(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 April 2019 (18.04.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/073321 A1

(51) International Patent Classification:
A61K 31/437 (2006.01) *A61K 31/44* (2006.01)
C07D 498/22 (2006.01)

(21) International Application Number:
PCT/IB2018/057099

(22) International Filing Date:
17 September 2018 (17.09.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201721035896 10 October 2017 (10.10.2017) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

WO 2019/073321 A1

(54) Title: EFFERVESCENT COMPOSITIONS COMPRISING RIFAXIMIN

(57) Abstract: The present disclosure relates to effervescent compositions comprising Rifaximin or salt thereof and manufacturing process for the same. The effervescent composition comprises at least one acidic agent and at least one basic agent along with one or more pharmaceutically acceptable excipient. The effervescent compositions provide quick dissolution upon contact with aqueous media, liberation of carbon dioxide results in pleasant taste, improved permeation across gastrointestinal membrane, and efficient release of drug therefore enhanced absorption, efficacy and better patient compliance in the treatment of traveler's diarrhea, Hepatic Encephalopathy and irritable bowel syndrome with diarrhea.

EFFERVESCENT COMPOSITIONS COMPRISING RIFAXIMIN

FIELD OF THE INVENTION

The present invention relates to effervescent compositions comprising Rifaximin for the treatment of Traveler's Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea.

BACKGROUND OF THE INVENTION

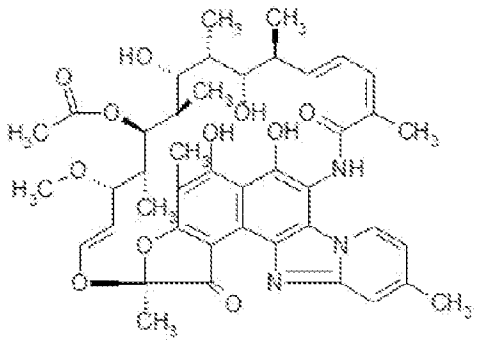
Traveler's diarrhea (TD) is a stomach and intestinal infection. TD is defined as the passage of unformed stool (one or more by some definitions, three or more by others) while traveling. It may be accompanied by abdominal cramps, nausea, fever, and bloating. Occasionally bloody diarrhea may occur. Most travelers recover within four days with little or no treatment. About 10% of people may have symptoms for a week. Recommendations for prevention include eating only properly cleaned and cooked food, drinking bottled water, and frequent hand washing. Primary treatment includes drinking lots of fluids and replacing lost salts (oral rehydration therapy). Antibiotics are recommended for significant or persistent symptoms.

Hepatic encephalopathy (HE) is an altered level of consciousness as a result of liver failure. Onset may be gradual or sudden. Other symptoms may include movement problems, changes in mood, or changes in personality. In the advanced stages it can result in a coma. Hepatic encephalopathy can occur in those with acute or chronic liver disease. Episodes can be triggered by infections, GI bleeding, constipation, electrolyte problems, or certain medications. Hepatic encephalopathy is possibly reversible with treatment. This typically involves supportive care and addressing the triggers of the event. Lactulose is frequently used to decrease ammonia levels. Certain antibiotics and probiotics are other potential options. A liver transplant may improve outcomes in those with severe disease.

Diarrhea is one of the symptoms often associated with irritable bowel syndrome (IBS). The key symptom of IBS is abdominal pain. The pain is associated with a change in the frequency or consistency of stool. The altered bowel habit may be chronic or recurrent diarrhea, or constipation. Some people have both diarrhea and constipation, just at

different times. Bloating or distention in the abdomen is also common. Mild signs and symptoms can often be controlled by managing stress and by making changes in diet and lifestyle. Laxatives, anticholinergic/antispasmodic agents, antidiarrheal agents, antidepressant medications, probiotics and antibiotics are the new therapies for Irritable Bowel Syndrome with Diarrhea which have been recently introduced and have been shown to effectively treat multiple symptoms of Irritable Bowel Syndrome with Diarrhea.

