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(54) **Title:** TASTE MASKED LIQUID PHARMACEUTICAL COMPOSITION OF (RS)-4-(ETHYL[l-(4-METHOXYPHENYL)PROPAN-2-YL]AMINO)BUTYL 3,4-DIMETHOXYBENZOATE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) **Abstract:** The present invention provides a taste masked liquid pharmaceutical composition of an active pharmaceutical ingredient, (RS)-4-(ethyl[l-(4- methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof.

Title: Taste masked liquid pharmaceutical composition of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof.

FIELD OF THE INVENTION

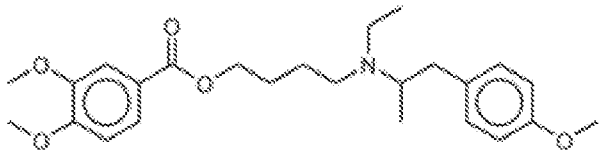
The present invention relates to taste masked liquid pharmaceutical composition of an active pharmaceutical ingredient (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof. The present invention is suitable for oral administration with enhanced taste acceptability and stability.

BACKGROUND OF THE INVENTION

Taste of any pharmaceutical active ingredient play a vital role during pharmaceutical formulation development. Many pharmaceutical active ingredients exhibit bitter taste while many have bitter after taste while few others have metallic taste. The development of final formulation considering the end user and end use always depends on many factors including taste of active ingredient.

There are many techniques in the art for masking taste of active ingredient during formulation development based on final formulation. If the formulation is in the form of solid dosage form like tablet, capsule, caplet or pellet, it becomes easy to hide bitter taste in capsule or by film coating or sugar coating.

A pharmaceutical active ingredient of structural formula (I) is chemically known as (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate and generically


Formula (I)

Known as mebeverine, herein referred as Formula (I). It is a white to almost white, crystalline powder having a very bitter taste. Active ingredient of formula (I) is an antispasmodic that has been successfully used in the management of IBS for many years. Mebeverine is a musculotropic agent that has antispasmodic activity and regulatory effects on the bowel function. Active ingredient of formula (I) is available in the market as COLOFAC® immediate release tablets and COLOFAC MR modified release capsules. COLOFAC® is available as 135 mg strength and indicated for symptomatic treatment of irritable bowel syndrome and other conditions usually included in this grouping, such as: chronic irritable colon, spastic constipation, mucous colitis, spastic colitis and effectively used to treat the symptoms of these conditions, such as: colicky abdominal pain and cramps, persistent, non-specific diarrhoea (with or without alternating constipation) and flatulence. COLOFAC® MR is available as 200 mg strength and indicated for the symptomatic relief of irritable bowel syndrome.

COLOFAC® is a sugar coated tablet and COLOFAC® MR is capsule form; therefore in both the marketed formulation bitter taste is of active ingredient is gets masked by sugar coating in COLOFAC® and do not get exposure because of capsule shell in COLOFAC® MR.

For some specific patient population like kids or children and geriatrics, swallowing of solid formulations like tablet, capsule or caplet is difficult and end up in low patient compliance and sometime may result in discontinuation of treatment. In such situation, liquid formulation is always preferred choice due to ease of administration without any swallowing difficulty for paediatric and geriatric patient.

In absence of licensed liquid pharmaceutical composition, liquid pharmaceutical composition or preparation is prepared or formulated by by grinding a tablet dosage form into a powder and mixing the powder with a vehicle or diluent in hospitals and pharmacies for use by paediatric or geriatric patients. Such type of dispensing a liquid pharmaceutical formulation from solid formulation result in to non uniform formulation with many excipient and even active ingredient remain undissolved based on varying solubility in vehicle. Administration of such preparation may result in to under dosing or overdosing to a patient.

For liquid formulation, taste masking is further a challenging task. It is very difficult to mask taste of bitter active ingredient as compared to solid formulations like tablet and capsules. In case of liquid formulation, it gets exposure with larger surface area and for longer time comparatively to solid formulations.

