



- (51) **International Patent Classification:**
A61K 9/02 (2006.01) *A61P 31/04* (2006.01)
A61K 31/437 (2006.01)
- (21) **International Application Number:**
PCT/GB2011/000786
- (22) **International Filing Date:**
23 May 2011 (23.05.2011)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
3363/MUM/2010 9 December 2010 (09.12.2010) 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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** SUPPOSITORIES COMPRISING RIFAXIMIN

(57) **Abstract:** A pharmaceutical composition comprising rifaximin in the form of a suppository dosage form.



WO 2012/076832 A1

SUPPOSITORIES COMPRISING REFAXIMIN

FIELD OF INVENTION:

5 The present invention relates to a pharmaceutical composition comprising an antibacterial drug for rectal or vaginal application and a process for preparing such pharmaceutical composition. In particular the invention relates to a medicated pharmaceutical composition which is capable of releasing the medicament evenly over the walls of the vaginal or rectal cavity.

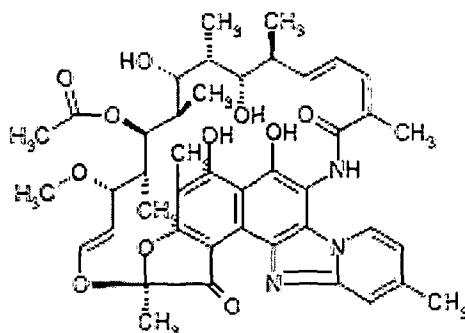
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BACKGROUND AND PRIOR ART:

One of the major obstacles to the development of highly potent pharmaceutical formulations is the poor water solubility of many drugs. Approximately 40% of potential drugs identified
15 by pharmaceutical companies are poorly soluble in water, which greatly hinders their clinical use. Low water solubility limits the bioavailability and absorption of these agents.

Rifaximin is a semisynthetic antibiotic belonging to the rifamycin class of antimicrobial drugs exhibiting in vitro activity against Gram-positive, Gram-negative and anaerobic
20 bacteria. Rifaximin acts by inhibiting bacterial ribonucleic acid (RNA) synthesis. Rifaximin is chemically named as[(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*S*,27*S*,28*E*)-5,6,21,23,25-pentahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-2,7 (epoxypentadeca-[1,11,13]trienimino)benzofuro [4,5-*e*]pyrido[1,2-*a*]-benzimidazole 1,15(2*H*)-dione,25-acetate]. Rifaximin has the following chemical formula.

25



Rifaximin has been indicated for the treatment of traveler's diarrhea caused by non-invasive strains of *Escherichia coli*, a micro-organism which is not able to penetrate into gastrointestinal (GI) mucosa and therefore remains in contact with gastrointestinal fluids. Rifaximin is highly effective in preventing and treating traveler's diarrhea, with fewer side effects and a low risk of developing antibiotic resistance.

Rifaximin is also approved for the treatment of pathologies whose etiology is in part or totally due to intestinal acute and chronic infections sustained by Gram-positive and Gram-negative bacteria, with diarrhea syndromes, altered intestinal microbial flora, summer diarrhea-like episodes, traveler's diarrhea and enterocolitis, pre- and post- surgery prophylaxis of the infective complications in gastro intestinal surgery; and hyperammonaemia therapy as coadjutant.

Rifaximin is a poorly water-soluble and minimally absorbed (<0.4%) drug with in vitro activity against enteric Gram-negative bacteria including enteric pathogens. [Gerard L *et al.*, Rifaximin, a non-absorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. Expert Review of Anti-infective therapy, 3(2), 201-211, (2005)].

It has also been reported that rifaximin is characterized by negligible systemic absorption, due to its chemical and physical characteristics [Descombe J J *et al.*, Pharmacokinetic study of rifaximin after oral administration in healthy volunteers. International Journal of Clinical Pharmacology Research, 14 (2), 51-56, (1994)].

Rifaximin has been described to be endowed with an antibacterial activity similar to the activity of rifampin [Venturini A. P. and Marchi E., Chemioterapia, 5 (4), 257-256, (1986)]. However, its mechanism of action differs from rifampin in that it is not absorbed through the systemic route after oral administration [Venturini A. P., Chemotherapy, 29, 1-3, (1983) and Cellai L. *et al.*, Chemioterapia, 3, (6), 373-377, (1984)] due to the zwitterionic nature of the compound, which cannot be absorbed by the gastrointestinal tract [Marchi E. *et al.*, Journal of Medicinal Chemistry., 28, 960-963, (1985)].