Rifaximin is non-aminoglycoside semi-synthetic, nonsystemic antibiotic derived from rifamycin SV. Chemically Rifaximin is (2S,16Z,18E,20S,21S,22R,23R,24R,25S,26S,27S,28E)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26octamethyl-2,7 (epoxypentadeca [1,11,13] trienimino) benzofuro[4,5-e] pyrido [1,2-á]-benzimidazole-1,15(2H)-dione,25acetate and its molecular weight is 785.9. Its empirical formula is $C_{43}H_{51}N_3O_{11}$. Rifaximin is represented by compound of structural formula I



(Formula I)

Rifaximin is red/orange microcrystalline powder soluble in methanol, chloroform, acetone and ethyl acetate. It is practically insoluble in water. It has a pKa of 6.77. The partition co-efficient (n-octanol-water) is 2.76.

The antibiotic Rifaximin was discovered in 1980 and originally patented in Italy as IT patent 1154655 granted on Jan 1987.

The Rifaximin tablet available under the trade name XIFAXAN® has a strength of 200mg. Further tablets having strength of 550mg is also available.

The 200mg of XIFAXAN® tablets are indicated for the treatment of Travelers' Diarrhea. The 550mg of XIFAXAN® tablets are indicated for the reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults and for the treatment of irritable bowel syndrome with diarrhea.

Chinese Patent Publication No. CN101623273B discloses dispersible tablet of Rifaximin. The dispersible tablet of Rifaximin creating a homogenous liquid before the drug is administered to the patient. This Chinese patent publication does not disclose effervescent technology/compositions for Rifaximin.

U.S. Patent No. 6,140,355 discloses pharmaceutical composition of effervescent vaginal tablets containing rifaximin. The said vaginal effervescent tablets are useful in the treatment of vaginal infections, particularly bacterial vaginosis; however, it does not discloses oral effervescent composition of Rifaximin which will be more permeable through GIT membrane, easily release results in more bioavailability in the treatment of Travelers' Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea.

U.S. Patent No. 8,642,573 discloses a method of maintaining remission of hepatic encephalopathy (HE) in a subject in need thereof comprising administering between about 1000 mg to about 1200 mg rifaximin daily to the subject for a period of 12 months or longer, thereby maintaining remission of HE.

U.S. Patent No. 8,309,569 discloses a method of providing acute treatment for diarrhea-associated Irritable Bowel Syndrome (dIBS) comprising: administering 1650 mg/day of rifaximin for 14 days to a subject in need thereof, wherein removing the subject from treatment after the 14 days results in a durability of response, wherein the durability of response comprises about 12 weeks of adequate relief of symptoms.

U.S. Patent No. 8,969,398 discloses a method of decreasing a subject's risk of a hepatic encephalopathy (HE) breakthrough episode comprising administering rifaximin daily for

a period of about 12 months or longer to a subject suffering from HE, thereby decreasing the subject's risk of an HE breakthrough episode, wherein a breakthrough episode is defined as an increase of the Conn score to Grade ≥ 2 or an increase in Conn score of 1 and asterixis grade of 1 for subjects having a baseline Conn score of 0.

U.S. Patent No. 9,364,467 discloses that the rehydration therapy can be administered before, during or after the administration of the 25-desacetyl rifaximin.

Currently, the commercially marketed product of Rifaximin for the treatment of Travelers' Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea is available in the form of conventional immediate release tablet.

The commercially marketed product of Rifaximin tablet 200mg taken orally three times a day for the treatment of Travelers' Diarrhea. The commercially marketed product of Rifaximin tablet 550 mg taken orally two times a day for reduction in risk of overt hepatic encephalopathy. The commercially marketed product of Rifaximin tablet 550 mg taken orally three times a day for the treatment of Irritable Bowel Syndrome with Diarrhea.

According to the Biopharmaceutical Classification System (BCS), Rifaximin is classified as BCS class IV drug which is low soluble and low permeable. Rifaximin possesses low intestinal permeability with low aqueous solubility. Since its low solubility and low permeability, commercially available conventional immediate release tablets and other product known in the prior art are less bioavailable and less efficacious in the treatment of Travelers' Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea.

Thus, there is an unmet need in the art to develop more bioavailable and more efficacious dosage form which will treat Travelers' Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea more efficiently.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide effervescent compositions comprising rifaximin which allow efficient release of rifaximin through the dosage form and more permeation of rifaximin through gastrointestinal membrane.

