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(54) Title: TASTE MASKED COMPOSITION CONTAINING A DRUG/POLYMER COMPLEX

(57) Abstract

A chewable taste masked formulation comprising a therapeutic agent (or drug) containing at least one basic group or atom optionally in the form of a salt, which is reacted with a polymer containing at least one acidic group to form a complex.

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TASTE MASKED COMPOSITION CONTAINING A DRUG/POLYMER COMPLEX

The present invention relates to therapeutic agent/polymer matrix complexes which have improved taste characteristics.

Many therapeutically active substances have an unpleasant taste or cause a numbing effect when administered by mouth to a patient.

Many therapeutic agent/polymer combinations are known but the therapeutic agent is coated with the polymer. The problem with such products is that they are liable to be broken when orally administered by the patient, particularly when chewed, thereby allowing the therapeutic agent to be in direct contact with the mouth, thus the taste and/or numbing sensation of the therapeutic agent is no longer effectively masked.

A further problem with copolymers of methacrylic acid and methyl methacrylate is that when complexed with therapeutic agents the product formed tends to be a gum.

One particular drug, dimenhydrinate, is useful for treating the symptoms associated with travel sickness. Dimenhydrinate has a numbing taste.

A preferred formulation of dimenhydrinate is in the form of a chewing gum or a chewable tablet which means that the conventional coating techniques using polymers such as anionic copolymers based on methacrylic acid and methylmethacrylate (such as Eudragit), are ineffective in masking the numbing taste because the conventional polymer coated dimenhydrinate complex is broken down when chewed by the patient.

Another drug, paroxetine, is useful for the treatment of depression, panic disorders and obssessive compulsive disorders. Paroxetine has an unpleasant bitter taste.

The present invention provides a therapeutic agent/polymer complex with superior taste masking qualities and can be prepared as a powder which is more easily formulated with other excipients to form conventional formulations.

Accordingly, the present invention provides a chewable taste masked formulation comprising a therapeutic agent (or drug) containing at least one basic group or atom optionally in the form of a salt which is reacted with a polymer containing at least one acidic group to form a complex.

A preferred therapeutic agent is dimenhydrinate or paroxetine.

The term "basic group or atom" is understood to mean a group capable of donating electrons. Such groups include optionally substituted amino groups or optionally substituted thio groups.

Suitable salts of therapeutic agents include acid addition salts which are suitably pharmaceutically acceptable salts such as the hydrochloride hemi-hydrate for

paroxetine.

It should be appreciated that in cases where the drug comprises two active components i.e. a basic one and an acidic one in the form of a salt, such as dimenhydrinate, which is the 8-chlorotheophylline salt of diphenhydramine then the term therapeutic agent in the form of a salt extends to both of these components.

Suitable polymers include polymethacrylates such as Eudragit L and S which are copolymers of methacrylic acid and methyl methacrylate and have a mean molecular weight of about 135,000.

The term "acidic group" is understood to mean a group capable of receiving electrons such as a carboxylic acid group.

The complexes of therapeutic agent (including salts thereof) with polymers can be in different weight ratios. For paroxetine and dimenhydrinate, the complexes are preferably in a weight ratio of therapeutic agent to polymer of 1:0.8 to 1:1.5. Preferably the weight ratio is 1:1.

The preparation of complexes of therapeutic agents (including salts thereof) with polymers may suitably be carried out by dissolving the polymer and the therapeutic agent (including salts thereof) in suitable solvents, such as iso-propanol, ethanol or diethyl ether, optionally at elevated temperatures such as 40°C, then for example adding a precipitating solvent such as n-hexane or evaporating the solvent and triturating the residue with a suitable solvent such as acetone. The resulting precipitated complex is suitably filtered and dried.

Alternatively, such complexes may be prepared by suspending and mixing the therapeutic agent (including salts thereof) and the polymer in water at ambient or elevated temperatures such as 25 to 60°C, preferably 50°C to 60°C, for 5 to 24 hrs. The resulting complex is suitably filtered and dried.