Hence in addition to poor water solubility, rifaximin has no systemic absorption, which poses a challenge to formulate suitable formulations of rifaximin.

Rifaximin is currently available as tablets, granules for oral suspension and ointment, 5 marketed in Europe and U.S.A. and in many other countries. Tablets, for example are currently marketed at the dosage of 200 mg for traveler's diarrhea under the brand name Xifaxan®.

US5314904 discloses therapeutic use of rifaximin in the treatment of vaginal infections, in 10 particular bacterial vaginosis. The patent discloses that the composition can be administered topically in the form of foam, a cream, a gel, a vaginal ovule or vaginal capsule.

US6140355 discloses a pharmaceutical composition for topical application on the vagina the composition being in the form of foam, or a cream.

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US5352679 discloses a pharmaceutical composition for treatment of gastric dyspepsia by oral administration of rifaximin, the composition being in the form of a tablet, a capsule, a sugar coated tablet, granules or a syrup.

20 US5886002 discloses a pharmaceutical composition of rifaximin for treatment of diarrhoea from cryptosporidiosis, the composition being in the form of a tablet, a capsule, a sugar coated tablet, granules or a syrup.

CN150914 discloses a rifaximin spray for treating bacterial rhinitis and inflammation of the 25 respiratory tract.

WO2009008005 discloses a multilayer tablet composition of rifaximin wherein one layer is an immediate release and the other is controlled release.

30 Further, as rifaximin exhibits a lower systemic absorption, there is yet a need to formulate rifaximin in a suitable dosage form.

One such dosage form is suppository. Suppositories are advantageous as they provide local action at the target site and in the case of rifaximin which is intestine.

The administration of medicaments in the form of suppositories is known in the art. In general usage, however, it has been found that upon liquefaction of the suppository some of the fluid containing the medicament flows out of the vaginal or rectal cavity leaving less of the medicament available for the intended therapeutic use. To counteract this loss of medicament, suppositories containing higher concentrations of the medicament are sometimes employed.

However, as a result of the higher concentration of medicament, the patient is exposed to higher doses of the drug than are actually required for successful treatment. In addition, the cost of the therapy is also unnecessarily increased due to the use of excess medicament.

Further for the suppository it is generally important that the stability of the drug be maintained during storage by insuring that the respective components of the suppository do not experience chemical or physical changes or that the proteins do not get decomposed, denatured, aggregated or reduces activity during storage. Further, it is important that the suppository should not only melt rapidly at body temperature within body cavities but also should not soften during summer or harden during winter nor absorb moisture from the ambient air. The suppository should withstand prolonged storage without causing putrefaction, deterioration, discoloration, mold growth or the denaturing of proteinaceous additives such as natural gelatin. Further the suppository should permit rapid release of the drug, should not contain substances that irritate the mucosa or produce local irritation, should provide a comfortable feel during use.

The use of a suppository is also advantageous in insane patients, in elderly patients who cannot swallow oral medication, bed ridden patients, unconscious patients, post operative patients who cannot be administered oral medication, or in infants.

While manufacturing suppositories one has to ensure that the drug is dispersed uniformly in the base and the suppositories have good emulsion stability. Further, the suppositories should

be manufactured by a simple process and should also be reproducible at an industrial scale.

Furthermore, the pharmaceutical formulation design must be performed with full consideration as to whether the suppository is intended to be administered for systemic action or local action and also whether the site of administration is at the rectum or vagina. For instance, if the site of administration is the rectum, the ease of absorption of the drug is a dominant factor and if the site of administration is the vagina, factors such as the possible effect of the suppository on the fetus and the feel of use which depends on the possibility of the base of remaining in the vagina are to be considered.

Thus, there is a need, to develop a rifaximin suppository formulation that overcomes the problems associated with the formulation of suppositories in the prior art.

OBJECT OF THE INVENTION:

The object of the present invention is to provide a pharmaceutical composition comprising rifaximin having improved stability during storage.

Another object of the present invention is to provide a process for preparing a pharmaceutical composition comprising rifaximin.

