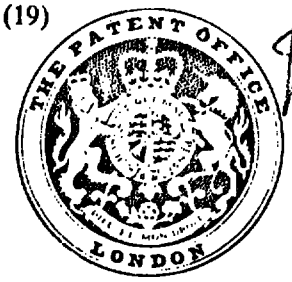
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(54) SUSTAINED RELEASE PHARMACEUTICAL COMPOSITION

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED Imperial Chemical House, Millbank, London SW1P 3JF 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 a sustained release pharmaceutical composition and more particularly it relates to a sustained release pharmaceutical composition containing propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

Propranolol hydrochloride is an important medicament which is widely used throughout the world. It is a β-adrenergic blocking agent which is mainly used for the treatment of angina pectoris, cardiac arrhythmias and hypertension. The chemical name for propranolol is dl-1-isopropylamino-3-(1-naphthoxy)-2-propanol. This compound and its acid-addition salts, and processes of manufacture thereof, are claimed in our United Kingdom patent No. 994,918. Furthermore, pharmaceutical compositions comprising at least one of these substances in admixture with a pharmaceutically-acceptable diluent or carrier are claimed in our United Kingdom patent No. 995,800. The present invention relates to a new sustained release pharmaceutical composition which, to the best of our knowledge and belief, is not disclosed in, nor rendered obvious by, said patent No. 995,800 nor elsewhere in the art.

According to the invention there is provided a sustained pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol or a pharmaceutically-acceptable acid-addition salt thereof in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose.

The term "spheroid" is well known in the pharmaceutical art, and means a spherical granule having a diameter of approximately 0.5 to 2mm. As a particularly suitable salt of propranolol there may be mentioned, for example, hydrochloride. A suitable microcrystalline cellulose is, for example, a the material sold as 'Avicel'-PH-101 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa, U.S.A.; 'Avicel' is a Trade Mark). According to one embodiment of the invention the uncoated spherioids may, for example, contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of microcrystalline cellulose.

A suitable form of ethylcellulose is that having a viscosity in the range of 5 to 100 cps at 20°C. (U.S. National Formulary XIII) (content of ethoxy groups 44 to 51% by weight), and more particularly a viscosity of 50 cps at 20°C. (content of ethoxy groups 48 to 49% by weight). A suitable form of hydroxypropyl methylcellulose is that having a viscosity in the range 3 to 100 cps at 20°C. (U.S. National Formulary XIII), and more particularly a viscosity of 6 cps at 20°C. The film coat may, for example, comprise 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose, and more particularly 90% by weight of ethylcellulose and 10% by weight of hydroxypropyl methylcellulose. In addition, the film coat may optionally contain up to 20% by weight of a plasticizer, for example a vegetable oil, for example castor oil, or glycerol, or a glyceryl ester of a fatty acid, for example glyceryl triacetate or glyceryl monoricinoleate. The film coat may comprise 5 to 15% by weight of the coated spheroids, and preferably 9 to 10% by weight thereof.

The sustained release composition of this invention may, for example, contain 100 to 200mg., and more particularly 160mg., of the medicament, for example propanolol hydrochloride.

The sustained release compositions of this invention may be manufactured by well known pharmaceutical manufacturing methods. For example, the spheroids may be manufactured on a conventional spheroniser in which a horizontal, rough-surfaced plate rotates inside a stationary vertical cylinder, and then film coated in conventional manner in a perforated coating drum, and finally the film coated spheroids filled into hard gelatine capsules using a conventional encapsulation machine.

The invention is illustrated but not limited by the following Example:-

EXAMPLE

Propranolol hydrochloride (60kg.) and microcrystalline cellulose (Avicel-PH-101; 40 kg.) were blended together in a 450 litre planetary mixer. Water (50kg.) was added, and the mixer was run for 10 minutes until a homogeneous, plastic mass was obtained. The mass was extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1mm. diameter.

