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COMPLETE SPECIFICATION

Pharmaceutical Preparations and a Process for the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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 pharmaceutical preparations and a process for the manufacture thereof. More particularly, the invention is concerned with pharmaceutical preparations which contain as the essential active ingredient the therapeutically valuable hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz - [1,4]epine.

7 - Chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz - [1,4]-epine is a therapeutically active compound, being useful as a muscle relaxant, sedative and anticonvulsant. At first glance, it would appear that the formulation of this compound into a suitable oral liquid dosage form would pose no particular problem since the hydrochloric acid salt thereof is water-soluble. However, the water-soluble hydrochloric acid salt, like the free base, has a distinctive bitter, astringent taste. Even when diluted (for example, with syrup solution), the salt produces an unpleasant transient, biting irritation of the mouth mucosa. Hitherto, a palatable oral dosage form of this compound has not been available. The present invention serves to provide such dosage forms.

Accordingly, in one of its embodiments, the invention is concerned with dosage forms which provide all of the therapeutic value of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride and which, at the same time, are devoid of the unpleasant taste which is normally associated with conventional dosage forms which contain this salt.

In a preferred aspect, the invention is concerned with stable, non-bitter tasting and non-irritative suspensions which contain as the essential active ingredient the hydrochloride salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine.

It has been found in accordance with the present invention that when the water-soluble 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdia [1,4]epine hydrochloride is mixed at room temperature or at a temperature elevated above room temperature with an aluminium silicate or a magnesium aluminium silicate there is obtained a water-insoluble product which possesses all of the therapeutic activity of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride but which does not exhibit the objectional taste characteristics of that salt.

It will be appreciated that the hydrochloride salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz - [1,4]epine reacts to some extent with the aluminium silicate or magnesium aluminium silicate to form a new insoluble salt by replacement of the hydrochloride moiety with that of the aluminium silicate or magnesium aluminium silicate. The extent of reaction in any given case can be ascertained both from the colour of the reaction mixture and the chloride ion concentration therein.

Accordingly, the pharmaceutical preparations provided by the present invention comprise a reaction mixture of the hydrochloric acid salt of 7 - chloro - 1 - methyl -

[*Price 5s. 0d.*]

5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine with an aluminium silicate or a magnesium aluminium silicate in the presence of water; there being present in said reaction mixture a ratio of at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound.

The aluminium silicate employed in accordance with this invention is a purified product derived from montmorillonite. An aluminium silicate of this nature is available commercially from the Georgia Kaolin Company, USA, under the trade name ALBAGEL. Magnesium aluminium silicates which can be employed are the refined complex magnesium aluminium silicates obtained from natural sources and available commercially from the R. T. Vanderbilt Co. USA, under the trade name VEEGUM. However, while the present invention will be described herein with particular reference to the use of VEEGUM and ALBAGEL, it will be appreciated that the invention is equally operable when other aluminium or magnesium aluminium silicates are used.

The reaction products of this invention are readily prepared. In a preferred embodiment, the water - soluble 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride is first dissolved in water. This can be accomplished by adding the salt to distilled water and stirring same therein at room temperature or at an elevated temperature. In an especially preferred embodiment, the aqueous solution of the aforesaid benzdiaz[1,4]epine hydrochloride is obtained by adding the salt to and mixing it with water which has been heated to a temperature within the range of from 70°C to 85°C. In a second step, the aluminium silicate or magnesium aluminium silicate is added to, and stirred in, the aqueous solution obtained as described earlier. Throughout this step, the reaction mixture is maintained at a temperature of from 70°C to 85°C and it is stirred continuously until the reaction has been completed. While many factors will influence the time required to effect the desired reaction, it has been found that a product having the desired characteristics is obtained when the reactants are mixed at a temperature of from about 70°C to 85°C for a period of up to about one hour.