It is another object of the present invention to provide effervescent compositions comprising rifaximin with more bioavailability and efficacy in the treatment of traveler's diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea.

It is another object of the present invention to provide effervescent compositions comprising rifaximin which results in better patient compliance in the treatment of traveler's diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea with less adverse effects.

It is yet another object of the present invention to provide a method for treating traveler's diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea involving administration of the effervescent compositions comprising rifaximin.

It is another object of the present invention is to provide method of treating Travelers' Diarrhea and Irritable Bowel Syndrome with Diarrhea by administering effervescent composition comprising Rifaximin along with oral rehydration therapy.

SUMMARY OF THE INVENTION

A first aspect of the present invention is to provide effervescent compositions comprising Rifaximin.

In another aspect of the present invention is to provide effervescent compositions comprising Rifaximin along with one or more pharmaceutically acceptable excipient.

In another aspect of the present invention is to provide effervescent tablet, effervescent capsule, effervescent granule, effervescent powder, effervescent disc or effervescent sachet of Rifaximin.

In another aspect of the present invention is to provide effervescent tablet, effervescent capsule, effervescent granule, effervescent powder, effervescent disc or effervescent sachet of Rifaximin comprising one or more pharmaceutically acceptable excipient.

In another aspect of the present invention is to provide process of manufacturing the effervescent compositions comprising Rifaximin.

In another aspect of the present invention is to provide method of treating traveler's diarrhea, reduction in risk of overt hepatic encephalopathy recurrence and method of treating irritable bowel syndrome with diarrhea by administering effervescent composition comprising Rifaximin.

In another aspect of the present invention is to provide method of decreasing a subject's risk of a hepatic encephalopathy (HE) breakthrough episode comprising administering Rifaximin for a period of about 6 months.

In another aspect of the present invention is to provide method of decreasing a subject's risk of a hepatic encephalopathy (HE) breakthrough episode comprises administering effervescent composition of Rifaximin for a period of about 6 months.

In another aspect of the present invention is to provide method of treating Travelers' Diarrhea and Irritable Bowel Syndrome with Diarrhea by administering effervescent composition comprising Rifaximin along with oral rehydration therapy.

DETAIL DESCRIPTION OF THE INVENTION

The present invention relates to effervescent compositions comprising Rifaximin.

The Rifaximin of the present invention may be present in the form of free base or its pharmaceutically acceptable salt.

The effervescent compositions of the present invention may be in the form of composition which is meant to be administered directly in to the gastrointestinal tract via oral route. The effervescent compositions of the present invention may float into the gastrointestinal tract.

The effervescent compositions of the present invention may be in the form of composition which is meant to be added into the glass of water just before administration and the drug solution or dispersion is to be drunk immediately.

The term effervescent composition according to present invention means, the composition of Rifaximin or salt thereof which upon contact with aqueous media produces carbon dioxide.

The term effervescent composition according to present invention also means the composition of rifaximin which comprises at least one acidic agent.

The term effervescent composition according to present invention also means the composition of rifaximin which comprises at least one basic agent.

Conventional solid delivery systems of rifaximin such as tablet must be ingested with water to disintegrate the dosage form, inside the stomach it has to disintegrate into small particles and the active ingredient has to be solubilized such that it can be absorbed into the blood plasma of the patient. The disintegration and solubilization processes of solid dosage forms delay the bioavailability of active ingredient.

The effervescent compositions of the present invention offer enhanced dissolution and absorption of rifaximin resulting in increased bioavailability.

According to present invention rifaximin are absorbed better from effervescent formulations as compared to dry, solid oral formulations.

The effervescent compositions of the present invention provide quick dissolution upon contact with aqueous media, liberation of carbon dioxide (CO_2) results in pleasant taste, improved permeation across GIT membrane therefore enhanced absorption.

The effervescent compositions comprising Rifaximin of the present invention may be in the form of effervescent tablet, effervescent capsule, effervescent granule, effervescent powder, effervescent disc or effervescent sachet.

The effervescent compositions comprising Rifaximin may contain one or more pharmaceutically acceptable excipient selected from the group consisting of diluents, acidic agent, basic agent, binders, disintegrants, solubilizing agent, sweeteners, flavor, pH regulating agent, surfactant, stabilizing agent, antioxidant, lubricant, glidant and coloring agents.

