PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Diluents for Chlordiazepoxide and Salts 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:—

The present invention is concerned with diluents for chlordiazepoxide and salts thereof and with a process for the manufacture of said diluents and parenteral solutions containing same.

Chlordiazepoxide [7-chloro-2-methylamino-5-phenyl-3H-benz[1,4]diazepine 4-oxide] is a very useful medicament; useful, for example, in relieving tension and anxiety. Parenteral administration of chlordiazepoxide solutions is a desirable mode of administration where oral medication is impracticable; for example, where the patient is unconscious or is a violent psychopath or where immediate onset of action is desired. However, attempts to form parenteral solutions of chlordiazepoxide have hitherto been unsuccessful due to the inherent instability of chlordiazepoxide and its hydrochloride salt in the presence of water. Furthermore, when aqueous solutions of the hydrochloride salt are injected intramuscularly, painful local reactions frequently occur. Additionally, the hydrochloride salt in simple aqueous solutions is not satisfactorily active when given intramuscularly or subcutaneously, although active when given by the intraperitoneal and ~~intravenous~~ routes.

It has now been discovered that a diluent comprising water, maleic acid, a parenteral surfactant and a stabilizing agent is capable of dissolving chlordiazepoxide or its hydrochloride to form relatively stable solutions in which the solubility of chlordiazepoxide is much higher than in aqueous solutions which do not contain the foregoing ingredients. Further, it has been found that these solutions can be injected intramuscularly with substantially no local irritation and that they are not only active when given by the intramuscular and subcutaneous routes but are also active when given intravenously and intraperitoneally.

Accordingly, in one of its aspects, the invention provides as diluents for chlordiazepoxide and its hydrochloride aqueous solutions containing approximately 0.25 to 2.5 per cent (preferably 0.8 to 2.0 per cent) of maleic acid, approximately 0.5 to 8 per cent (preferably 1 to 8 per cent) of a pharmaceutically acceptable polyoxyethylene surfactant and approximately 5 to 50 per cent (preferably 10 to 20 per cent) of a water-soluble parenterally acceptable monohydroxy or polyhydroxy alkane (including *cyclo*alkane) as stabilizing agent. The foregoing percentages are based on the total weight of the aqueous solution. It is also desirable, although not essential, to employ approximately 0.01 to 2 per cent of a preservative.

Two preferred surfactants for use in the diluent composition are:

(a) A solid block polyoxyethylene polymer having a molecular weight of about 8750 and composed of 80 per cent by weight of polyoxyethylene groups and 20 per cent by weight of polyoxypropylene groups and where the polyoxyethylene groups are in the terminal portions of the molecules [e.g. that marketed under the name Pluronic F-68 by Wyandotte Chemicals Corp. of Wyandotte, Michigan].

(b) Polyoxyethylene sorbitan monoesters of higher saturated or olefinically unsaturated monocarboxylic acids, e.g. that known as Polysorbate 20 [polyoxyethylene-(20)-sorbitan monolaurate] or Polysorbate 80[polyoxyethylene-(20)-sorbitan monooleate].

The upper limit of the quantity of surfactant used depends on the particular surfactant; for example, with Polysorbate 80 and Pluronic

[Price 4s. 6d.]

F-68 the upper limit is about 8 per cent (with from 2 to 6 per cent being preferred) and with Polysorbate 20 the upper limit is about 4 per cent. 4 per cent Polysorbate 80 or Pluronic F-68 is preferred in the practice of the invention. A necessary characteristic of the surfactant is, of course, that it is parenterally acceptable.

The hydroxy-containing compound used as stabilizing agent in the diluents is preferably a parenterally acceptable C_2 to C_6 alkanol such as ethanol or, more preferably, a parenterally acceptable polyhydroxy alkane such as glycerine, propylene-glycol, sorbitol or glucose. The quantity of stabilizing agent employed will depend, in part, on the particular stabilizing agent chosen. For example, ethanol is preferably used in a concentration of about 10 per cent, glycerine and propylene-glycol can be used in the approximate range of 5 to 50 per cent, and sorbitol and glucose can be used in the approximate range of 5 to 20 per cent. About 20 per cent propylene-~~gylcol~~ glycol is preferred. It will be appreciated that the solubility range of the hydroxy-containing stabilizing agent in water should admit of the concentration range required.

Since the diluent of the invention is to be used by the physician to form a solution of chloridazepoxide for parenteral injection immediately prior to use, it is desirable to include a preservative to help prevent bacterial contamination. The preservative should, of course, be pharmaceutically acceptable and the quantity of preservative employed will depend, in part, on the particular preservative chosen. For example, phenol can be used in the approximate range of 0.25 to 0.5 per cent, cresol in the approximate range of 0.2 to 0.5 per cent, methyl and propyl *p*-hydroxy-benzoates totalling about 0.2 per cent, sodium ethylmercurithiosalicylate about 0.01 per cent, benzyl alcohol in the approximate range of 0.5 to 2.0 per cent. Benzyl alcohol in a concentration of about 1.5 per cent is preferred.

The parenteral solutions of chlordiazepoxide or of its hydrochloride should contain an amount of diluent such that from about 0.5 mols to about 2 mols (preferably about 1.0 mol) of maleic acid is present per mol of chlordiazepoxide. The parenteral solutions are useful for parenteral injection for the relief of acute agitation and hyperactivity and are indicated where rapid action is required or oral administration is not feasible. The quantity of solution which is administered to a patient will depend on the particular diagnosis, the response of the patient, the age and body weight of the patient, etc. In a typical adult dosage a sufficient quantity of the solution will be given to provide approximately 25 to about 250 mg (e.g. about 50 to 100 mg) of chlordiazepoxide.