For active ingredient of RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate, liquid formulation with taste masking is challenging. One more formulation of active ingredient of RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate is approved by MHRA in the form of suspension with pamoate salt form to Chemidex Pharma. It is available as 50 mg/ml sugar free oral suspension and contains Microcrystalline cellulose, carboxymethylcellulose sodium, citric acid monohydrate, sodium citrate, polysorbate 20, polyoxyl 40 hydrogenated castor oil, disodium pamoate monohydrate, sodium benzoate, saccharin sodium, banana flavour, simethicone emulsion, purified water. This formulation is in suspension form wherein the drug particles remain suspended in vehicle and also requires conversion of mebeverine in to pamoate salt. Suspension formulation further offers many drawbacks of physical stability issues like sedimentation and compaction, difficulty in formulation development, uniform and accurate dosing is challenge.

Considering all the difficulties describe above, it would be desirable to develop a taste masked liquid pharmaceutical composition of active ingredient of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof. More particularly, there exists a need for a taste masked liquid pharmaceutical composition in the form of clear solution that overcome bitter taste issue, physical stability, chemical stability and offer palatable taste.

SUMMARY OF THE INVENTION

The invention provides a taste masked liquid pharmaceutical composition of (RS)-4-(ethyl[1-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof.

The main aspect of the present invention is a liquid pharmaceutical formulation with taste masking comprising;

a) (RS)-4-(ethyl[l-(4-methoxyphenyl) propan-2-yl] amino)butyl 3,4-dimethoxy benzoate or pharmaceutically acceptable salts thereof,

b) at least one sweetener,

c) an auxiliary agent,

d) at least one preservative and

e) one or more pharmaceutically acceptable excipient.

As per one aspect, the active ingredient (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate is in the form of its hydrochloride salt.

Another aspect of the present invention is process for preparing liquid pharmaceutical formulation with taste masking comprising steps of;

a) adding preservative in suitable solvent,

b) adding sweetener,

c) adding auxiliary agent,

d) adding (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof,

e) adding flavouring agent and

f) adding purified water to make up to final volume and ensuring pH between 2.0 to 4.0.

DETAILED DESCRIPTION OF THE INVENTION

The main purpose of this invention is to provide a taste masked liquid pharmaceutical composition of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof.

Inventors of the present invention have surprisingly found that the stable and palatable formulation of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof can be prepared using perfect blend of sweetener and auxiliary agent along with pharmaceutically acceptable excipients.

The term "pharmaceutically-acceptable salts" as used herein includes salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Suitable pharmaceutically-acceptable acid addition salts of mebeverine may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic

acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methane sulfonic, ethanesulfonic, 2-hydroxyethane sulfonic, pantothenic, benzenesulfonic, toluene sulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, malonic, galactaric and galacturonic acid. Preferably the pharmaceutically acceptable salt for present invention is hydrochloride.

The term "about" as and where used in this specification means +10% of the mentioned value. However when the term "about" is used in connection with pH, it should be considered as +2 unit of the pH value.

For the present invention, the active pharmaceutical ingredient is (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof which can be identified as mebeverine or structural formula (I) and all this term represent the same active pharmaceutical ingredient and can be used interchangeably.

The active ingredient for present invention, (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate is preferably in the form of hydrochloride salt.

As per one embodiment, the (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or its pharmaceutically acceptable salt is present in the range from 0.1 to 10% w/v.

As per one embodiment the liquid pharmaceutical formulation with taste masking property comprises (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof, at least one sweetener, an auxiliary agent, at least one preservative and one or more pharmaceutically acceptable excipient.

Sweetener as per present invention is selected from group consisting of saccharin, saccharin sodium, aspartame, cyclamate, invert syrup, sucralose, acesulfame, acesulfame potassium, neotame, thaumatin, neohesperidine, neohesperidine dihydrochalcone, sucrose, trehalose, lactose, fructose, xylitol, mannitol, sorbitol or combinations thereof.

In a preferred embodiment invert syrup is to be used as sweetener. In another preferred embodiment, combination of invert syrup and sucralose to be used.

As per one embodiment, the sweetener is to be used in the range from 50 to 85 %w/v, preferably in the range from about 70 to 80 %w/v.

