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(54) COMPOSITIONS FOR TREATING GASTROINTESTINAL DISORDERS

(71) 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 relates to compositions which are therapeutically useful in the treatment of gastrointestinal disorders, and a process for the manufacture thereof. More particularly the present invention relates to compositions comprising 7 - chloro - 1,3 - di - hydro - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzo - diazepin - 2 - one, hereinafter referred to as diazepam, and β - diisopropyl - aminoethyl xanthene - 9 - carboxylate methohalide, hereinafter referred to as propantheline halide, and a process for the manufacture thereof.

The combination of diazepam or an acid addition salt thereof with a pharmaceutically acceptable acid and propantheline halide has been found to be extremely effective in the therapeutic treatment of gastrointestinal disorders such as peptic ulcer, hyperchlorhydria, ulcerative or spastic colon, "nervous stomach", irritable spastic colon, mucous colitis, duodenitis, gastritis, biliary dyskinesia, pylorospasms, cardiospasm, anxiety states having gastrointestinal manifestations and other functional or organic disorders of the digestive tract. This effectiveness is due to the complete anticholinergic action of propantheline halide together with the ability of diazepam to effectively relieve the anxiety-tension syndrome often manifest with gastrointestinal disorders of the type described previously.

In addition to the free base of diazepam, any salt thereof with a conventional pharmaceutically acceptable acid, such acid being organic or inorganic in nature, may be utilized in forming the compositions of the present invention. For example, one can use a salt of diazepam with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid or the like or a salt with an organic acid such as acetic acid, benzoic acid, lactic acid, malic acid, benzene or toluene sulfonic acid, maleic acid, salicylic acid and the like. The preferred salt of diazepam for forming the compositions of the present invention is the hydrochloride.

In formulating the compositions of the present invention, the use of "propantheline halide" indicates propantheline chloride, bromide or iodide, with the bromide being preferred.

The compositions of the invention are prepared by mixing together the two active components and the pharmaceutically acceptable carrier and forming the resulting mixtures into suitable oral dosage forms, e.g., pressed or coated tablets. Moreover, the compositions of the present invention can be formulated into solutions, syrups, oily suspensions and the like. Additionally, the compositions of the present invention can be provided in the form of hard shell capsules. If desired, the compositions of the present invention can be formulated into dosage forms suitable for parenteral administration. The methods and techniques by which these various dosage forms are prepared are the conventional procedures of the art. The applications of such procedures to the compositions of the present invention will be readily apparent to one skilled in the art.

In formulating the compositions of the present invention into the aforementioned dosage forms, one can use, as the pharmaceutically acceptable carrier, any of the various adjuvants or excipients ordinarily employed in formulating pharmaceutical products. Thus, for example, in the formulation of tablets, these optional ingredients include fillers such as coprecipitated aluminum hydroxide-calcium carbonate, dicalcium phosphate and lactose; disintegrating agents such as maize starch; and lubricating agents such as talc and calcium stearate. Where the compositions of the pre-

sent invention are to be provided in liquid form for examples as solutions, syrups or suspensions in oil, examples of conventional adjuvants and excipients employed include water, sugar syrup, vegetable oils such as arachis oil, suitable edible suspending agents, suitable edible sweetening agents and preservatives of the type well known in the pharmaceutical art.

The active ingredients of the invention can also be used in rectal suppository form by mixing them with suppository adjuvant materials, e.g., fatty acid esters of glycerine, or glycols, e.g., cocoa butter, propylene glycol monostearate, by techniques well known to the art.

The ratio of active ingredients which comprise the compositions of the instant invention may vary over a considerable range, for example, from one to twenty-five, preferably from three to seven and one-half parts by weight of propantheline halide per each part by weight of diazepam or the equivalent amount of a salt thereof with a pharmaceutically acceptable acid. A typical adult dosage of the active ingredients of the present invention constitutes from 1 mg to 25 mg, preferably from 2 mg to 10 mg of diazepam or the equivalent amount of a salt thereof with a pharmaceutically acceptable acid and from 5 mg to 30 mg, preferably from 7-1/2 mg to 15 mg of propantheline halide. For example, a tablet containing as active ingredients 5 mg of diazepam and 15 mg of propantheline bromide would in most therapeutic situations be administered to an adult patient three or four times daily. Smaller dosages are, of course, utilized for children or elderly or debilitated patients. The above ranges are not critical and dosages outside these ranges can be employed since the specific dosages and relative amounts of active ingredients depend upon the condition being treated and the needs of the patient.

The following examples are given to illustrate the invention.