While the ratio of the aluminium silicate or magnesium aluminium silicate to 7 - chloro - 1 - methyl - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride is to some extent critical, it is nevertheless variable within certain limits. In general, at least about 9.0 parts by weight of the aluminium silicate or magnesium aluminium silicate should be provided for each part by weight of the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine compound used. Obviously, greater quantities of the aluminium silicate or magnesium aluminium silicate can be employed, if desired. However, no particular advantage is derived from the use of more than 60 parts by weight of the aluminium silicate or magnesium aluminium silicate for each part of the hydrochloric acid salt of the benzdiaz[1,4]epine. In preparing the preferred products of the invention from 12 to 33 parts by weight of the aluminium silicate or magnesium aluminium silicate are used for each part by weight of the 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride.

The quantity of water which is used in the aforementioned preferred embodiment for preparing the aqueous solution of the hydrochloride salt is not particularly critical. However, it will be appreciated that a sufficient quantity of water should be provided to completely dissolve the salt. In addition, the amount of water present in the system should be such that, when the aluminium silicate or magnesium aluminium silicate is added thereto, a free-flowing, easily stirrable reaction mixture is obtained. These objectives can be accomplished by using from 2.5 parts to 15 parts by weight of water for each part by weight of the aluminium silicate or magnesium aluminium silicate to be subsequently added to the solution.

The aqueous reaction system described in the preceding paragraphs can contain a preservative or a mixture of preservatives as an optional ingredient. The preservative or preservative mixture can be added to the water either before or after the solution therein of the 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride. Alternatively, the preservative or preservative mixture can be incorporated into the system after the formation of the water-insoluble reaction product. In general, any preservative which is water-soluble, nonionic stable under the reaction conditions and suitable for pharmaceutical use can be employed. However, in a preferred embodiment, the hydrochloride salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine is added to and dissolved in water which has dissolved therein effective amounts of the preservatives methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

The aqueous reaction products which are obtained in the preferred embodiment of this invention are used directly (i.e. without removing the water therefrom) in formulating liquid dosage forms (e.g. aqueous suspensions for oral administration). The manner in which the products are used for this purpose will be readily apparent. In general,

these liquid dosage forms can be prepared by any conventional procedure or technique using adjuvants and excipients normally used in formulating such dosage forms. For example, the liquid dosage forms of the invention can contain as adjuvants suitable suspending agents such as polyoxyethylene-sorbitan fatty acid esters (for example, polyoxyethylene - sorbitan monooleate and polyoxyethylene - sorbitan monolaurate), polyoxyethylene esters of fatty acids (for example, polyoxyethylene - (8) stearate and polyoxyethylene - (40) stearate), preservatives (for example, benzoic acid, methyl *p* - hydroxy - benzoate, propyl *p* - hydroxy - benzoate and sorbic acid), buffers (for example, lactic acid and citric acid), sweetening agents (for example, sugar or artificial sweetening agents), antifoaming agents, colouring agents and flavouring agents. While the quantity of the essential active ingredient present in the suspensions provided by this invention can vary widely, the preferred suspensions provide from 5 mg to 25 mg of the benzdiaz[1,4]epine compound per 5 ml.

The aqueous suspensions which are produced using the reaction products of this invention are noteworthy in several respects. Primarily, the suspensions have completely acceptable stability characteristics. If sedimentation occurs in prolonged storage, the suspensions can be reconstituted simply by shaking the container in which they are provided (e.g. a bottle) prior to use. This is of significant importance since it facilitates the administration of the drug in proper, safe and specified amounts. Furthermore, the suspensions produced from the present products are noteworthy in that they are completely palatable. They are non-irritating and they are devoid of the unpleasant taste which is associated with the various conventional oral dosage forms, including liquid dosage forms, of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride. This is exceedingly significant since it ensures the patient's acceptance of the therapeutically valuable medicament.