The examples of diluents include but not limited to mannitol, sorbitol, xylitol, cellulose derivatives, starch, maltodextrin, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide or mixture thereof.

The examples of acidic agents include but not limited to citric acid, malic acid, tartaric acid, fumaric acid, adipic, anhydrides and salts of acid or mixture thereof.

The examples of basic agents include but not limited to potassium carbonate, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, arginine carbonate, glycine carbonate or mixture thereof.

The examples of binders include but not limited to, ethyl cellulose, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose sodium, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, methyl cellulose, povidone, starch or mixture thereof.

The examples of disintegrants include but not limited to croscarmellose sodium, carboxymethyl cellulose, chitosan, carboxymethyl cellulose calcium, carboxymethyl cellulose sodium, crospovidone, hydroxypropyl cellulose, microcrystalline cellulose, methyl cellulose, starch, sodium starch glycolate or mixture thereof.

The examples of solubilizing agent include but not limited to polyethylene glycol, polyvinylpyrrolidone, dextran, or mixture thereof.

The examples of sweeteners include but not limited to saccharose, glucose, maltose, galactose and artificial sweeteners, such as acesulfame potassium, sodium saccharin, cyclamates, sucralose or mixture thereof.

The examples of flavor include but not limited to fruit flavor, peppermint flavor, sour cherry flavor, orange flavor or mixture thereof.

The examples of pH regulating agent include but not limited to fumarate, citrate, phosphate, carbonate, tartrate, acetate, amino acid salts or mixture thereof.

The examples of surfactant include but not limited to polysorbate, sodium lauryl sulphate, polyoxyethylene, polyoxypropylene glycol or mixture thereof.

The examples of stabilizing agent include but not limited to tocopherol, cyclodextrin tetrasodium edetate, nicotinamide or mixture thereof.

The examples of antioxidants include but not limited to BHA, BHT, Sodium sulfate or mixture thereof.

The examples of lubricant include but not limited calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate or mixture thereof.

The examples of glidant include but not limited to silicon dioxide, talc, stearic acid, magnesium stearate, calcium stearate or mixture thereof.

The examples of coloring agents include but not limited to titanium dioxide and dye suitable for food such as those known as FD & C dyes and natural coloring agents such as grape skin extract, beet red powder, beta-carotene, annato, carmine, turmeric, paprika or mixture thereof.

In another aspect of the present invention is to provide process of manufacturing the effervescent compositions comprising Rifaximin.

The effervescent compositions comprising Rifaximin of the present invention can be manufactured by process such as direct compression, dry granulation, wet granulation, roller compaction and hot melt extrusion. The process of manufacturing effervescent composition comprising mixing Rifaximin along with one or more one or more pharmaceutically acceptable excipient like diluents, acidic agent, basic agent, binders, disintegrants, solubilizing agent, sweeteners, flavor, pH regulating agent, surfactant, stabilizing agent, antioxidant, lubricant, glidant and coloring agents. Preferably the manufacturing process may involve direct compression, dry granulation or wet granulation approach.

The effervescent composition can comprise any suitable amount of the Rifaximin in order to produce an effective blood level of the Rifaximin in the travelers' diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea. The weight percentage of Rifaximin can be 2% to 50%, preferably 5 to 40 % based on the total weight of composition. The amount of Rifaximin thereof may ranges from 50mg to 800mg, preferably 100mg to 700 mg, more preferably 150mg, 200mg, 250mg, 300mg, 350mg, 400mg, 450mg, 500mg, 550mg, 600mg, 650mg, and 700mg.

The effervescent composition can comprise any suitable amount of the one or more pharmaceutically acceptable excipient like diluents, acidic agent, basic agent, binders,

disintegrants, solubilizing agent, sweeteners, flavor, pH regulating agent, surfactant, stabilizing agent, antioxidant, lubricant, glidant and coloring agents.

The acidic agent is present in the effervescent composition in an amount of about 1% to about 60% based on the total weight of the composition; preferably in an amount of about 3% to about 50%; more preferably in an amount of about 5% to about 40%. The basic agent is present in the effervescent composition in an amount of about 5% to about 80% based on the total weight of the composition; preferably in an amount of about 10% to about 70% more preferably in an amount of about 15% to about 60%.