Auxiliary agent as used herein is the substance used to enhance the effective taste masking in the formulation. As per present invention auxiliary agent is selected from group consisting of Levomenthol, monoammonium glycyrrhizinate, L-arginine, L-lysine, citric acid, lactic acid, cineol and myrtol.

In a preferred embodiment, Levomenthol is to be used as an auxiliary agent. The auxiliary agent as per present invention is to be used in the range from 0.01 to 0.04 % w/v, preferably in the range from 0.02 to 0.03 %w/v.

In one embodiment, combination of sweetener and auxiliary agent is to be used for enhanced taste masking effect. In a preferred embodiment combination of invert syrup and Levomenthol is to be used. In yet preferred embodiment, combination of invert syrup, sucralose and Levomenthol is to be used for more effective taste masking effect.

In one preferred embodiment, invert syrup and Levomenthol is to be used in ratio from 0.8 to 0.000444 to 1.2 to 0.000296, preferably in the ratio of 1:0.00037 for effective taste masking result of liquid formulation.

In one embodiment the liquid formulation also contains one or more pharmaceutically acceptable excipient selected from preservative, flavouring agent, pH modifier and solvent.

Preservative for present invention is selected from group consisting of benzoic acid, methyl paraben, ethyl paraben, propyl paraben, butyl paraben, sodium benzoate and benzalkonium chloride. Benzoic acid is preferred one.

Flavouring agent for present invention is selected from group consisting of rape, banana, vanilla, cherry, citrus, peach, strawberry, bubble gum, peppermint, wintergreen or combination thereof. In a preferred embodiment combination of one or more flavouring agent is to be used. In yet preferred embodiment, combination of banana and vanilla flavour is to be used.

pH modifier is to be used to adjust the pH of final formulation in the range from about 2.0 to 4.0 preferably about 3.0 to 4.0 and more preferably at about 3.5. As a pH

modifier, sodium hydroxide or hydrochloric acid can be used. Preferably sodium hydroxide in the form of solution can be used.

As a solvent for the liquid formulation of present invention, glycerine, alcohols, propylene glycol, polyethylene glycol, purified water, ethanol, isopropyl alcohol or combinations thereof can be used. According to solubility and requirement of active ingredient and excipient any suitable solvent from above list can be used. For making final volume of the formulation purified water is to be used.

As per another embodiment of the present invention the liquid pharmaceutical formulation of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof is to be advised to administer in dosage of 135 mg to 405 mg per day. In a preferred embodiment, the liquid pharmaceutical formulation of present invention is advised to administer as 13.5 ml of composition three times a day.

As per one more embodiment of the present liquid pharmaceutical formulation is to be used for treatment of irritable bowel syndrome and other conditions including chronic irritable colon, spastic constipation, mucous colitis, spastic colitis, colicky abdominal pain and cramps, persistent, non-specific diarrhoea with or without alternating constipation and flatulence.

As per one embodiment, the present invention is a liquid pharmaceutical formulation with taste masking comprising

a) 0.1 to 10 % w/v of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate hydrochloride,

b) 50 to 80% w/v of invert syrup,

c) 0.01 to 0.04 % w/v of levomenthol,

d) Benzoic acid

e) one or more pharmaceutically acceptable excipient.

As per another embodiment, the present invention is a liquid pharmaceutical formulation with taste masking comprising

a) 1.0 % w/v of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate hydrochloride,

b) 75 % w/v of invert syrup,

c) 0.028 % w/v of levomenthol,

d) Benzoic acid

e) one or more pharmaceutically acceptable excipient.

Yet one more embodiment, the present invention is a liquid pharmaceutical formulation with taste masking comprising

a) 1.0 % w/v of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate hydrochloride,

b) 75 % w/v of invert syrup and 0.6 % w/v of sucralose,

c) 0.028 % w/v of levomenthol,

d) Benzoic acid

e) one or more pharmaceutically acceptable excipient.

The liquid pharmaceutical formulation of the present invention is chemically and physically stable without any precipitation or crystallization during stability study and further overcame problem of bitter taste.

The liquid pharmaceutical formulation of present invention being in the form of solution also offers an advantage of clear formulation, uniform dosing, no physical stability problem and also offers very less chances of medication error.