In the preceding paragraphs there has been described a preferred process for producing the products of this invention and the use of such products in formulating liquid dosage forms. It will be appreciated that the products can be prepared by other methods and that, whether produced by the preferred method or by some other method, they can be used in formulating dosage forms other than liquid dosage forms. For example, a water-insoluble non-bitter, non-irritating product can be obtained by mixing the water-soluble 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride with the aluminium silicate or magnesium aluminium silicate in the presence of a quantity of water which is substantially less than that used in the preferred embodiment described earlier. Thus, a completely satisfactory product is obtained by mixing the essential active ingredient and the aluminium silicate or magnesium aluminium silicate in the presence of a quantity of water which is sufficient to obtain a moist homogeneous mixture. The product thus obtained can be used directly (i.e. without first drying same) in producing an aqueous suspension or it can be dried and subsequently used in formulating a liquid oral dosage form (e.g. a suspension) or a solid oral dosage form (e.g. tablets or capsules). Furthermore, an aqueous product obtained according to the preferred embodiment can be dried, if desired, and subsequently used in formulating a liquid or solid oral dosage form.

The following Examples illustrate the invention:

EXAMPLE 1

0.105 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride were dissolved in 25.0 ml of distilled water in which 0.09 g of methyl *p* - hydroxy - benzoate and 0.02 g of propyl *p* - hydroxy - benzoate had previously been dissolved. The resulting solution was heated to, and maintained at, a temperature within the approximate range of from 80°C to 85°C. At this temperature, 2.5 g of magnesium aluminium silicate was added with stirring to the solution; the magnesium aluminium silicate used was the commercially available product which is marketed under the trade name VEEGUM NEUTRAL. The resulting mixture was stirred for *ca* 1 hour at a temperature within the approximate range of from 80°C to 85°C.

To the aqueous reaction product obtained as described in the preceding paragraph there were added 0.5 g of MYRJ 45 [polyoxyethylene - (8) stearate marketed by Atlas Chemical Industries, Inc.,—the word 'MYRJ' being a Registered Trade Mark] and 40.0 g of sucrose. There was then added a solution containing 4.0 ml of distilled water, 0.01 g of disodium ethylenediamine - tetraacetic acid dihydrate, 0.15 g of sodium hydroxide, 0.25 g of benzoic acid, 0.10 g of sodium cyclamate, 0.01 g of sodium saccharin, 21.0 g of sorbitol and 1.1 g of lactic acid. A mixture of 12.5 g of glycerine, 0.4 g of gum tragacanth and 8.0 ml of distilled water was subsequently added and to the resulting mixture there was finally added a dispersion containing 0.003 g of ANTIFOAM C (a silicone type antifoaming agent having a silicone content of 30%, marketed by Dow Corning Corporation) and 0.1 ml of

water. The pH of the mixture was then adjusted to within the range of from 3.7 to 4.0 by means of sodium hydroxide. Favouring materials were added as needed to the resulting suspension, then the suspension was diluted to a volume of 100 ml with distilled water and subsequently homogenised and deaerated.

Each 5 ml of the suspension thus obtained contained 5 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride. The suspension was completely palatable. It was non-irritating to the mouth mucosa and was devoid of the bitter, astingent taste which normally characterises suspensions containing 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride. Furthermore, the suspension exhibited excellent stability characteristics when allowed to stand at normal room temperatures.

Example 2

0.09 g of methyl *p* - hydroxy - benzoate and 0.02 g of propyl *p* - hydroxy - benzoate were dissolved in 25.0 ml of distilled water. 0.105 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride were added to the resulting solution and dissolved therein. The solution thus obtained was heated to a temperature within the approximate range of from 80°C to 85°C and at this temperature there were added, with stirring, 6.0 g of magnesium aluminium silicate (VEEGUM NEUTRAL). The resulting mixture was stirred at a temperature within the approximate range of from 80°C to 85°C for *ca* 1 hour.

55.0 g of sugar were added to, and dissolved in, the aqueous reaction product prepared as described in the preceding paragraph. To the solution there was then added a solution containing 3.0 ml of distilled water, 0.13 g of sodium hydroxide, 0.25 g benzoic acid, 0.01 g of disodium ethylenediamine - tetraacetic acid dihydrate. 21.0 g of sorbitol, 12.5 g of glycerine and 1.25 g of lactic acid and to the resulting mixture there was added a dispersion containing 0.0033 g of ANTIFOAM C and 0.1 ml of distilled water. Flavouring agents were then added as needed, following which the pH of the mixture was adjusted to *ca* 3.7 with sodium hydroxide. Sufficient distilled water was subsequently added to the product to bring the volume to 100 ml. The resulting suspension was finally homogenised and deaerated.