Complexes of therapeutic agents (including salts thereof) and polymers may be formulated into conventional chewable dosage forms such as chewable tablets, candies, chewing gums, or soft chewable gelatin capsules using techniques generally known in the art or methods described or analogious to those described in the examples.

Preferably dimenhydrinate/polymer complexes may be in the form of chewing gums or chewable tablets and paroxetine/polymer complexes may be in the form of chewable tablets or chewing gums.

The following examples are illustrative of the present invention.

Example 1

The Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC), was obtained by stepwise dissolving 10 g of Copolymer (Eudragit L) and 10 g of dimenhydrinate in 100 ml of isopropanol, which was heated

to 40°C until dissolved then 200 ml of n-hexane were added to precipitate the resulting product which was then filtered and dried.

The 16.8 g of CDC gave the following analytical results.

Appearance	:	white powder
Numbing taste	:	absent
Dimenhydrinate (HPLC assay)	:	45.78 mg/100 mg of CDC.

Example 2

The Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC), was obtained by adding 1.5 kg of Dimenhydrinate and 1.5 kg of Copolymer (Eudragit L) to 22.5 litres of water, stirring at room temperature (about 20°C) for 5 hours, heating to 50°C, stirring at 50°C for 4 hours, cooling to room temperature, stirring for 2 hours at room temperature, filtering and drying.

The 2.81 kg of CDC, gave the following analytical results:

Appearance	:	white powder
Numbing taste	:	absent
Dimenhydrinate (HPLC assay)	:	46.27 mg/100 mg of CDC
Moisture (K.F.)	:	0.54%

Chewable Tablets

Examples 3 - 5

The following were granulated and admixed in a conventional manner and formed into tablets of 150 mg (Example 3), 300 mg each (Example 4) and 600 mg each (Example 5).

	Example No.		
	3	4	5
Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC)(g)	50	100	200
Pregelatinized starch (g)	12.5	25	50
Lactose (g)	15	30	60
Saccharin sodium (g)	5	10	20
Mint dry flavour (g)	5	10	20
Sorbitol (g)	58.5	117	234
Ammonium glycyrrhizinate (g)	1.5	3	6
Magnesium stearate (g)	2.5	5	10

Candies

Example 6

Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC) (g)	100
Sucrose (g)	1944
Liquid glucose (g)	1944
Mint flavour (g)	12

The formulation of example No. 6 was prepared by heating the sucrose and the liquid glucose dissolved in purified water, then drying the mass obtained and dispersing in the mass the CDC and the mint flavour. The final dispersion was pressed into candies of 4 g each.

Chewing Gums

Examples 7 & 8

	Example No. 7	8
Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC) (g)	50	100
Gum base (g)	495	495
Sorbitol (g)	637.5	587.5
Mint oil (g)	10.7	10.7
Menthol (g)	16.5	16.5
Aspartame (g)	7.6	7.6
Magnesium stearate (g)	12.7	22.7

Milled gum base is mixed with sorbitol (ca 40% of total amount), menthol (ca 90% of total amount) and aspartame (ca 25% of total amount). The blend is wetted with purified water, kneeded, granulated and then dried at about 40°C. The dried granules are mixed with CDC, mint oil, magnesium stearate and the remaining amounts of sorbitol, menthol and aspartame. This final mixture is pressed into chewing gums of 1230 mg each. The chewing gums can be film coated by conventional film coating procedures.

Soft Chewable Gelatin Capsule

Example 9

Complex of Dimenhydrinate and Copolymer of methacrylic acid and methyl methacrylate (CDC) (g)	100
Gelatin (g)	900
Glycerol (g)	345
Saccharin sodium (g)	5
Orange flavour (g)	50
Purified water (g)	450

The formulation of the Example 11 is prepared by dissolving the gelatin and glycerol in the purified water heated to 70°C and then, after cooling to 50°C, adding the saccharin sodium, the orange flavour and the CDC. The mass obtained is continually stirred, and processed with a conventional rotary-die process, to obtain soft chewable gelatin capsules of 1850 mg each.