The invention is further illustrated by the following examples, which are by no means intended to limit the scope of the invention but are given by way of illustration.

Example

Example 1

Sr. No.	Ingredients	Qty/100ml
1	RS)-4-(ethyl[1-(4-methoxyphenyl)propan-2-yl] amino) butyl 3,4-dimethoxybenzoate hydrochloride	1.00 g
2	Glycerol	20.00 g
3	Benzoic acid	0.060 g
4	Propylene glycol	1.78 g
5	Banana Flavour	0.375 g
6	Vanilla Flavour	0.375 g
7	Levomenthol	-
8	Sucralose	-
9	Invert syrup	75.00 g
10	Purified water	Up to 100 ml
11	Sodium hydroxide solution (1 N)	QS to pH 3.5

Procedure:

1. Benzoic acid was dissolved in glycerol with heating at 80-90°C to get a clear colourless solution and later kept aside to cool at room temperature.
2. Invert syrup was added to solution of step 1) by mixing for 15-20 minutes to get a clear colourless to pale yellow solution.

3. RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxy benzoate hydrochloride was dissolved separately in 20 ml of purified water by mixing for 10-15 minutes to get clear colourless to pale yellow solution.
4. Solution of step 3) was mixed with solution of step 2) to get clear colourless to pale yellow solution.
5. Banana and vanilla flavour were mixed with solution of step 4) by mixing to get clear colourless to pale yellow solution.
6. pH of solution of step 5) was checked and found 3.5. If not to be adjusted to pH 3.5 using NaOH solution.
7. Purified water was added to solution of step 6) and mixed to get clear colourless to pale yellow solution and to make final volume.

Example 2

Sr. No.	Ingredients	Qty/100ml
1	RS)-4-(ethyl[1-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate hydrochloride	1.00 g
2	Glycerol	20.00 g
3	Benzoic acid	0.060 g
4	Propylene glycol	1.78 g
5	Banana Flavour	0.375 g
6	Vanilla Flavour	0.375 g
7	Levomenthol	-
8	Sucralose	0.600 g
9	Invert syrup	75.00 g
10	Purified water	Up to 100 ml
11	Sodium hydroxide solution (1 N)	QS to pH 3.5

Procedure:

As per example 1. Only change is sucralose was added in to step 3) solution.

Example 3

Sr. No.	Ingredients	Qty/lOOml
1	RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl] amino)butyl 3,4-dimethoxybenzoate hydrochloride	1.00 g
2	Glycerol	20.00 g
3	Benzoic acid	0.060 g

4	Propylene glycol	1.78 g
5	Banana Flavour	0.375 g
6	Vanilla Flavour	0.375 g
7	Levomenthol	0.028 g
8	Sucralose	-
9	Invert syrup	75.00 g
10	Purified water	Up to 100 ml
11	Sodium hydroxide solution (I N)	QS to pH 3.5

Procedure:

As per example 1. Only change is levomenthol was added in to step 3) solution after dissolving in propylene glycol.

Example 4

Sr. No.	**Ingredients**	**Qty/100ml**
1	RS)-4-(ethyl[1-(4-methoxyphenyl)propan-2-yl] amino) butyl3,4-dimethoxybenzoate hydrochloride	1.00 g
2	Glycerol	20.00 g
3	Benzoic acid	0.060 g
4	Propylene glycol	1.78 g
5	Banana Flavour	0.375 g
6	Vanilla Flavour	0.375 g
7	Levomenthol	0.028 g
8	Sucralose	0.600 g
9	Invert syrup	75.00 g
10	Purified water	Up to 100 ml
11	Sodium hydroxide solution (1 N)	QS to pH 3.5

Procedure:

As per example 1. Only change is levomenthol was added in to step 3) solution after dissolving in propylene glycol followed by addition of sucralose.

Example 5: Evaluation of taste

The taste of liquid formulations prepared in example 1 to example 4 was checked by panel method. For this purpose, 10 human volunteers were selected and about 5 ml formulations was placed on tongue and taste evaluated after 15 seconds.

