.

25. A pharmaceutical preparation as claimed in any of Claims 21 to 24 wherein the solid compound is obtained from imipramine base which has been set free from the corresponding salt by solvent extraction after making alkaline.

26. A pharmaceutical preparation as claimed in any of Claims 21 to 24 wherein the solid compound is obtained from imipramine base which has been set free from the corresponding salt by passing through an anion-exchange resin column.

27. A pharmaceutical preparation as claimed in Claim 26 wherein the anion-exchange resin is a polystyrene type polymer containing quaternary ammonium groups and cross-linked with divinyl benzene.

28. A pharmaceutical preparation as claimed in any of claims 21 to 28 wherein the solid compound is obtained from a cation-exchange resin having a degree of cross-linkage of from 2% to 6%.

29. A pharmaceutical preparation as claimed in any of claims 21 to 28 wherein the solid compound is obtained from a cation exchange resin having a particle size in the range of from 1 to 150 microns.

30. A pharmaceutical preparation as claimed in Claim 29 wherein the particle size of the cation-exchange resin is in the range of from 5 to 80 microns.

31. A pharmaceutical preparation as claimed in any one of Claims 21 to 30 wherein the solid compound is obtained from a cation-exchange resin which a polymethacrylic acid.

32. A pharmaceutical preparation as claimed in any one of Claims 21 to 30 wherein the solid compound is obtained from a cation-exchange resin which is a copolymer of methacrylic acid and divinyl benzene.

33. A pharmaceutical preparation as claimed in any one of Claims 21 to 32 wherein the solid compound is obtained from the base and resin in a proportion of imipramine base to resin of from 10% to 50% on a dry weight to weight basis.

34. A pharmaceutical preparation as claimed in claim 33 wherein the solid compound is obtained from the base and resin in a proportion of imipramine base to resin of from 20% to 30% on a dry weight to weight basis.

35. A pharmaceutical preparation as claimed in any one of Claims 21 to 34 wherein the resin-drug compound is in suspension in a carrier liquid medium in which water is present as the greatest (by weight) single component.

36. A pharmaceutical preparation as claimed in any one of Claims 21 to 35

wherein the proportion of imipramine base present in the liquid medium is in the range of from 0.001 to 0.25 parts by weight per unit part by volume.

37. A pharmaceutical preparation as claimed in any one of Claims 21 to 36 wherein the liquid medium contains one or more sweeteners, flavours, colloid thickening agents, colours and preservatives.

38. A pharmaccutical preparation as claimed in Claim 21 when prepared in accordance with Example 1 or 2.

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