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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/145, 47/44, 9/00

A1

(11) International Publication Number: WO 92/04893

(43) International Publication Date: 2 April 1992 (02.04.92)

(21) International Application Number: PCT/US91/06493

(22) International Filing Date: 10 September 1991 (10.09.91)

(30) Priority data:
581,866 13 September 1990 (13.09.90) US

(60) Parent Application or Grant
(63) Related by Continuation
US 581,866 (CIP)
Filed on 13 September 1990 (13.09.90)

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: NON-AQUEOUS LIQUID ORAL SUSPENSIONS

(57) Abstract

Pharmaceutically elegant liquid oral compositions comprise a histamine H_2-antagonist such as cimetidine in an edible oily vehicle. The compositions are extremely palatable and minimize the bitter taste associated with these compounds. Other pharmaceutical additives well known to the art may be optionally added.

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NON-AQUEOUS LIQUID ORAL SUSPENSIONS

This invention relates to pharmaceutical compositions suitable for oral administration which comprise histamine H_2-antagonists and result in an improved taste. Preferably, it relates to non-aqueous liquid oral suspensions which comprises cimetidine in an oily vehicle.

BACKGROUND OF THE INVENTION

Cimetidine is a histamine H_2-antagonist which has been used for a number of years in the treatment of duodenal, gastric, stomal and recurrent ulceration. It has also been employed for reflux oesophagitis and other conditions where reduction of gastric acid has been shown to be beneficial for example, persistent dyspeptic symptoms with or without ulceration. Cimetidine is absorbed almost exclusively in the small intestine where liquid compositions could be absorbed more quickly and efficiently than tablets.

It is known that cimetidine has a very bitter taste and the majority of the oral compositions containing cimetidine are considered unpalatable. The unpleasant taste associated with cimetidine is much more noticeable in liquid oral compositions, particularly in aqueous vehicles. This has presented a major problem in the preparation of liquid oral compositions. There

has been a long standing need for an elegant, palatable liquid oral composition which will mask the unpleasant taste of cimetidine.

U.S. Patent 4,861,592 discloses aqueous buffered cimetidine suspensions as an approach to overcome the unpleasant taste of cimetidine. U.S. Patent 4,918,103 is representative of non-aqueous pharmaceutical vehicles employed to overcome stability problems associated with non steroidal anti-inflammatory drugs. U.S. Patents 4,639,367 and 4,752,465 disclose aerosol foams having the consistency of whipped cream employed as an alternative to liquid medicines having a bad taste. U.S. Patent 4,079,131 discloses anhydrous pharmaceutical vehicles employed to prepare permanent suspensions for water sensitive drugs.

DESCRIPTION OF THE INVENTION

According to the present invention there is provided a palatable non-aqueous liquid oral pharmaceutical suspension which comprises a histamine H_2-antagonist, preferably cimetidine, in an edible oily vehicle. By employing a one phase oily vehicle, it was unexpectedly discovered that the unpleasant taste of cimetidine associated with aqueous liquid vehicles was significantly minimized.

The oily vehicle employed in this invention may be, for example, an edible vegetable oil such as soybean oil, partially hydrogenated soybean oil, corn oil, sunflower oil, or peanut oil. The synthetic edible oils which are commercially available and are equivalent to the vegetable oils may also be employed in this invention. For example, the triglycerides of the C_8-C_{10} fatty acids of fractionated coconut oil which are available under the trade name of "Miglyol". Specifically, Miglyol is a triglyceride of capric and caprylic acids with glycerol. The oils may also include sugar fatty acids known as "Olestras".

The partially hydrogenated soybean oils are particularly preferred. A species of this group of edible vegetable oils is commercially available under the trade name of "Durkex". Most preferably, Durkex 25 is employed in the compositions of this invention.

The above edible oils will be present in the non-aqueous pharmaceutical compositions of this invention in a range of from about 40% to about 90%, preferably from about 50 to about 80%.

