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(54) THIXOTROPIC FILLING MEDIUM FOR HARD GELATIN CAPSULES

(71) We, LILLY INDUSTRIES LIMITED, a British company of Henrietta House, Henrietta Place, London, W.1., 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 filling media for hard gelatin capsules, to methods of preparing such media, to filled capsules and to methods of filling capsules.

In current commercial pharmaceutical usage, gelatin capsules fall into two categories. There are soft gelatin capsules which are used to contain materials in semisolid, liquid or paste form, and hard gelatin capsules which are used to contain materials in powder form. Soft gelatin capsules suffer from the disadvantages that they require significantly more gelatin for encapsulation of a given dose of pharmaceutically active compound than hard gelatin capsules and that they are made and filled by contract manufacturers. Hard gelatin capsules are supplied by specialist manufacturers for filling by the producer of the material to be encapsulated. Quality control considerations favour capsule filling by the producer of the filling material and considerable increases in the price of gelatin favour the use of hard gelatin capsules. However, if hard gelatin capsules are used to contain materials other than in powder form there have been problems of leaking of capsule contents in handling which can only be overcome by time-consuming and cumbersome operations such as banding of the capsule after filling. Such operations add greatly to production costs.

It has now been surprisingly discovered that pharmaceutically active substances which are semisolid, liquid or paste-like in nature can be formulated with selected pharmaceutically inert carriers to provide a capsule filling medium which can be readily

introduced into hard gelatin capsule cases using existing types of machinery, but which remains within filled capsules with no problems of leakage in packing and handling of the capsules, without the necessity of banding or other modification of the filled capsule.

According to the present invention there is provided a method of filling a hard gelatin capsule with a pharmaceutically active substance which is liquid, semisolid or paste-like, which method comprises formulating said active substance into a thixotropic mixture with a pharmaceutically inert carrier and filling the capsule with said thixotropic mixture.

Further in accordance with the invention there is provided a filled capsule comprising a hard gelatin containing a mixture of a unit dose of a liquid, semi-solid or paste-like pharmaceutically active substance and at least one pharmaceutically inert carrier, said mixture being thixotropic.

It will be readily appreciated that the nature and quantities of the or each inert carrier will be chosen so as to produce the thixotropic property of the mixture and will depend upon the nature and quantity of the pharmaceutically active substance. For example, if the active substance is liquid and is highly potent so that a small quantity forms a unit dose, the inert carriers may be an inert oil together with a thickening agent chosen to confer thixotropic properties on the mixture. For an active substance in liquid form which is administered in high unit dose, the inert carrier may simply be a thickening agent chosen to confer thixotropic properties. The relative proportions of the constituents of the thixotropic mixtures should be such that the mixture will be sufficiently viscous not to leak from filled capsules over the whole range of storage temperatures to which the filled capsules may be exposed.

By the term "thixotropic mixture", as used

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herein, is meant a mixture, the rheological properties of which are such that the mixture has a relatively high viscosity under conditions of low stress but a decreased viscosity under conditions of high stress. As will be appreciated, the thixotropic nature of the mixture enables the mixture to be introduced into the capsule whilst in a state of low viscosity, whereafter, once in the capsule and under conditions of low stress, the mixture assumes a relatively high viscosity, thereby reducing leakage tendency.

Suitable thixotropic mixtures forming capsule filling media in accordance with the invention have been found to have viscosities in the range from 500 to 5000 centipoises, preferably 1000 to 3000, measured at 20°C at 450 r.p.m. on a Haake "Rotoviscometer" Model RV1, and surface tensions measured at 20°C by the well-known microscope cover slip method of greater than 20 dynes/cm², preferably greater than 30 dynes/cm².

Examples of suitable pharmaceutically active substances for use in the capsule filling media include materials which are normally semisolid such as clofibrate and methyl pentynol, and other liquid, semi-solid or paste-like substances which either singly or in combination are commonly formulated in soft gelatin capsules.