Yet another object of the present invention is to provide a method for treatment and/or prevention of colonic diseases which comprises administering a pharmaceutical composition comprising rifaximin.

SUMMARY OF THE INVENTION:

According to one aspect of the present invention there is provided a pharmaceutical composition comprising rifaximin or a pharmaceutically acceptable salt, solvate, derivative, hydrate, enantiomer, polymorph, complex, or mixtures thereof.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising rifaximin or a pharmaceutically acceptable salt, solvate, derivative, hydrate, enantiomer, polymorph, complex or mixtures thereof wherein the rifaximin may or may not be in the nanosize range.

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According to yet another aspect of the present invention there is provided a process for preparing a pharmaceutical composition comprising rifaximin or a pharmaceutically acceptable salt, solvate, derivative, hydrate, enantiomer, polymorph, complex or mixtures thereof wherein rifaximin may or may not be in a nanosize range.

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According to a further aspect of the present invention there is provided a method of treatment and/or prevention of colonic diseases which comprises administering a pharmaceutical composition comprising rifaximin or a pharmaceutically acceptable salt, solvate, derivatives hydrate, enantiomer, polymorph, complex or mixtures thereof wherein rifaximin may or may

15 not be in a nanosize range.

DETAILED DESCRIPTION OF THE INVENTION:

Suppository as a dosage form is smaller than any other medicinal preparations for internal
20 use. Particularly, it has an advantage that it can be easily dosed to children. Further, when the drug is administered in the dosage form of suppository, the drug is not available for any decomposition by acid, alkali, digestive enzymes and the like and hence does not cause gastro enteric troubles.

25 Suppositories can avoid decomposition of drugs by acid or enzyme in gastrointestinal tract when the drugs are orally administered. They can also avoid irritation, stimulation to the gastrointestinal mucosa which is caused by direct contact of drugs with the mucosa. In addition, suppositories are physiologically less affected by such factors as variations of pH in gastrointestinal tract, the gastric empty rate, mobility of gastrointestinal tract, mutual actions
30 between food components, and the like.

Moreover, where the delivery of a medicine in the form of injection may cause serious ill effects, these ill effects can be minimized by a local delivery in the form of a suppository only to the affected portion.

- 5 The inventors of the present invention have developed compositions for suppositories which sustain a melting point higher than the body temperature under dry storage conditions but, when inserted into body cavity, become moist due to the moisture in the cavities and thus quickly melt or gel at the body temperature.
- 10 Rifaximin is a poorly water-soluble drug exhibiting minimal absorption. Rifaximin is also characterized by negligible systemic absorption, due to its chemical and physical characteristics.

The desired therapeutic effect is achieved by diffusion of rifaximin throughout the vaginal or
15 rectal cavity and by preventing the liquefied suppository from flowing out of the vaginal or rectal cavity. The availability of rifaximin is thus increased by the resultant increase in the adhesion properties and the extension of the time during which the rifaximin resides in the vaginal or rectal cavity. The unique combination of ingredients results in a homogeneous medicated pharmaceutical composition which is capable of distributing rifaximin throughout
20 the vaginal or rectal cavity.

The term "rifaximin" is used in broad sense to include not only "rifaximin" *per se* but also its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable
25 derivatives, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable complexes, etc.

The pharmaceutical composition of the present invention may comprise rifaximin in a crystalline form, amorphous form, or may be nanosized, or may be present in the form of a
30 complex of cyclodextrin and PVP or mixtures thereof.

According to one embodiment of the present invention, the rifaximin may be present in the nanosize form.

According to another embodiment, the pharmaceutical composition of the present invention
5 is in the form of a suppository.

Nanonization of hydrophobic or poorly water-soluble drugs generally involves the production of drug nanocrystals through either chemical precipitation (bottom-up technology) or disintegration (top-down technology). Different methods may be utilized to reduce the
10 particle size of the hydrophobic or poorly water soluble drugs. [Huabing Chen *et al.*, discusses the various methods to develop nanoformulations in "Nanonization strategies for poorly water-soluble drugs," Drug Discovery Today, Volume 00, Number 00, March 2010].

Nanosizing leads to increase in the exposure of surface area of rifaximin particles leading to
15 an increase in the rate of dissolution.

In certain embodiments, the present invention thus provides a pharmaceutical composition, comprising rifaximin wherein rifaximin is in the nanosize range.