The histamine H_2-antagonist employed in the non-aqueous liquid suspensions of this invention may be for example, cimetidine, ranitidine, famotidine, nizatidine, etintidine, lupitidine, nifentidine, niperotidine, roxatidine, sufotidine, tuvatidine and zaltidine. Preferably, the H_2-antagonist of this invention is cimetidine. It is well known that cimetidine can exist in at least five different polymorphic forms. Unless otherwise specified it is intended to include all polymorphs whether separated or mixtures thereof.

The H_2-antagonist of this invention will be present in the non-aqueous suspension in a nontoxic but effective amount to produce systemically effective histamine H_2-antagonistic activity. The suspension will contain from about 1.0% to about 12.0% W/V of the antagonist, preferably from about 4.0% to about 8.0% W/V.

The H_2-antagonists are administered in conventional liquid dosage unit forms; preferably in teaspoon quantities. A teaspoon is equivalent to 5 ml. of the oral liquid composition. The active ingredient, for example, cimetidine will normally be administered in an amount of from about 50 mg. to about 600 mg. per dosage unit, advantageously from about 200 mg. to about 400 mg. per dosage unit. Equal doses within the ranges given above will be administered preferably from about one to about four times a day.

Other histamine H_2-antagonists, for example, those noted above, can also be present in the compositions of this invention in a nontoxic but pharmaceutically effective amount.

The concentration will vary with the H_2-antagonist employed and the unit dosage required. The compositions will contain the H_2-antagonist in an amount within dosage unit ranges which are well known to the medical art.

To further enhance the basic compositions of this invention other pharmaceutically acceptable additives well known to the art may be optionally added. Exemplary of these additives would be flavoring agents such as peppermint, vanilla, licorice, cinnamon, chocolate, spearmint or a combination of flavors; sweetening agents selected from aspartame, sodium cyclamate, calcium cyclamate or sodium saccharin; preservatives such as, for example, methylparaben, propylparaben, butylparaben, benzoic acid and sorbic acid; emulsifying and surface active agents selected from nontoxic anionics such as sodium lauryl sulfate, cationics such as benzalkonium chloride or a non-ionic agent such as polyoxyethylene sorbitan monopalmitate (Tween 40), sorbitan fatty acid esters, such as, sorbitan monopalmitate (Span 40) and natural emulsifiers selected from acacia, gelatin lecithin and cholesterol; antioxidants selected from butylated hydroxyanisole, butylated hydroxytoluene or tertiary butylhydroquinone; and thickening agents such as silicon dioxide (Syloid) or colloidal silicon dioxide (Cab-O-Sil). These thickening agents may be present in an amount of from about 0.1% to about 5.0% of the composition.

Sugars such as, for example, mannitol, sorbitol, confectioners sugar, lactose, fructose and glucose may be employed as both thickening and sweetening agents. The sugars may be present in the nonaqueous compositions of this invention in an amount of from about 10% to about 40%.

The selection and amounts of the above pharmaceutically acceptable additives and their use in the nonaqueous compositions of this invention is within the skill of the pharmaceutical art except as specifically set forth herein.

The compositions are prepared following the conventional techniques well known to those skilled in the art involving variously mixing, suspending and dispersing the ingredients as appropriate to give the desired composition.

The invention is further illustrated by the following examples which are not intended to be limited in scope.

Example 1

Ingredient	% W/V
Cimetidine	4.0
Confectioners Sugar NF 12X	25.0
Mannitol	10.0
Cab-O-Sil	0.2
Propylparaben	0.1
Tertiary Butylhydroquinone	0.02
Vanilla Flavor	0.5
Peppermint Flavor	0.5
Partially Hydrogenated Soybean Oil (Durkex 25) q.s.	100.0 ml.

50 ml. of Durkex 25 was placed in a propeller mixer and the propylparaben was dissolved in the oil. The flavors and butylhydroquinone were then added to the solution followed by the other ingredients with moderate mixing until the mixture was smooth and homogenous. The remaining Durkex was added with continued moderate mixing. The mixture was removed from the mixer and homogenized to a smooth consistency.