There was obtained a stable and palatable (i.e. non-bitter and non-irritating to the mouth mucosa) aqueous suspension containing 5 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz - [1,4]epine hydrochloride per 5 ml of suspension.

Example 3

0.09 g of methyl *p* - hydroxy - benzoate and 0.02 g of propyl *p* - hydroxy benzoate were dissolved in 25.0 ml of distilled water. 0.105 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride were added to the resulting solution and dissolved therein. The solution was then heated to a temperature within the approximate range of from 80°C to 85°C, following which 3.0 g of aluminium silicate were added with stirring (the aluminium silicate employed was a product available under the trade name ALBAGEL). The resulting mixture was then stirred at a temperature within the approximate range of from 80°C to 85°C for *ca* 1 hour.

To the aqueous reaction product obtained as described in the preceding paragraph, there were added 55.0 g of sugar followed by a solution containing 3.0 ml of distilled water, 0.13 g of sodium hydroxide, 0.25 g of benzoic acid, 0.1 g of disodium ethylenediamine-tetraacetic acid dihydrate, 21.0 g of sorbitol, 12.5 g of glycerine and 1.25 g of lactic acid. A dispersion containing 0.003 g of ANTIFOAM C and 0.1 ml of distilled water was subsequently added, then flavouring agents were incorporated into the mixture as needed and the pH was adjusted to *ca* 3.7 with sodium hydroxide. Distilled water was then added in a quantity sufficient to bring the volume to 100 ml and the suspension thus obtained was finally homogenised and deaerated. There was thus obtained a stable aqueous suspension containing 5 gm of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]-epine hydrochloride per 5 ml of suspension. The suspension was completely palatable. It was non-irritating to the mouth mucosa, and was devoid of the bitter, astingent taste characterising conventional aqueous suspensions of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride.

Example 4

0.09 g of methyl *p* - hydroxy - benzoate and 0.02 g of propyl *p* - hydroxy - benzoate were dissolved in 28 ml of distilled water. 0.525 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride were subsequently added to the resulting solution and dissolved therein. The solution was then heated to a temperature within the approximate range of from 80°C to 85°C, following which 10.5 g of magnesium aluminium silicate (VEEGUM NEUTRAL) were added with stirring. The resulting mixture was stirred at a temperature within the approximate range of from 80°C to 85°C for *ca* 1 hour.

To the aqueous reaction product obtained as described in the preceding paragraph there were added 0.75 g of polyoxyethylene-(2) stearate (sold commercially under the trade mark MYRJ 45), 55.0 g of sucrose and 12.5 g of glycerine. A solution containing 1.5 ml of distilled water, 0.11 g of sodium hydroxide, 0.25 g of benzoic acid, 0.01 g of disodium ethylenediamine - tetraacetic acid dihydrate, 21.0 g of sorbitol and 1.15 g of lactic acid was then added, followed by a dispersion containing 0.0033 g of ANTIFOAM C and 0.1 ml of distilled water. The resulting suspension was adjusted to pH 3.7 using sodium hydroxide, then a sufficient volume of distilled water was added to bring the suspension to a volume of 100 ml. The suspension thus obtained was homogenised and deaerated.

Each 5 ml of the resulting stable aqueous suspension contained 25 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride. The suspension was completely palatable. It was non-irritating to the mouth mucosa and was devoid of the bitter, astringent taste which characterises conventional aqueous suspensions of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride.

EXAMPLE 5

The following is an alternative method for manufacturing a palatable pharmaceutical preparation containing 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride.