It is of interest that acids such as nitric, sulphuric, acetic, lactic, adipic, malic, citric, glucuronic, glutamic, galacturonic, pyroglutamic and tartaric acid are no substitute for the maleic acid in the diluent of the invention as they do not form readily soluble salts or complexes with chlordiazepoxide. Although ascorbic acid forms a readily soluble salt, it is not as useful as maleic acid because it is less stable.

The following examples of diluents and parenteral solutions incorporating same are given by way of illustration:

EXAMPLE 1

A diluent which is suitable for preparing a parenteral solution is prepared by forming an aqueous solution of the following ingredients:

Ingredients	Composition per ml
Polyoxyethylene-(20)-sorbitan-monooleate	40 mg
Benzyl alcohol	15 mg
Maleic acid	16 mg
Sodium hydroxide	5.2 mg
Propylene-glycol	0.20 ml
Sterile water for injection	q.s. to 1 ml

In the foregoing formulation sodium hydroxide is present to adjust the pH to about 2.8. This is within the desired range; that is to say within the approximate range of 2.2 to 3.5 (preferably about 3).

2 ml of the foregoing diluent are then mixed with 100 mg of chlordiazepoxide hydrochloride. The resulting solution, which is readily obtained by gently agitating the chlordiazepoxide hydrochloride in the diluent, is suitable for parenteral injection (e.g. intramuscularly).

It is of interest that chlordiazepoxide hydrochloride is soluble in the foregoing diluent up to a concentration of 250 mg per ml of diluent, whereas the solubility of chlordiazepoxide hydrochloride in distilled water at the same pH (2.8, adjusted with sodium hydroxide) is only 50 mg per ml of water.

EXAMPLE 2

50 ml of sterile water for injection (at 25° C) are mixed with 16 ml of propylene-glycol. To this are added with stirring 1.2 g of benzyl alcohol, 3.2 g of polyoxyethylene-(20)-sorbitan monooleate and 1.28 g of maleic

acid. Then, a 10 per cent sodium hydroxide solution is slowly added until a pH of 3.0 ±0.1 is obtained (about 4.16 ml of sodium hydroxide solution). Thereafter, sterile water for injection is added to form 80 ml of solution. The solution is then thoroughly mixed, filtered, and filled into sterile ampoules. The air in the ampoules is replaced with nitrogen and the ampoules are sealed. The ampoules are sterilized for 0.5 hours at 100°C. The ampoules are now suitable for use by the physician for mixing with chlordiazepoxide or its hydrochloride.

EXAMPLE 3

A diluent which is suitable for preparing a parenteral solution is prepared using the ingredients listed in Example 1 except that Pluronic F-68 is used in place of polyoxyethylene-(20)-sorbitan monooleate.

EXAMPLE 4

The process of Example 2 is repeated except that ~~Pluronic~~ F-68 is used in place of polyoxyethylene-(20)-sorbitan monooleate.

WHAT WE CLAIM IS:—

1) A diluent for chlordiazepoxide and its hydrochloride which comprises an aqueous solution containing approximately 0.25 to 2.5 per cent of maleic acid, approximately 0.5 to 8 per cent of a parenterally acceptable polyoxyethylene surfactant and approximately 5 to 50 per cent of a water-soluble parenterally acceptable monohydroxy or polyhydroxy alkane as stabilizing agent the percentages being based on the total weight of the aqueous solution.

2) A diluent as claimed in claim 1, wherein the maleic acid content is from 0.8 to 2.0 per cent, the surfactant content is from 1 to 8.0 per cent and the stabilizing agent content is from 10 to 20 per cent.

3) A diluent as claimed in claim 1 or claim 2, which includes a preservative in its composition.

4) A diluent as claimed in claim 3, wherein the preservative is benzyl alcohol and is present in an amount of 1.5 per cent.

5) A diluent as claimed in any one of the preceding claims, wherein said surfactant is *either* a solid block polyoxyethylene polymer having a molecular weight of about 8750 and composed of 80 per cent by weight of terminally situated polyoxyethylene groups and 20 per cent by weight of polyoxypropylene groups or a polyoxyethylene sorbitan monoester of a higher saturated or olefinically unsaturated monocarboxylic acid.

6) A diluent as claimed in claim 5, wherein said monoester is polyoxyethylene-sorbitan monooleate.

7) A diluent as claimed in any one of the preceding claims, wherein said stabilising agent is propylene-glycol and is present in an amount of 20 per cent.

8) Diluents substantially as hereinbefore described with reference to and as illustrated in the examples.

9) A parenteral solution of chlordiazepoxide or its hydrochloride comprising chlordiazepoxide or its hydrochloride and a diluent claimed in claim 1—the maleic acid content of said parenteral solution being in the approximate range of 0.5 to 2.0 mols per mol of chlordiazepoxide.

10) A process for the manufacture of the diluent as claimed in claim 1 and parenteral solution claimed in claim 9, substantially as described with reference to the examples.

W. D. WHITAKER
Patent Agent
for F. Hoffmann-la Roche & Co.
Aktiengesellschaft.

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2) A diluent as claimed in claim 1, wherein the maleic acid content is from 0.8 to 2.0 per cent, the surfactant content is from 1 to 8.0 per cent and the stabilizing agent content is from 10 to 20 per cent.

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