The damp extrudates (in batches of 15 to 20kg.) were placed in a spheroniser in which the rotating disc (diameter 68cm.) rotated at 300 to 400 r.p.m. The rotation was continued for 20 minutes, and the resulting spheroids were then dried at 60°C. in a fluidised bed drier. The dried spheroids were passed over a 1.4mm. screen, and those which passed through were subjected to a 0.7mm. screen. The over-and under-sized spheroids were discarded.

Acceptable spheroids (100kg.) were placed in a perforated coating drum fitted with a 0.5mm. screen and rotating at 17 r.p.m. A film formulation consisting of ethylcellulose (5kg.) and hydroxypropyl methylcellulose (5kg.) dissolved in a mixture of dichloromethane (100 litre) and methanol (100 litre) was sprayed onto the rotating spheroids at a rate of 750ml. per minute using a standard airless spray system. The resulting film coated spheroids were passed over a 1.4mm. screen to remove any aggregates, and then filled into hard gelatine capsules using a conventional encapsulation machine, such that each capsule contained 160mg. of propranolol hydrochloride. There was thus obtained a sustained release composition containing propranolol hydrochloride.

WHAT WE CLAIM IS:-

1. A sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol or a pharmaceutically-acceptable acid-addition salt thereof in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose.

2. A composition as claimed in claim 1 in which the acid-addition salt of propranolol is the hydrochloride.

3. A composition as claimed in claim 1 or 2 in which the uncoated spheroids contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of non-water-swellable microcrystalline cellulose.

4. A composition as claimed in any one of claims 1 to 3 in which the film coat comprises 5 to 15% by weight of the coated spheroids.

5. A composition as claimed in claim 4 in which the film coat comprises 9 to 10% by weight of the coated spheroids.

6. A composition as claimed in any one of claims 1 to 5 in which the ethylcellulose has a viscosity in the range 5 to 100 cps at 20°C.

7. A composition as claimed in claim 6 in which the ethylcellulose has a viscosity of 50 cps at 20°C.

8. A composition as claimed in any one of claims 1 to 7 in which the hydroxypropyl methylcellulose has a viscosity in the range 3 to 100 cps at 20°C.

9. A composition as claimed in claim 8 in which the hydroxypropyl methylcellulose has a viscosity of 6 cps at 20°C.

10. A composition as claimed in any one of claims 1 to 9 in which the film coat comprises 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose.

11. A composition as claimed in claim 10 in which the film coat comprises 90% by weight of ethylcellulose and 10% by weight of hydroxypropyl methylcellulose.

12. A composition as claimed in any one of claims 1 to 9 in which the film coat contains up to 20% by weight of a plasticizer.

13. A composition as claimed in claim 12 in which the plasticizer is a vegetable oil, or glycerol, or a glyceryl ester of a fatty acid.

14. A composition as claimed in any one of claims 1 to 13 which contains 100 to 200 mg. of propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

15. A composition as claimed in claim 14 which contains 160 mg. of propranolol hydrochloride.

16. A sustained release pharmaceutical composition as claimed in claim 1 consisting of a hard gelatine capsule containing film

The sustained release composition of this invention may, for example, contain 100 to 200mg., and more particularly 160mg., of the medicament, for example propanolol hydrochloride.

The sustained release compositions of this invention may be manufactured by well known pharmaceutical manufacturing methods. For example, the spheroids may be manufactured on a conventional spheroniser in which a horizontal, rough-surfaced plate rotates inside a stationary vertical cylinder, and then film coated in conventional manner in a perforated coating drum, and finally the film coated spheroids filled into hard gelatine capsules using a conventional encapsulation machine.