The formulations listed below were prepared following the procedure of Example 1.

Example 2

Ingredients	% W/V
Cimetidine	8.0
Mannitol	40.0
Aspartame	0.1
Cab-O-Sil	0.2
Propylparaben	0.1
Tertiary Butylhydroquinone	0.02
Vanilla	0.5
Peppermint	0.5
Durkex 25 q.s.	100.0 ml.

Example 3

Ingredients	% W/V
Ranitidine	4.0
Mannitol	40.0
Aspartame	0.1
Tertiary Butylhydroquinone	0.02
Cab-O-Sil	0.2
Propylparaben	0.1
Peppermint	0.5
Durkex q.s.	100.0 ml.

Example	**4**	**5**	**6**	**7**	**8**	**9**
Cimetidine	4.0	4.0	4.0	4.0	4.0	4.0
Confectioners suger NF	30.0	--	25.0	30.0	--	--
Mannitol	10.0	40.0	--	10.0	40.0	40.0
Aspartame	--	0.1	0.1	--	0.1	0.1
Cab-O-Sil	0.2	0.4	--	0.2	0.4	0.2
Propylpraben	0.1	0.1	--	0.1	0.1	0.1
Tertiary Butyl-hydroquinone quinone	0.02	0.02	--	0.02	0.02	0.02
Vanilla	0.5	0.5	--	0.5	0.5	0.5
Peppermint	0.5	0.5	--	0.5	0.5	0.5
Durkex, q.s.	100 ml					

What is claimed is:

1. A non-aqueous liquid pharmaceutical composition for oral administration comprising a nontoxic effective amount of a histamine H_2-antagonist and an edible oily vehicle.

2. The composition according to Claim 1 wherein the H_2-antagonist is cimetidine.

3. The composition of Claim 2 wherein the cimetidine is present in an amount of from about 1.0% to about 12.0% W/V of the composition.

4. The composition of Claim 2 wherein the edible oily vehicle comprises soybean oil, partially hydrogenated soybean oil, corn oil, sunflower oil, peanut oil, coconut oil, or fractionated coconut oil.

5. The composition of Claim 4 wherein the oily vehicle is partially hydrogenated soybean oil.

6. The composition of Claim 4 wherein the oily vehicle is present in an amount of from about 40% to about 90% W/V of the composition.

7. The composition of Claim 4 wherein the composition includes sugars selected from the group consisting of mannitol, sorbitol, lactose, fructose or confectioners sugar.

8. The composition of Claim 7 wherein the sugar is present in an amount of from about 10% to about 40% W/V.

9. The composition of Claim 8 which further includes a thickening agent.

10. The pharmaceutical composition of Claim 9 comprising from about 4.0% to about 8.0% of cimetidine, from about 10% to about 40% of mannitol from about 0.1% to about 5.0% of Cab-O-Sil and from about 40% to about 90% of partially hydrogenated soybean oil.

11. The pharmaceutical composition of Claim 1 wherein the histamine H_2-antagonist is ranitidine.

INTERNATIONAL SEARCH REPORT

International A ation No PCT/US 91/06493

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/145 A 61 K 47/44 A 61 K 9/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0273390 (ASTRA LAKEMEDEL AB) 6 July 1988, see claims 1-3; page 2, lines 56-57; page 3, lines 59-60; page 5, lines 9-12, 44-46	1-4,7,9
Y		5-6,8, 10-11
X	GB,A,2218333 (GLAXO GROUP LIMITED) 15 November 1989, see claims 1,11,15; page 4, lines 2-24; page 5, lines 16-22, 31-33; page 12, lines 31-32; page 13, example 13	1,11
Y		2-10
X	FR,A,2643263 (GLAXO CANADA INC.) 24 August 1990, see claim 12; page 3, lines 25-32; page 5, lines 1-9	1,11

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27-11-1991	23. 12. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme. M. van der Drift

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9106493 SA 51951

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/12/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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