The binder is present in the effervescent composition in an amount of about 0.5% to about 30% based on the total weight of the composition; preferably in an amount of about 1% to about 10%. The disintegrant is present in the effervescent composition in an amount of about 1% to about 20% based on the weight of the composition.

The solubilizing agent is present in the effervescent composition in an amount of about 0.1% to about 20% based on the total weight of the composition. The sweetener is present in the effervescent composition in an amount of about 0.0001% to about 6% based on the total weight of the composition; preferably in an amount of about 0.001% to about 2%.

The flavor is present in the effervescent composition in an amount of about 0.001% to about 10% based on the total weight of the composition; preferably in an amount of about 0.01% to about 3%. The lubricant is present in the effervescent composition in an amount of about 0.1% to about 6% based on the total weight of the composition.

The glidant is present in the effervescent composition in an amount of about 0.1% to about 10% based on the total weight of the composition. The coloring agent is present in the effervescent composition in an amount of about 0.1% to about 5% based on the total weight of the composition. The antioxidant is present in the effervescent composition in an amount of about 0.01% to about 1% based on the total weight of the composition.

According to present invention, not only the choice of acidic and basic agent affect performance but the ratio of acid to base will also affect the performance of the effervescent composition of Rifaximin. Accordingly, it was observed that an acid to base ratio in the formulation ranging from 1:3 to 3:1. The acidic agents may be like citric acid, malic acid, tartaric acid, fumaric acid, adipic acid, anhydrides and salts of acid or mixture thereof. Preferably acidic agent is citric acid. The basic agents may be like sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate, arginine carbonate. Preferably basic agent is sodium bicarbonate, sodium carbonate or mixture thereof.

Acidic and basic agent present in the effervescent composition reacts with aqueous media; wherein acid neutralizes base with the liberation of carbon dioxide and formation of acid salt and water.

According to the Biopharmaceutical Classification System (BCS), Rifaximin is classified as BCS class IV drug which is low soluble and low permeable. Rifaximin possesses low intestinal permeability with low aqueous solubility.

The effervescent compositions comprising Rifaximin of the present invention therefore allows quick release and dissolution of active ingredient when comes in contact with aqueous media.

The effervescent compositions comprising Rifaximin of the present invention reacts with aqueous media and produces carbon dioxide by effervescent reaction. The carbon dioxide produced by effervescent reaction allows enhanced permeability of Rifaximin due to an alteration of the paracellular as well as transcellular pathway. The paracellular pathway is the primary route of absorption for active ingredients in which solutes diffuse into the intercellular space between epithelial cells. The carbon dioxide produced by effervescent alters (widens) the intercellular space between cells, which leads to greater absorption of active ingredients. The effervescent compositions comprising Rifaximin of the present invention also promote transcellular absorption by inducing a change in the cell membrane structure.

The effervescent compositions comprising rifaximin of the present invention reacts with aqueous media and produces carbon dioxide by effervescent reaction. The said dosage form allows minimum loss of Rifaximin through first pass metabolism results in increased systemic bioavailability of rifaximin in the treatment of traveler's diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea.

The effervescent compositions comprising rifaximin of the present invention shows quick disintegration and dissolution upon contact with water. The effervescent composition of the present invention when formulated as tablet has a disintegration time of about 300 seconds or less. Preferably, the disintegration time of the effervescent tablet is about 90 seconds or less. The disintegration time is measured in 200 ml of water at room temperature of about 25°C±5°C.

The effervescent compositions comprising Rifaximin of the present invention upon dissolution has pH ranges from 4 to 6.5. The pH is measured in 200 ml of water at room temperature of about 25°C±5°C.

The effervescent compositions comprising Rifaximin of the present invention has pleasant taste which allows patient acceptability and better compliance in the treatment of traveler's diarrhea, hepatic encephalopathy and irritable bowel syndrome with diarrhea.

The effervescent compositions comprising Rifaximin of the present invention can be made up of any weight with suitable quantities of Rifaximin and pharmaceutically acceptable excipient.