Example 1

The following ingredients were blended together thoroughly to form a premix:

Ingredient	mg/tablet
Diazepam	5 mg
Propantheline bromide	15 mg
Corn starch	15 mg

The premix is then combined and blended with the following ingredients:

Ingredient	mg/tablet
Microcrystalline cellulose	60 mg
Lactose	104 mg
Magnesium stearate	1 mg

Thereafter, the mixture was compressed into tablets, weighing 200 mg each, utilizing a flat-faced beveled edge punch. The tablets were sealed and sugar coated by sealing with shellac, subcoating with syrup and dusting powder, coloring and smoothing with syrup and waxing and polishing.

Example 2

The process of Example 1 was carried out using the same quantities of ingredients except that 10 mg of diazepam was utilized in place of 5 mg and the tablets weighed 205 mg each.

Example 3

The following ingredients were blended thoroughly for about 15 minutes in a suitable container:

Ingredient	mg/capsule
Diazepam	2 mg
Propantheline	7-1/2 mg
Lactose	149-1/2 mg
Corn Starch	30 mg
Magnesium Stearate	1 mg
Talc	5 mg

The above blend was then passed through a comminuting machine and then blended for an additional 5 minutes. The mixture was then filled into hard-shell capsules, each of which contained approximately 195 mg of the composition.

Example 4

The process of Example 3 was carried out using the same quantities except that 7-1/2 mg of lactose was replaced with 7-1/2 mg of propantheline, thus bringing the propantheline content of each 195 mg capsule to 15 mg.

Example 5

Five mg of diazepam hydrochloride, 15 mg of propantheline bromide, 38.45 mg of white beeswax, 96.1 mg of polyoxyethylene sorbitan mono - oleate (Polysorbat 80) and 1105.45 mg of propylene glycol monostearate were mixed together, heated and shaped into the form of a rectal suppository.

WHAT WE CLAIM IS:—

1) A therapeutic composition comprising a pharmaceutically acceptable carrier in association with propantheline halide and diazepam or a salt thereof with a pharmaceutically acceptable acid.

2) A therapeutic composition according to claim 1, wherein said salt of diazepam with a pharmaceutically acceptable acid is the hydrochloride salt and said propantheline halide is propantheline bromide.

3) A therapeutic composition in unit dosage form suitable for internal administration comprising a pharmaceutically acceptable carrier

sent invention are to be provided in liquid form for examples as solutions, syrups or suspensions in oil, examples of conventional adjuvants and excipients employed include water, sugar syrup, vegetable oils such as arachis oil, suitable edible suspending agents, suitable edible sweetening agents and preservatives of the type well known in the pharmaceutical art.

The active ingredients of the invention can also be used in rectal suppository form by mixing them with suppository adjuvant materials, e.g., fatty acid esters of glycerine, or glycols, e.g., cocoa butter, propylene glycol monostearate, by techniques well known to the art.

The ratio of active ingredients which comprise the compositions of the instant invention may vary over a considerable range, for example, from one to twenty-five, preferably from three to seven and one-half parts by weight of propantheline halide per each part by weight of diazepam or the equivalent amount of a salt thereof with a pharmaceutically acceptable acid. A typical adult dosage of the active ingredients of the present invention constitutes from 1 mg to 25 mg, preferably from 2 mg to 10 mg of diazepam or the equivalent amount of a salt thereof with a pharmaceutically acceptable acid and from 5 mg to 30 mg, preferably from 7-1/2 mg to 15 mg of propantheline halide. For example, a tablet containing as active ingredients 5 mg of diazepam and 15 mg of propantheline bromide would in most therapeutic situations be administered to an adult patient three or four times daily. Smaller dosages are, of course, utilized for children or elderly or debilitated patients. The above ranges are not critical and dosages outside these ranges can be employed since the specific dosages and relative amounts of active ingredients depend upon the condition being treated and the needs of the patient.

The following examples are given to illustrate the invention.

EXAMPLE 1

The following ingredients were blended together thoroughly to form a premix:

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The premix is then combined and blended with the following ingredients:

Ingredient	mg/tablet
Microcrystalline cellulose	60 mg
Lactose	104 mg
Magnesium stearate	1 mg

Thereafter, the mixture was compressed into tablets, weighing 200 mg each, utilizing a flat-faced beveled edge punch. The tablets were sealed and sugar coated by sealing with shellac, subcoating with syrup and dusting powder, coloring and smoothing with syrup and waxing and polishing.

EXAMPLE 2

The process of Example 1 was carried out using the same quantities of ingredients except that 10 mg of diazepam was utilized in place of 5 mg and the tablets weighed 205 mg each.