0.105 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride were mixed with 2.10 g of magnesium aluminium silicate (VEEGUM). A sufficient quantity of water was added to, and stirred into, the dry mix to yield a moist homogeneous mixture. The moist homogeneous mixture was dried at a temperature of *ca* 45°C, following which it was pulverised. There was thus obtained a dry powdery product which was substantially tasteless. This product, in admixture with conventional tabletting excipients and adjuvants, was compressed into tablets which were completely palatable (i.e. the tablets were devoid of any bitter, astingent taste and they were non-irritating to the mouth mucosa). Suspensions produced from the dry product were similarly palatable.

The procedure described in the preceding paragraph was repeated using 2.1 g of aluminium silicate (ALBAGEL) instead of the magnesium aluminium silicate. The dry product thus obtained was used in formulating oral dosage forms (i.e. tablets and suspensions). Each of such dosage forms were completely palatable, being devoid of a bitter, stringent taste and being non-irritating to the mouth mucosa.

WHAT WE CLAIM IS:—

1) A pharmaceutical preparation comprising a reaction mixture of the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,4 - dihydro - 1H - benzdiaz-[1,4]epine with an aluminium silicate or magnesium aluminium silicate in the presence of water; there being present in the reaction mixture at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound.

2) A preparation as set forth in claim 1, wherein there is present from 12 parts to 33 parts by weight of an aluminium silicate for each part by weight of said benzdiaz-[1,4]epine compound and wherein there is present from 2.5 parts to 15 parts by weight of water for each part by weight of said aluminium silicate.

3) A preparation as set forth in claim 1, wherein there is present from 12 parts to 33 parts by weight of magnesium aluminium silicate for each part by weight of said benzdiaz[1,4]epine compound and wherein there is present from 2.5 parts to 15 parts by weight of water for each part by weight of said magnesium aluminium silicate.

4) The preparation as set forth in claim 2, wherein the reactants have been admixed at a temperature within the range of from 70°C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

5) A preparation as set forth in claim 3, wherein the reactants have been admixed at a temperature within the range of from 70° C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

6) A stable and palatable pharmaceutical aqueous suspension for oral administration comprising (1) water, (2) a reaction product produced by mixing in the presence of water, an aluminium silicate or magnesium aluminium silicate and the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in a ratio of at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound and (3) inert pharmaceutical excipients.

7) A suspension as set forth in claim 6, wherein from 5.0 mg to 25.0 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride are present in each 5 ml of suspension.

8) A process for the manufacture of a pharmaceutical preparation which comprises mixing the hydrochloric acid salt of 7 -

To the aqueous reaction product obtained as described in the preceding paragraph there were added 0.75 g of polyoxyethylene-(2) stearate (sold commercially under the trade mark MYRJ 45), 55.0 g of sucrose and 12.5 g of glycerine. A solution containing 1.5 ml of distilled water, 0.11 g of sodium hydroxide, 0.25 g of benzoic acid, 0.01 g of disodium ethylenediamine - tetraacetic acid dihydrate, 21.0 g of sorbitol and 1.15 g of lactic acid was then added, followed by a dispersion containing 0.0033 g of ANTIFOAM C and 0.1 ml of distilled water. The resulting suspension was adjusted to pH 3.7 using sodium hydroxide, then a sufficient volume of distilled water was added to bring the suspension to a volume of 100 ml. The suspension thus obtained was homogenised and deaerated.

Each 5 ml of the resulting stable aqueous suspension contained 25 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride. The suspension was completely palatable. It was non-irritating to the mouth mucosa and was devoid of the bitter, astringent taste which characterises conventional aqueous suspensions of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride.

EXAMPLE 5

The following is an alternative method for manufacturing a palatable pharmaceutical preparation containing 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride.

0.105 g of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine hydrochloride were mixed with 2.10 g of magnesium aluminium silicate (VEEGUM). A sufficient quantity of water was added to, and stirred into, the dry mix to yield a moist homogeneous mixture. The moist homogeneous mixture was dried at a temperature of *ca* 45°C, following which it was pulverised. There was thus obtained a dry powdery product which was substantially tasteless. This product, in admixture with conventional tabletting excipients and adjuvants, was compressed into tablets which were completely palatable (i.e. the tablets were devoid of any bitter, astingent taste and they were non-irritating to the mouth mucosa). Suspensions produced from the dry product were similarly palatable.