The other physical parameters of effervescent compositions of present invention like appearance, thickness, weight variation, hardness, friability, smell, taste, after taste were found to be satisfactory.

The composition of Rifaximin in the present invention, due to effervescent technology provides more bioavailability, efficacy and better patient compliance in the treatment of

Traveler's Diarrhea, Hepatic Encephalopathy and Irritable Bowel Syndrome with Diarrhea.

In another aspect of the present invention is to provide method of treating Travelers' Diarrhea and Irritable Bowel Syndrome with Diarrhea by administering effervescent composition comprising Rifaximin along with oral rehydration therapy.

In Travelers' Diarrhea and in Irritable Bowel Syndrome with Diarrhea, there is loss of water from the body a condition called dehydration. In order to treat or prevent dehydration oral rehydration therapy is used in the treatment of Traveler's Diarrhea and in Irritable Bowel Syndrome with Diarrhea along with effervescent composition of Rifaximin.

The oral rehydration therapy involves drinking water with modest amounts of sugar and salt. The formula for oral rehydration salt contains ingredient like glucose and salt like sodium, potassium, citrate and chloride.

The effervescent compositions comprising Rifaximin of the present invention can be packaged in suitable air tight containers and moisture proof packs.

EXAMPLES:

In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these are not intended to limit the scope of the present invention in any way.

Example 1:

Sr. No.	Ingredients	Weight (mg/tab)	% w/w
1.	Rifaximin	500	20
2.	Citric acid anhydrous	260	10.4
3.	Sodium bicarbonate	750	30

4.	Sodium citrate dihydrate	594	23.76
5.	Mannitol	248	9.92
6.	Sucralose	12.5	0.5
7.	Polyvinyl pyrrolidone	62.5	2.5
8.	Forest fruit flavor	4.0	0.16
9.	Colloidal silicon dioxide	50	2.0
10.	Magnesium stearate	19	0.76
Tablet weight		**2500**	**100.00**

Manufacturing Process:

1. Rifaximin, Sodium bicarbonate, Mannitol, Polyvinyl pyrrolidone, Sucralose, Forest fruit flavor and Colloidal silicon dioxide were sifted through ASTM #40; Citric acid anhydrous and Sodium citrate dihydrate were sifted through #20 and mixed.
2. Magnesium stearate was sifted through ASTM #60.
3. Blend of step 1 was mixed with Magnesium stearate of step 2.
4. The blend of step 3 was compressed into tablet using tablet compression machine and suitable toolings.

Example 2:

Sr. No.	Ingredients	Weight (mg/tab)	% w/w
1.	Rifaximin	500	19.42
2.	Citric acid anhydrous	260	10.10
3.	Sodium bicarbonate	750	29.13
4.	Sodium citrate dihydrate	594	23.07
5.	Mannitol	248	9.63
6.	Sucralose	12.5	0.49
7.	Polyvinyl pyrrolidone	62.5	2.43
8.	Forest fruit flavor	4	0.16
9.	Colloidal silicon dioxide	50	1.94

10.	Magnesium stearate	19	0.74
11.	Crospovidone	75	2.91
Tablet weight		**2575**	**100.00**

Manufacturing Process:

1. Rifaximin, Sodium bicarbonate, Mannitol, Polyvinyl pyrrolidone, Crospovidone, Sucralose, Forest fruit flavor and Colloidal silicon dioxide were sifted through ASTM #40; Citric acid anhydrous and Sodium citrate dihydrate were sifted through #20 and mixed.
2. Magnesium stearate was sifted through ASTM #60.
3. The blend of step 1 was mixed with Magnesium stearate of step 2.
4. The blend of step 3 was compressed into tablet using tablet compression machine and suitable tooling.

Example 3:

Sr. No.	Ingredients	Weight (mg/sachet)	% w/w in each sachet
1.	Rifaximin	500	16.67
2.	Citric acid anhydrous	814.012	27.13
3.	Sodium bicarbonate	1635.734	54.52
4.	Neotame	0.054	0.002
5.	Taste masking agent	0.2	0.007
6.	Orange flavor	50	1.67
Sachet weight		**3000**	**100.00**

Manufacturing Process:

1. Rifaximin, Orange flavor, Neotame, Taste masking agent and Sodium bicarbonate were sifted through ASTM #40; Citric acid anhydrous was sifted through #20 and mixed for 20 min in a controlled temperature and humidity conditions.
2. Blend of step 1 was filled in Aluminum sachet and heat sealed.