20 The nanoparticles of the present invention can be obtained by any of the process such as but not limited to milling, precipitation, homogenization and the like.

The pharmaceutical composition of the present invention may comprise rifaximin having an effective particle size range of less than 2000nm, preferably below 1000nm.

25

According to one embodiment of the present invention, the process of milling comprises dispersing rifaximin particles in a liquid dispersion medium in which rifaximin is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of rifaximin to the desired effective average particle size.

30

The pharmaceutical composition according to the present may comprise 200mg of rifaximin.

The dose of the pharmaceutical composition of the present invention may be varied as appropriate for such factors as the frequency of administration per day, the content of rifaximin in a single suppository and the severity of the disease to be treated.

- 5 The present invention thus provides a pharmaceutical composition comprising rifaximin, one or more suppository vehicles and optionally other pharmaceutically acceptable carriers.

Alternatively, present invention also provides a pharmaceutical composition comprising rifaximin, one or more suppository vehicles and optionally other pharmaceutically acceptable
10 carriers in a soft capsule.

Thus, the invention encompasses two embodiments of suppository formulation

In one embodiment, the rifaximin is dispersed within a solidified suppository vehicle. In this
15 embodiment, any excipients may be dispersed within the solidified suppository vehicle along with the rifaximin. Suitable excipients include surfactants, sucrose fatty acid esters, stabilizers, pH adjusting agents, isotonic agents, viscosity-adjusting agents, preservatives, as described below. In addition, and additional active ingredient may be dispersed in the solidified suppository vehicle.

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In another embodiment, the rifaximin and a suppository vehicle are disposed within a soft capsule, which is preferably a gelatin capsule. In this embodiment, any excipients may be dispersed within the suppository vehicle along with the rifaximin. Suitable excipients include surfactants, sucrose fatty acid esters, stabilizers, pH adjusting agents, isotonic agents,
25 viscosity-adjusting agents, preservatives, as described below. In addition, and additional active ingredient may be dispersed in the suppository vehicle. In this embodiment, the suppository vehicle is typically not solidified and may be a liquid.

In both embodiments the suppository vehicle may be aqueous or fatty.

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Thus viewed from one aspect the invention provides a soft capsule comprising rifaximin one or more suppository vehicles and optionally other pharmaceutically acceptable carriers, wherein the capsule shell may comprise gelatin, glycerol, sorbitol solution, plant polysaccharides or their derivatives like carrageenans and modified forms of starch and
5 cellulose.

The following description relating to the suppository vehicle and the excipients applies equally to either of the above embodiments, except that in the first embodiment the suppository vehicle will be selected to be suitable as solid vehicle, whereas in the second
10 embodiment it will be selected to be suitable for use within a capsule.

The suppository vehicle comprises a suppository base and certain adjuvants and additives suitable for making such formulations. The suppository base may be an aqueous base that has hydrophilic properties or a fatty base material that has hydrophobic properties.

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The fatty based (oleaginous base) suppositories used in the present invention include materials that are commonly used for making suppositories such as cocoa butter, palm oil, coconut oil, lard; waxes, such as lanolin and vasoline; fatty acids, such as, oleic, stearic, and lauric acids, polyethylene glycols or mixtures of mono, di, and triglycerides of fatty acids of
20 C₁₀ to C₂₀ chain length.

Suitable examples of fatty base that can be used in the present invention comprise olive oil, soyabean oil, vegetable oil, hydrogenated castor oil, other hydrogenated fatty acids, petrolatum, various forms of paraffin, stearic acid and oleic acid, polyethylene glycol 1,000-
25 8,000 (PEG=polymer of ethylene oxide, mol. wt. 1,000-8,000); cocoa butter, NF (fat obtained from the roasted seed of Theobroma cacao); Suppocire AI, A, B, C, D, AS2, BS2, AT, AS2X, BS2X, CS2X (Semi-synthetic glycerides- Multi purpose vehicles), Suppocire AIM, AM, BM, BCM, CM, DM (Semi-synthetic glycerides- Low Reactivity Vehicles), Suppocire AIML, AML, BML (Semi-synthetic glycerides- Low Reactivity Vehicles
30 Compatible With Large Amounts Of Powders), Suppocire AP, BP, CP, DP (Saturated polyglycolysed glycerides- Absorption Enhancers), Suppocire NA 0, NAI 10, NA 10, NAS 10, NA 15, NAIS 10, NCS 10 (Semi-synthetic glycerides- Low Reactivity Vehicles),