Examples of pharmaceutically inert carriers which are suitable for use in capsule filling media in accordance with the invention are fatty materials of vegetable origin, such as oil of theobroma and carnauba wax; vegetable oils, such as arachis oil, cotton seed oil, maize oil, olive oil, palm kernel oil and soya bean oil; hydrogenated vegetable oils; fatty materials of animal origin, such as spermaceti, beeswax and lanolin and its derivatives, hydrocarbons; ceresin; mineral oil; paraffin wax; C₁₂₋₁₈ fatty alcohols, such as cetyl alcohol and stearyl alcohol; C₁₂₋₁₈ fatty acids, such as lauric acid, myristic acid, palmitic acid and stearic acid; fatty acid esters, such as glyceryl stearate, isopropyl myristate and ethyl oleate; mixed esters which may be solid semi-synthetic glycerides, such as Witepsol (registered Trade Mark), Suppocire (registered Trade Mark), Massa Esterinum (registered Trade Mark) and Massupol (registered Trade Mark), or liquid semi-synthetic glycerides such as Miglyol 812 (registered Trade Mark) and Labrafils (registered Trade Mark); amides or alcoholic amides of fatty acids, such as Comperlan KD (registered Trade Mark) and Ciramide (registered Trade Mark); metallic stearates, such as a mixture of the di- and tri-stearates of aluminium; liquid or solid silicones, such as dimethylpolysiloxane; macrogols such as the Carbowaxes (registered Trade Mark); and silica derivatives such as bentonite, Veegum (registered Trade Mark), Cab-O-Sil (registered Trade Mark) and Aer-

osil (registered Trade Mark). The carrier is chosen so as to form a thixotropic mixture containing the pharmaceutically active substance.

The capsule filling media in accordance with the invention may be filled into hard gelatin capsules using standard automatic capsule filling machinery modified only in that the conventional powder dosing parts are replaced by a known form of semisolid filling head [e.g. oil/paste filling attachment available from Fratelli Zanasi S.p.A. and Höfliger and Karg (Bosch Gruppe) Verpackungsmaschinen] hitherto used for filling hard gelatin capsules prior to a banding operation.

The invention will be better understood from the following illustrative examples thereof.

EXAMPLE 1.

A Clofibrate formulation was introduced into size 0 hard gelatin capsules such that each capsule contained the following amounts of capsule filling medium constituents:

Arachis oil	— 270 mg.	
Beeswax	— 30 mg.	
Clofibrate	— 300 mg.	95

The capsule filling medium was prepared by heating the Arachis oil to 70°C, adding the beeswax, mixing thoroughly and allowing to cool with stirring. The Clofibrate was then added and the mixture was thoroughly stirred. The capsules were filled on an automatic filling machine having its powder dosing parts replaced by a semisolid filling head.

The capsules are stable when stored at 36°C for 6 months and no leakage of capsule contents is observed. The capsules release their contents in the stomach within ten minutes.

EXAMPLE 2.

A Clofibrate formulation was introduced into size 0 hard gelatin capsules such that each capsule contained the following amounts of capsule filling medium constituents:

Aerosol 200 (registered Trade Mark)	— 30 mg.	120
Clofibrate	— 500 mg.	

The Aerosil 200 was slowly added to the Clofibrate with stirring, and the capsules were filled as in Example 1.

EXAMPLE 3.

A cod liver oil formulation was introduced into size 0 hard gelatin capsules such that each capsule contained the following 130

amounts of capsule filling medium constituents:

- 5 Beeswax — 60 mg.
Cod liver oil — 600 mg.

10 The cod liver oil was heated to 70°C. The beeswax was then added with stirring and stirring was continued while the mixture was allowed to cool. The capsules were filled as in Example 1.

EXAMPLE 4.

15 A Vitamin A (Palmitate) formulation was introduced into size 4 hard gelatin capsules such that each capsule contained the following amounts of capsule filling medium constituents:

- 20 Vitamin A (Palmitate) — 50,000 i.u.
Arachis Oil — 100 mg.
Beeswax — 20 mg.

25 The capsule filling medium was prepared and the capsules filled by methods similar to those described in Example 1.

WHAT WE CLAIM IS:—

30 1. A method of filling a hard gelatin capsule with a pharmaceutically active substance which is liquid, semi-solid or paste-like, which method comprises formulating said active substance into a thixotropic mixture with a pharmaceutically inert carrier and filling the capsule with said thixotropic mixture.

40 2. A method according to claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples 1 to 4.

3. A hard gelatin capsule whenever filled by the method of claim 1 or 2.

45 4. A filled capsule comprising a hard gelatin capsule containing a mixture of a unit dose of a liquid, semi-solid or paste-like pharmaceutically active substance and at least one pharmaceutically inert carrier, said mixture being thixotropic.

50 5. A filled capsule according to claim 4, substantially as hereinbefore described.

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