Example 4:

Sr. No.	Ingredients	Weight (mg/sachet)	% w/w per sachet
1.	Rifaximin	500	7.15
2.	Citric acid anhydrous	814.012	11.46
3.	Sodium bicarbonate	1635.7	23.00
4.	Neotame	0.054	0.0008
5.	Taste masking agent	0.2	0.0028
6.	Orange flavor	50	0.70
7.	Sodium chloride	520	7.32
8.	Glucose, anhydrous	2700	38.03
9.	Potassium chloride	300	4.23
10.	Trisodium citrate dihydrate	580	8.17
Weight of granules per sachet		**7100**	**100.00**

Manufacturing Process:

1. Rifaximin, Orange flavor, Neotame, Taste masking agent and Sodium bicarbonate were sifted through ASTM #40; Sodium chloride, trisodium citrate were sifted through ASTM #30.
2. Glucose anhydrous, Potassium chloride and Citric acid anhydrous was sifted through #20.
3. Materials from step: 1 and Step: 2 were mixed in a suitable sized blender.
4. The blend of step 3 was filled in Aluminium sachet and heat sealed.

CLAIMS

1. An effervescent composition comprising Rifaximin or salt thereof.
2. An effervescent composition comprising Rifaximin or salt thereof; at least one acidic agent and at least one basic agent.
3. An effervescent composition according to claim 2, wherein acidic agent is selected from the group consisting of citric acid, malic acid, tartaric acid, fumaric acid, adipic acid, anhydrides and salts of acid or mixture thereof.
4. An effervescent composition according to claims 2 and 3, wherein acidic agent is preferably citric acid.
5. An effervescent composition according to claims 2, 3 and 4, wherein the amount of the acidic agent ranges from 5 % to 40 % by weight of composition.
6. An effervescent composition according to claim 2, wherein basic agent is selected from the group consisting of sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate, arginine carbonate, glycine carbonate or mixture thereof.
7. An effervescent composition according to claims 2 and 6, wherein basic agent is preferably sodium bicarbonate, sodium carbonate or mixture thereof.
8. An effervescent composition according to claims 2, 6 and 7, wherein the amount of the basic agent ranges from 15 % to 60 % by total weight of composition.
9. An effervescent composition according to claim 2, wherein the ratio of acidic agent to basic agent ranges from 1:3 to 3:1.
10. An effervescent composition according to claims 1 and 2 further comprises one or more pharmaceutically acceptable excipient selected from the group consisting of diluents, acidic agent, basic agent, binders, disintegrants, solubilizing agent, sweeteners, flavor, pH regulating agent, surfactant, stabilizing agent, antioxidant, lubricant, glidant and coloring agents.
11. A method of treatment of Traveler's Diarrhea, hepatic encephalopathy and Irritable Bowel Syndrome with Diarrhea in a subject in need of such treatment which comprises administering to said subject an effervescent composition according to claim 1.

12. The method of treatment according to claim 11 further comprising administering rehydration therapy to the subject.
13. An effervescent composition comprising Rifaximin or salt thereof for use in the treatment of Traveler's Diarrhea, hepatic encephalopathy and Irritable Bowel Syndrome with Diarrhea.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/057099

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/437,C07D498/22,A61K31/44 Version=2018.01

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, C07D

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US5314904 A (ALFA WASSERMANN SPA[IT]) 24 May 1994 Column 12, Example 11	1-10

☐ 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
12-12-2018	12-12-2018
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Abhas Kumar Bhoi Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/057099

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 11-13
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 11-13 include methods for treatment of the human body by therapy, and therefore relate to a subject matter which this International Searching Authority is not required, under the provisions of Article 17 (2)(a)(i)of the PCT and Rule 39.1(iv) of the

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/IB2018/057099

Citation	Pub.Date	Family	Pub.Date
US 5314904 A	24-05-1994	EP 0547294 A1	23-06-1993
		JP 2834951 B2	14-12-1998
		CA 2073601 C	09-07-1996