Results are mentioned in below table

Formulation	Volunteer									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Example 1	2	2	2	3	2	2	2	3	2	4
Example 2	2	2	3	2	2	2	2	2	2	2
Example 3	0	0	0	1	0	0	0	1	0	1
Example 4	0	0	0	1	0	0	0	0	0	0

0=Palatable, 1= Normal, 2=Slightly bitter, 3=bitter, 4= Extremely bitter

Example 6: Stability study

Based on taste parameter result it was found that formulation of example 4 found satisfactory and acceptable compared to rest. Therefore stability study of formulation of Example 4 was conducted at different temperature and relative humidity conditions for 6 months in Type III 100ml Amber glass bottle and results are as described below;

I. Storage Condition : 40±2°C/75±5% RH

Test	Specification	Month				
		0	1	2	3	6
Description	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution
Odour	Banana	Banana	Banana	Banana	Banana	Banana
pH	2.0-4.0	3.10	3.00	2.97	2.67	3.04
Density (gm/ml)	1.2212-1.2710	1.2412	1.2449	1.2365	1.2458	1.2695

Assay	*Drug	95.0-105.0%	100.3	102.0	98.5	100.3	99.4
	Benzoic Acid	95.0-105.0%	97.8	98.8	97.5	95.8	95.3
Related Substances By HPLC							
Impurity B		NMT 0.2%	ND	0.01	ND	ND	ND
Impurity C		NMT 0.2%	0.01	0.020	ND	0.020	0.085
Impurity D		NMT 0.2%	0.01	ND	ND	0.070	0.073
SMUI		NMT 0.2%	0.02	0.022	0.035	0.010	0.115
Total Impurity		NMT 0.3%	0.18	0.190	0.140	0.249	0.283

SMUI= Single Max Unknown Impurity
*Drug = (RS)-4-(ethyl[l-(4-methoxy phenyl) propan-2-yl] amino) butyl 3,4-dimethoxy benzoate hydrochloride

II. Storage Condition : 25±2°C/60±5 % RH

Test		**Specification**	**Month**				
			0	**1**	**2**	**3**	**6**
Description		clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution
Odour		Banana	Banana	Banana	Banana	Banana	Banana
pH		2.0-4.0	3.10	3.07	3.03	2.77	3.08
Density (gm/ml)		1.2212-1.2710	1.2412	1.2443	1.2393	1.2456	1.2669
Assay	* Drug	95.0-105.0%	100.3	101.5	98.9	100.8	100.4
	Benzoic acid	95.0-105.0%	97.8	98.4	98.1	95.3	95.5
Related Substances By HPLC							
Impurity B		NMT 0.2%	ND	0.01	ND	ND	ND
Impurity C		NMT 0.2%	0.01	0.01	ND	ND	0.019
Impurity D		NMT 0.2%	0.01	ND	ND	0.02	0.018
SMUI		NMT 0.2%	0.02	0.02	0.01	0.01	0.131
Total Impurity		NMT 0.3%	0.18	0.17	0.11	0.16	0.168

SMUI= Single Max Unknown Impurity
*Drug = (RS)-4-(ethyl[l-(4-methoxy phenyl) propan-2-yl] amino) butyl 3,4-dimethoxy benzoate hydrochloride

III. Storage Condition : 30±2°C/65±5 % RH

Test		Specification	Month				
			0	1	2	3	6
Description		clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution	clear colourless to pale yellow solution
Odour		Banana	Banana	Banana	Banana	Banana	Banana
pH		2.0-4.0	3.10	3.02	2.96	2.73	3.10
Density (gm/ml)		1.2212-1.2710	1.2412	1.2431	1.2378	1.2455	1.2685
Assay	*Drug	95.0-105.0%	100.3	100.9	99.1	100.6	101.0
	Benzoic acid	95.0-105.0%	97.8	97.8	98.3	95.4	96.1
Related Substances By HPLC							
Impurity B		NMT 0.2%	ND	0.01	ND	ND	ND
Impurity C		NMT 0.2%	0.01	0.011	ND	ND	0.043
Impurity D		NMT 0.2%	0.01	ND	ND	0.030	0.037
SMUI		NMT 0.2%	0.02	0.019	0.016	0.010	0.121
Total Impurity		NMT 0.3%	0.18	0.170	0.113	0.197	0.220