Suppocire NAI, NAI 25A, NA 35, NA I 50, NA 50, NAS 40, NAS 50, NAS 55, NAIS 90, (Semi-synthetic glycerides- Large Scale Production Vehicles), Suppocire NAI 25, NA, NB, NC, ND, NAL, NBL, NAX, NBX, NCX (Semi-synthetic glycerides- Multi purpose vehicles), Suppocire AIX (semi-synthetic glycerides with ethoxylated fatty acid esters containing 95% mono, di and triglycerides and 5% polysorbate 65); Ovicure WL 2944, WL 3264, WL 3460 (Semi-synthetic glycerides- Vehicles for Vaginal Pessaries); Witepsol H 5 (Hydrogenated Coco-Glycerides), Witepsol H 12 (Hydrogenated Coco-Glycerides), Witepsol H 15 (Hydrogenated Coco-Glycerides), Witepsol H 19 (Hydrogenated Coco-Glycerides + Glyceryl Ricinoleate), Witepsol H 175, Witepsol H 185 (Hydrogenated Coco-Glycerides), Witepsol H 32 (Hydrogenated Coco-Glycerides), Witepsol H 35 (Hydrogenated Coco-Glycerides), Witepsol H 37 (Hydrogenated Coco-Glycerides). Witepsol W 25 (Hydrogenated Coco-Glycerides), Witepsol W 31 (Hydrogenated Coco-Glycerides), Witepsol W 32 (Hydrogenated Coco-Glycerides), Witepsol W 35 (Hydrogenated Coco-Glycerides), Witepsol W 45 (Hydrogenated Coco-Glycerides), Witepsol S 51 (Hydrogenated Coco-Glycerides + Cetareth-25 + Glyceryl Ricinoleate), Witepsol S 52, Witepsol S 55 (Hydrogenated Coco-Glycerides + Cetareth-25 + Bees Wax), Witepsol S 58 (Hydrogenated Coco-Glycerides + Cetareth-25 + Glyceryl Ricinoleate), Witepsol E 75 (Hydrogenated Coco-Glycerides + Bees Wax), Witepsol E 76 (Hydrogenated Coco-Glycerides), Witepsol E 85 (Hydrogenated Coco-Glycerides), MASSA ESTARINUM 299 (Hydrogenated Coco-Glycerides), MASSA ESTARINUM B (Hydrogenated Coco-Glycerides), MASSA ESTARINUM BC (Hydrogenated Coco-Glycerides + Glyceryl Ricinoleate), MASSA ESTARINUM C (Hydrogenated Coco-Glycerides), MASSA ESTARINUM E (Hydrogenated Coco-Glycerides + Cetareth-25 + Bees Wax), SOFTISAN 378 (Hydrogenated Coco-Glycerides); Pharmazol™

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The aqueous base suppositories that can be used in the present invention include polymers of ethylene oxide, e.g., polyethylene glycols (PEG). These polymers of PEG vary in molecular weight, from 200-8000 g/mol. Also as the molecular weight of PEG increases, the hardness of PEG also increases. By combining different proportions of PEG polymers, a suppository base can be made to desired consistency and characteristics. Glycerinated gelatin is also used in this type of suppositories, but mostly as the base for vaginal suppositories. Other types of bases can also be used, such as Polysorbate. The aqueous base can be used alone or used in

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combination with other base materials to produce suppositories of varying consistency and solubility.

The pharmaceutical composition of the present invention may further comprise emulsifiers.

- 5 Emulsifiers assure good stability in emulsification and provide satisfactory shape upon solidification of the suppository. Such emulsifiers include but are not limited to nonionic surfactants, anionic surfactants, cationic surfactants and amphoteric surfactants or mixtures thereof.
- 10 Suitable nonionic surfactants may comprise sorbitan fatty acid esters, glycerol fatty acid esters, glycerol (covering the glycerin and conc. glycerin listed in the Pharmacopeia of Japan), decaglycerin fatty acid esters, polyglycerin fatty acid esters, propylene glycol fatty acid esters, pentaerythritol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol fatty acid esters, polyoxyethylene glycerin fatty acid esters,
- 15 polyethylene glycol fatty acid esters, sucrose fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene phytosterols, polyoxyethylene phytostanols, polyoxyethylene polyoxypropylene glycol, polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil, polyoxyethylene lanolin, polyoxyethylene lanolin alcohol, beeswax derivatives, polyoxyethylene alkylamines and polyoxyethylene fatty acid amides or mixtures thereof .