The invention is illustrated but not limited by the following Example:-

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Acceptable spheroids (100kg.) were placed in a perforated coating drum fitted with a 0.5mm. screen and rotating at 17 r.p.m. A film formulation consisting of ethylcellulose (9kg.) and hydroxypropyl methylcellulose (1kg.) dissolved in a mixture of dichloromethane (100 litre) and methanol (100 litre) was sprayed onto the rotating spheroids at a rate of 750ml. per minute using a standard airless spray system. The resulting film coated spheroids were passed over a 1.4mm. screen to remove any aggregates, and then filled into hard gelatine capsules using a conventional encapsulation machine, such that each capsule contained 160mg. of propranolol hydrochloride. There was thus obtained a sustained release composition containing propranolol hydrochloride.

WHAT WE CLAIM IS:-

1. A sustained release pharmaceutical composition consisting of a hard gelatine capsule containing film coated spheroids, the said spheroids comprising, prior to coating, 40 to 65% by weight of propranolol or a pharmaceutically-acceptable acid-addition salt thereof in admixture with non-water-swellable microcrystalline cellulose, and the said spheroids having a film coat comprising ethylcellulose optionally together with hydroxypropyl methylcellulose.

2. A composition as claimed in claim 1 in which the acid-addition salt of propranolol is the hydrochloride.

3. A composition as claimed in claim 1 or 2 in which the uncoated spheroids contain 50 to 60% by weight of propranolol hydrochloride and 50 to 40% by weight of non-water-swellable microcrystalline cellulose.

4. A composition as claimed in any one of claims 1 to 3 in which the film coat comprises 5 to 15% by weight of the coated spheroids.

5. A composition as claimed in claim 4 in which the film coat comprises 9 to 10% by weight of the coated spheroids.

6. A composition as claimed in any one of claims 1 to 5 in which the ethylcellulose has a viscosity in the range 5 to 100 cps at 20°C.

7. A composition as claimed in claim 6 in which the ethylcellulose has a viscosity of 50 cps at 20°C.

8. A composition as claimed in any one of claims 1 to 7 in which the hydroxypropyl methylcellulose has a viscosity in the range 3 to 100 cps at 20°C.

9. A composition as claimed in claim 8 in which the hydroxypropyl methylcellulose has a viscosity of 6 cps at 20°C.

10. A composition as claimed in any one of claims 1 to 9 in which the film coat comprises 80 to 100% by weight of ethylcellulose and 20 to 0% by weight of hydroxypropyl methylcellulose.

11. A composition as claimed in claim 10 in which the film coat comprises 90% by weight of ethylcellulose and 10% by weight of hydroxypropyl methylcellulose.

12. A composition as claimed in any one of claims 1 to 9 in which the film coat contains up to 20% by weight of a plasticizer.

13. A composition as claimed in claim 12 in which the plasticizer is a vegetable oil, or glycerol, or a glyceryl ester of a fatty acid.

14. A composition as claimed in any one of claims 1 to 13 which contains 100 to 200 mg. of propranolol or a pharmaceutically-acceptable acid-addition salt thereof.

15. A composition as claimed in claim 14 which contains 160 mg. of propranolol hydrochloride.

16. A sustained release pharmaceutical composition as claimed in claim 1 consisting of a hard gelatine capsule containing film

coated spheroids, the spheroids containing, prior to coating, 60% by weight of propranolol hydrochloride in admixture with 40% by weight of non-water-swellable microcrystalline cellulose, the said spheroids having a film coat consisting of 90% by weight of ethylcellulose having a viscosity of 50 cps at 20°C. and 10% by weight of hydroxypropyl methylcellulose having a viscosity of 6 cps at 20°C., the film coat comprising 9 to 10% by weight of the coated spheroids, and each capsule containing 160 mg, of propranolol hydrochloride.

DR R ALLERTON,
Agent for the Applicants.

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* C L M S *

(9)

ERRATA

SPECIFICATION NO 1561204

Page 1, line 38, *after* sustained *insert* release

Page 1, line 54, *after* example, *insert* the

Page 1, line 55, *after* example, *delete* a

Page 1, line 61, *for* spherioids *read* spheroids

Page 2, line 4, *for* propanolol *read* propranolol

THE PATENT OFFICE
25 March 1980

Bas 75632/8