The procedure described in the preceding paragraph was repeated using 2.1 g of aluminium silicate (ALBAGEL) instead of the magnesium aluminium silicate. The dry product thus obtained was used in formulating oral dosage forms (i.e. tablets and suspensions). Each of such dosage forms were completely palatable, being devoid of a bitter, stringent taste and being non-irritating to the mouth mucosa.

WHAT WE CLAIM IS:—

1) A pharmaceutical preparation comprising a reaction mixture of the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,4 - dihydro - 1H - benzdiaz-[1,4]epine with an aluminium silicate or magnesium aluminium silicate in the presence of water; there being present in the reaction mixture at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound.

2) A preparation as set forth in claim 1, wherein there is present from 12 parts to 33 parts by weight of an aluminium silicate for each part by weight of said benzdiaz-[1,4]epine compound and wherein there is present from 2.5 parts to 15 parts by weight of water for each part by weight of said aluminium silicate.

3) A preparation as set forth in claim 1, wherein there is present from 12 parts to 33 parts by weight of magnesium aluminium silicate for each part by weight of said benzdiaz[1,4]epine compound and wherein there is present from 2.5 parts to 15 parts by weight of water for each part by weight of said magnesium aluminium silicate.

4) The preparation as set forth in claim 2, wherein the reactants have been admixed at a temperature within the range of from 70°C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

5) A preparation as set forth in claim 3, wherein the reactants have been admixed at a temperature within the range of from 70° C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

6) A stable and palatable pharmaceutical aqueous suspension for oral administration comprising (1) water, (2) a reaction product produced by mixing in the presence of water, an aluminium silicate or magnesium aluminium silicate and the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine in a ratio of at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound and (3) inert pharmaceutical excipients.

7) A suspension as set forth in claim 6, wherein from 5.0 mg to 25.0 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine hydrochloride are present in each 5 ml of suspension.

8) A process for the manufacture of a pharmaceutical preparation which comprises mixing the hydrochloric acid salt of 7 -

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chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine with an aluminium silicate or magnesium aluminium silicate in the presence of water, there being used at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound.

9) A process as set forth in claim 8, wherein there is used from 12 parts to 33 parts by weight of aluminium silicate for each part by weight of said benzdiaz[1,4]-epine compound and from 2.5 parts to 15 parts by weight of water for each part by weight of said aluminium silicate.

10) A process as set forth in claim 8, wherein there is used from 12 parts to 33 parts by weight of magnesium aluminium silicate for each part by weight of said benzdiaz[1,4]epine compound and from 2.5 parts to 15 parts by weight of water for each part by weight of said magnesium aluminium silicate.

11) A process as set forth in claim 9, wherein the reactants are mixed at a temperature within the range of from 70°C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy - benzoate.

12) A process as set forth in claim 10, wherein the reactants are mixed at a temperature within the range of from 70°C to 85°C and wherein the reaction mixture also contains a mixture of methyl *p* - hydroxy - benzoate and propyl *p* - hydroxy benzoate.

13) A process for the manufacture of a stable and palatable aqueous pharmaceutical suspension for oral administration which comprises admixing (1) water, (2) a reaction product produced by mixing in the presence of water, an aluminium silicate or magnesium aluminium silicate and the hydrochloric acid salt of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz-[1,4]epine in a ratio of at least 9.0 parts by weight of said silicate for each part by weight of said benzdiaz[1,4]epine compound and (3) inert pharmaceutical excipients.

14) A process as set forth in claim 13, wherein from 5.0 mg to 25.0 mg of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz [1,4]epine hydrochloride are used per 5 ml of suspension.

15) A process for the manufacture of a pharmaceutical preparation, substantially as described with reference to the foregoing Examples.

16) A pharmaceutical preparation, when manufactured by the process claimed in any one of claims 8 to 15 inclusive.

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