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Suitable anionic surfactants may comprise alkyl sulfates, polyoxyethylene alkyl ether sulfates, N-acylamino acid or salts thereof, and polyoxyethylene alkyl ether phosphates or mixtures thereof.

- 25 Suitable cationic surfactants may comprise alkyl ammonium salts and alkylbenzyl ammonium salts or mixtures thereof.

Suitable amphoteric surfactants may comprise betaine acetate and lecithin or mixtures thereof.

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The greater the amount of the emulsifier, the higher is the stability in emulsification, which hence suits manufacturing purposes; however, if too much emulsifier is employed, air

bubbles are prone to occur during the preparation of the pharmaceutical composition and the solidified pharmaceutical composition will involve air entrapment and shrinkage to cause nonuniformity in properties and lower hardness. Excessive emulsifier may also be a problem with the safety of pharmaceuticals. Further, depending on the type of the emulsifier and its combination with the medicinal component, excessive emulsifier may reduce the releasability of the drug, thereby deteriorating the performance of the suppository;

The pharmaceutical composition of the present invention may further comprise sucrose fatty acid esters which are generally referred to as sugar esters are monoesters, diesters, triesters constituted of sucrose and one or more fatty acids or mixtures thereof.

The pharmaceutical composition of the present invention may further comprise stabilizers such as among amino acids or salts thereof, proteins and sugars. Specifically, amino acids include basic amino acids such as arginine and lysine, as well as acidic amino acids such as glutamic acid and aspartic acid; proteins include gelatin and albumin; and sugars include disaccharides such as sucrose and maltose, as well as sugar alcohols such as mannitol and sorbitol. Amino acid salts are available in two salt types, one with inorganic acids and the other with organic acids, and either will do if they can be used as pharmaceuticals.

The pharmaceutical composition of the present invention may further comprise pH adjusting agents such as but not limited to hydrochloric acid, acetic acid, citric acid, lactic acid or any other suitable acids that can be used in pharmaceutical products.

Alternatively, buffer solutions comprising these acids in combination with other salts such as but not limited to sodium chloride, potassium chloride, calcium chloride may be added. If desired, both acids and buffer solutions may be used as pH adjusting agents.

The pharmaceutical composition of the present invention may further comprise isotonic agents such as sodium chloride and potassium chloride, antiseptics typified by paraoxybenzoic acid esters such as methyl paraoxybenzoate and propyl paraoxybenzoate.

The pharmaceutical composition of the present invention may further comprise viscosity-adjusting agents such as microcrystalline wax, beeswax, paraffin or cetyl palmitate sodium stearate.

- 5 The pharmaceutical composition of the present invention may further comprise preservatives such as methyl paraben or propyl paraben.

The pharmaceutical composition of the present invention may further include antioxidants, coloring agents, fragrances, anti-fissuring agents, additives for adjusting hardness and feel, or
10 any other additives that can customarily be added.

The pharmaceutical composition of the present invention may provide immediate and/or modified release such as delayed, sustained, pulsed, controlled, targeted and programmed release.

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The pharmaceutical composition of the present invention may provide a multilayered suppository having two or more layers with different release rates, or a method of preparing the sustained-release suppository preparation as a suppository having a core and two or more layers with different release rates.

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The pharmaceutical composition of the present invention may provide as an effervescent pharmaceutical composition of rifaximin for rectal or vaginal administration.

The pharmaceutical composition of the present invention may be administered either rectally
25 or into the vagina and a suitable route should be selected as appropriate for the indicated disease or the object of use as to whether a systemic or local action is desired.

The pharmaceutical composition of the present invention may be administered by an applicator for applying medicaments to a body cavity as disclosed, for example, in U.S. Pat. No. 2,007,626 and U.S. Pat. No. 2,105,710.

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The pharmaceutical composition according to the present invention may further comprise at least one additional active ingredient.

Additional active agents may be selected from, but not limited to one or more of anti-inflammatory agents, steroids (e.g. corticosteroids), additional antibiotics, anti-fungal agents, anti-viral agents, analgesics, or anti-neoplastic agents.