The soft gelatin capsules are then dried at 20°C and 20% relative humidity for five days.

Example 10

The Complex of paroxetine and Copolymer of methacrylic acid and methyl metacrylate (CPC), was obtained by mixing a solution of 3g of Copolymer (Eudragit L) in 150 ml of ethanol with a solution of 3 g of paroxetine base in 100ml of diethyl ether and stirring at room temperature for 12 hours. The solvent was then evaporated under vacuum and the residue was triturated with acetone. The precipitate was collected by suction filtration, washed with acetone and dried.

The 4.6 g of CPC gave the following analytical results.

Appearance	: white powder
Bitter taste	: absent
Melting point	: 215-230°C
Paroxetine (HPLC assay)	: 42.50mg/100mg of CPC
Loss on drying	: 0.4%

Example 11

The Complex of paroxetine and Copolymer of methacrylic acid and methyl methacrylate (CPC), was obtained by adding 10g of paroxetine hydrochloride hemihydrate, 10g of Copolimer (Eudragit L) and 2.3g of sodium hydrogen carbonate to 300 ml of water. The mixture was stirred at room temperature for 12 hours, heated to 60°C and stirred at 60°C for 12 hours. After cooling to room temperature, the precipitate was collected by suction filtration, washed with water and dried.

The 18 g of CPC gave the following analytical results.

Appearance	: off-white powder
Bitter taste	: absent
Melting point	: 195-235°C
Paroxetine (HPLC assay)	: 43.53mg/100mg of CPC
Moisture (K.F)	: 6.3%

Chewable tablets

Examples 12, 13 & 14

Example No.	12	13	14
Complex of paroxetine and Copolymer of methacrylic acid and methyl methacrylate (CPC) (g)	23	46	69
Pregelatinized starch (g)	5	10	15
Aspartame (g)	10	10	10
Strawberry dry flavour (g)	50	50	50
Sorbitol (g)	409	381	353
Magnesium stearate (g)	3	3	3

CDC and pregelatinized starch are mixed, wetted with purified water, kneeded, granulated and then dried at about 40°C. The dried granules are mixed with sorbitol, lactose, saccharin sodium, ammonium glycyrrhizinate, mint dried aroma and magnesium stearate, then the final mixture is pressed into tablets of 150 mg, 300 mg or 600 mg.

Bioequivalence Studies

In a cross-over single dose study on 12 healthy volunteers, chewable tablets 50 mg (corresponding to 100 mg of complexed dimenhydrinate were demonstrated to be bio-equivalent to swallow soft gelatin capsules (50 mg) of non-complexed dimenhydrinate product.

Claims

1. A chewable taste masked formulation comprising a therapeutic agent (or drug) containing at least one basic group or atom optionally in the form of a salt which is reacted with a polymer containing at least one acidic group to form a complex.

2. A chewable taste masked formulation according to claim 1 in which the therapeutic agent is dimenhydrinate or paroxetine.

3. A chewable taste masked formulation according to claim 1 in which the therapeutic agent is in the form of the hydrochloride hemi-hydrate of paroxetine.

4. A chewable taste masked formulation according to claim 1 to 3 in which the polymer is Eudragit.

5. A chewable taste masked formulation accoding to claim 1 to 4 in which the weight ratio of therapeutic agent to drug is 1:0.8 to 1:1.5.

6. A chewable taste masked formulation according to claim 1 to 5 in which the complex of therapeutic agent and polymer is formulated into chewable tablets, candies, chewing gums, or soft chewable gelatin capsules.

7. A chewable taste masked formulation according to claim 6 in which the polymer complex is in the form of chewing gums or chewable tablets.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 212 641 (G. D. SEARLE & CO.) 4 March 1987 see claims 1-3,8,9 see example 6 -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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