SMUI= Single Max Unknown Impurity

*Drug = (RS)-4-(ethyl[l-(4-methoxy phenyl) propan-2-yl] amino) butyl 3,4 dimethoxy benzoate hydrochloride

CLAIMS

[CLAIM **1].** A liquid pharmaceutical formulation with taste masking comprising

a) 0.1 to 10% w/w of (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof,

b) 50 to 85% w/w of at least one sweetener,

c) 0.01 to 0.04 % w/w of an auxiliary agent and,

d) one or more pharmaceutically acceptable excipient selected from preservative, flavouring agent, pH modifier and solvent.

[CLAIM **2].** The liquid pharmaceutical formulation with taste masking according to claim 1, wherein (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate is in the form of hydrochloride salt.

[CLAIM **3].** The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein sweetener is selected from group consisting of saccharin, saccharin sodium, aspartame, cyclamate, invert syrup, sucralose, acesulfame, acesulfame potassium, neotame, thaumatin, neohesperidine, neohesperidine dihydrochalcone, sucrose, trehalose, lactose, fructose, xylitol, mannitol, sorbitol or combinations thereof.

[CLAIM **4].** The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein sweetener is combination of sucralose and invert syrup.

[CLAIM **5].** The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein sweetener is invert syrup.

[CLAIM 6]. The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein auxiliary agent is selected from group consisting of Levomenthol, monoammonium glycyrrhizinate, L-arginine, L-lysine, citric acid, lactic acid, cineol and myrtol.

[CLAIM 7]. The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein ratio of invert syrup to Levomenthol is in the range from 0.8 to 0.000444 to 1.2 to 0.000296.

[CLAIM 8]. The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein formulation is pH in the range from about 2.0 to 4.0.

[CLAIM 9]. The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein preservative is selected from group consisting of benzoic benzoic acid, methyl paraben, ethyl paraben, propyl paraben, butyl paraben, sodium benzoate and benzalkonium chloride.

[CLAIM 10]. The liquid pharmaceutical formulation with taste masking according to any preceding claims, wherein flavouring agent is selected from group consisting of rape, banana, vanilla, cherry, citrus, peach, strawberry, bubble gum, peppermint, wintergreen or combination thereof.

[CLAIM 11]. The liquid pharmaceutical formulation with taste masking according to any preceding claims is to be used for treatment of irritable bowel syndrome and other conditions including chronic irritable colon, spastic constipation, mucous colitis, spastic colitis, colicky abdominal pain and cramps,

persistent, non-specific diarrhoea with or without alternating constipation and flatulence.

[CLAIM 12]. The liquid pharmaceutical formulation with taste masking according to any preceding claim is prepared by process comprising steps of;

a) adding preservative in purified water,
b) adding sweetener,
c) adding auxiliary agent,
d) adding (RS)-4-(ethyl[l-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate or pharmaceutically acceptable salts thereof,
e) adding flavouring agent and
f) adding purified water to make up to final volume and ensuring pH between 2.0 to 4.0.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/052768

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/Q8 A61K9/10 A61K47/26 A61K31/24 A61P1/Q6
ADD.

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)
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 practicable, search terms used)
EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Anonymous : "SUMMARY OF PRODUCT CHARACTERISTICS: Mebeveri ne 50mg/5ml Sugar Free Oral Suspensi on" , , 11 November 2015 (2015-11-11) , pages 1-5 , XP055390947, Retri eved from the Internet: URL: http://www.mhra. gov.uk/home/groups/spc pi 1/documents/spcpi l/conl449209160749 .pdf [retri eved on 2017-07-14] Page 1, points: 1 to 4.1. Page 3, point 6.1.	1-12
Y	US 2003/032600 Al (ULRICH STEPHEN A [US] ET AL) 13 February 2003 (2003-02-13) cl aims 1-4, 11-14, 23-38	1-12

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

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2017	31/07/2017

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/052768

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