5

Suitable antibiotics include, but are not limited to, dapsone, chloramphenicol, neomycin, cefaclor, cefadroxil, cephalixin, cephradine, erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin, dicl oxacillin, cyclacillin, picloxacillin, hetacillin, methicillin, nafcillin, penicillin, polymyxin, tetracycline, amphotericin-b, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin, azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrroinitrin, siccanin, tubercidin, viridin, picloxacillin, hetacillin, methicillin, nafcillin, penicillin, polymyxin or tetracycline.

15 Suitable antifungal agents include but are not limited to, allylamines such as butenafine, naftifine, imidazoles such as bifonazole, butoconazole, chlordanol, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole, sulconazole, tioconazole, triazoles such as fluconazole, itraconazole, saperconazole, terconazole, and others such as acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlophenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole, dihydrochloride, exalamide, flucytosine, halethazole, hexetidine, Ioflucarban, nifuratel, potassium iodide, propionates, propionic acid, pyrrhione, salicylanilide, sulbentine, tenonitroazole, triacetin, ujothion, undecylenic acid.

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Antifungal agents may also include, polyenes such as amphotericin-b, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin, azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrroinitrin, siccanin, tubercidin, viridin, allylamines such as butenafine, naftifine, imidazoles such as bifonazole, butoconazole, chlordanol, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole,

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sulconazole, tioconazole, triazoles such as fluconazole, itraconazole, saperconazole, terconazole, acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlophenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole, dihydrochloride, exalamide, flucytosine, halethazole, hexetidine, Ioflucarban, nifuratel, potassium iodide, propionates, propionic acid, pyrithione, salicylanilide, sulbentine, tenonitroazole, triacetin, ujothion or undecylenic acid.

Other therapeutic agents can include a steroidal or non-steroidal antiinflammatory agent. Non-steroidal anti-inflammatory agents, include, but are not limited to, aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetmetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflum[iota]c acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam; salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone and pharmaceutically acceptable salts thereof and mixtures thereof.

Suitable corticosteroids include but are not limited to, hydrocortisone, i.e., 11-17- 21-trihydroxypregn-4-ene-3,20-dione or Cortisol, Cortisol acetate, hydrocortisone phosphate, hydrocortisone 21 -sodium succinate, hydrocortisone tebutate, corticosterone, corticosterone acetate, cortisone, cortisone acetate, cortisone 21B- cyclopentanepropionate, cortisone phosphate, triamcinolone hexacetonide, dexamethasone phosphate, desonide, betamethasone dipropionate, mometasone furate.

- Antineoplastic agents may also be included in the pharmaceutical composition of the present invention along with rifaximin which include, but are not limited to, vincristine, vinblastine, vindesine, busulfan, chlorambucil, spiroplatin, cisplatin, carboplatin, methotrexate, adriamycin, mitomycin, bleomycin, cytosine arabinoside, arabinosyl adenine, 5 mercaptopurine, mitotane, procarbazine, dactinomycin (antinomycin D), daunorubicin, doxorubicin hydrochloride, taxol, plicamycin, aminoglutethimide, estramustine, flutamide, leuprolide, megestrol acetate, tamoxifen, testolactone, trilostane, amsacrine (m-AMSA), asparaginase (L-asparaginase), etoposide, and interferon α -2a and 2b.
- 10 Antiviral agents may also be included in the pharmaceutical composition of the present invention along with the rifaximin which include, but are not limited to, acyclovir, amantadine, azidothymidine, ribavirin and vidarabine.

There is further provided a process for preparing the pharmaceutical composition of the 15 present invention.

The pharmaceutical composition of the present invention may be prepared by moulding, the process involves that suppository base is melted using the least possible amount of heat, and then the liquid mass so obtained is poured into moulds having the desired nominal capacity.

20

The suppositories produced by moulding are oblong and smooth, and they have a uniform appearance. Melting is intended to provide a uniform distribution of the drug in the base mass.

- 25 Also, the pharmaceutical composition of the present invention may be prepared by encapsulating the dispersion of rifaximin along with one or more fatty bases in a soft capsule and further drying the soft capsule.