EXAMPLE 3

The following ingredients were blended thoroughly for about 15 minutes in a suitable container:

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Corn Starch	30 mg
Magnesium Stearate	1 mg
Talc	5 mg

The above blend was then passed through a comminuting machine and then blended for an additional 5 minutes. The mixture was then filled into hard-shell capsules, each of which contained approximately 195 mg of the composition.

EXAMPLE 4

The process of Example 3 was carried out using the same quantities except that 7-1/2 mg of lactose was replaced with 7-1/2 mg of propantheline, thus bringing the propantheline content of each 195 mg capsule to 15 mg.

EXAMPLE 5

Five mg of diazepam hydrochloride, 15 mg of propantheline bromide, 38.45 mg of white beeswax, 96.1 mg of polyoxyethylene sorbitan mono - oleate (Polysorbat 80) and 1105.45 mg of propylene glycol monostearate were mixed together, heated and shaped into the form of a rectal suppository.

WHAT WE CLAIM IS:—

1) A therapeutic composition comprising a pharmaceutically acceptable carrier in association with propantheline halide and diazepam or a salt thereof with a pharmaceutically acceptable acid.

2) A therapeutic composition according to claim 1, wherein said salt of diazepam with a pharmaceutically acceptable acid is the hydrochloride salt and said propantheline halide is propantheline bromide.

3) A therapeutic composition in unit dosage form suitable for internal administration comprising a pharmaceutically acceptable carrier

and from 1 mg to 25 mg of diazepam (or a sufficient amount of a salt thereof with a pharmaceutically acceptable acid to provide from 1 mg to 25 mg of diazepam) and from 5 mg to 30 mg of propantheline halide in each dosage unit.

4) A composition according to claim 3, wherein said propantheline halide is propantheline bromide.

5) A composition according to claim 3 or claim 4, wherein said unit dosage form contains 2 mg diazepam and 15 mg propantheline bromide.

6) A composition according to claims 3 or claim 4, wherein said unit dosage form contains 5 mg diazepam and 15 mg propantheline bromide.

7) A composition according to claim 3, wherein said dosage unit is a capsule.

8) A composition according to claim 3, wherein said dosage unit is a tablet suitable for oral administration and containing from 2 mg to 10 mg of diazepam (or a sufficient amount of a salt thereof with a pharmaceutically acceptable acid to provide from 2 mg to 10 mg of diazepam) and from 7.5 mg to 15 mg of propantheline halide.

9) A composition according to claim 8, wherein each tablet contains 10 mg of diazepam and 15 mg of propantheline bromide.

10) A process for the manufacture of a therapeutic composition which comprises mixing together diazepam or a pharmaceutically acceptable salt thereof and propantheline halide and a pharmaceutically acceptable carrier and forming the resulting mixture into dosage forms.

11) A process as claimed in claim 10, wherein diazepam hydrochloride and propantheline bromide are used as the active ingredients.

12) A process as claimed in claim 10, which comprises mixing diazepam or a pharmaceutically acceptable acid addition salt thereof and propantheline halide with a pharmaceutically acceptable carrier and forming the resulting mixture into unit dosage forms to obtain a therapeutic composition for internal administration comprising from 1 mg to 25 mg diazepam (or a sufficient amount of a salt thereof to provide from 1 mg to 25 mg of diazepam and from 5 mg to 30 mg of propantheline halide in each dosage unit.

13) A process as claimed in claim 12, wherein propantheline bromide is used as propantheline halide.

14) A process as claimed in claim 12 or claim 13 wherein a unit dosage form is prepared containing 2 mg of diazepam and 15 mg of propantheline bromide.

15) A process as claimed in claim 12 or claim 13, wherein a unit dosage form is prepared containing 5 mg of diazepam and 15 mg of propantheline bromide.

16) A process as claimed in claim 12, wherein capsules are formed as unit dosage forms.

17) A process as claimed in claim 12, wherein tablets are prepared as unit dosage form containing from 2 mg to 10 mg of diazepam (or a sufficient amount of a pharmaceutically acceptable acid addition salt thereof to provide from 2 mg to 10 mg of diazepam) and from 7.5 mg to 15 mg of propantheline halide.

18) A process as claimed in claim 17, wherein tablets are formed containing 10 mg of diazepam and 15 mg of propantheline bromide.

19) A process for the preparation of the therapeutic compositions claimed in any one of claims 1 to 9 inclusive, substantially as hereinbefore described with reference to the foregoing Examples.

20) Therapeutic compositions as claimed in any one of claims 1 to 9 inclusive, when prepared according to the process claimed in any one of claims 10 to 19 inclusive.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
24 Southampton Buildings,
Chancery Lane,
London, W.C.2.

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