Alternatively, the suppositories may be prepared by producing a suppository mixture 30 granulate containing active drug, optionally and other pharmaceutical excipients commonly used and polyethylene glycol, compressing the produced mass to suppositories by a method known per se for the production of tablets.

The suppositories may be prepared by hand moulding by rolling the well blended suppository base containing rifaximin into a desired shape, wherein the suppository base is first grated and kneaded with rifaximin until the resultant mass is plastic and thoroughly blended.

5

Also, the suppositories may also be prepared by compression moulding which process involves forcing a mixed mass of grated suppository base and rifaximin into a special compression mould.

- 10 In a further embodiment, the pharmaceutical composition according to the present invention may be used to treat a bacterial infection, e.g., acute hemorrhoidal disease, irritable bowel syndrome, travelers diarrhea, small intestinal anal disease, Crohn's disease, chronic pancreatitis, pancreatic insufficiency, colitis, hepatic encephalopathy, antibiotic associated colitis, and/or diverticular disease

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The present invention further provides a method of treatment and/or prevention of colonic diseases, which method comprising administering to a subject in need thereof an effective amount of rifaximin, wherein the rifaximin may or may not be in the nanosize range.

- 20 The following examples are for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention.

Example 1

Sr. No.	Ingredients	Qty/Unit
1.	Rifaximin	200 mg
2.	Witepsol H 15	2.8 gm

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Process

- 1) Witepsol H 15 was melted at a temperature of about 50-60°C.
- 2) Rifaximin was added to the melted mass obtained in step (1) and further homogenized.
- 3) The molten mass obtained in step (2) was congealed at a temperature of 36-40°C.

- 4) The congealed mass was filled in the suppository moulds.
- 5) The suppositories so obtained were congealed to room temperature.

Example 2

5

Sr. No.	Ingredients	Qty/Unit
1.	Rifaximin	200 mg
2.	Suppocire NA 15	2.8 gm

Process

- 1) Suppocire NA 15 was melted at a temperature of about 50-60°C.
- 2) Rifaximin was added to the melted mass obtained in step (1) and further homogenized.
- 10 3) The molten mass obtained in step (2) was congealed at a temperature of 36-40°C.
- 4) The congealed mass was filled in the suppository moulds.
- 5) The suppositories so obtained were congealed to room temperature.

Example 3

15

Sr. No.	Ingredients	Qty/Unit
1.	Rifaximin	200 mg
2.	Suppocire NA 25	2.8 gm

Process

- 1) Suppocire NA 25 was melted at a temperature of about 50-60°C.
- 2) Rifaximin was added to the melted mass obtained in step (1) and further homogenized.
- 20 3) The molten mass obtained in step (2) was congealed at a temperature of 36-40°C.
- 4) The congealed mass was filled in the suppository moulds.
- 5) The suppositories so obtained were congealed to room temperature.

Example 4

25

Sr. No.	Ingredients	Qty/Unit
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1.	Rifaximin	200 mg
2.	Suppocire BM	2.8 gm

Process

- 1) Suppocire BM was melted at a temperature of about 50-60°C.
- 2) Rifaximin was added to the melted mass obtained in step (1) and further homogenized.
- 5 3) The molten mass obtained in step (2) was congealed at a temperature of 36-40°C.
- 4) The congealed mass was filled in the suppository moulds.
- 5) The suppositories so obtained were congealed to room temperature.

Example 5

10

Sr. No.	Ingredients	Qty/Unit
1.	Rifaximin	200 mg
2.	Ovicure WL 3264	2.8 gm

Process

- 1) Ovicure WL 3264 was melted at a temperature of about 50-60°C.
- 2) Rifaximin was added to the melted mass obtained in step (1) and further homogenized.
- 15 3) The molten mass obtained in step (2) was congealed at a temperature of 36-40°C.
- 4) The congealed mass was filled in the suppository moulds.
- 5) The suppositories so obtained were congealed to room temperature.

Example 6

20

Sr. No.	Ingredients	Qty (Mg/ Capsule)
1.	Rifaximin	200
2.	Soyabean oil USP	2700
3.	Hydrogenated castor oil	100
	Total	3000
Shell Composition		
Sr. No.	Ingredients	Qty (%w/w)

1.	Gelatin USP	42
2.	Glycerol USP	16
3.	Sorbitol Solution USP	4.00
4.	Purified water USP	38.00

Process

- 1) Rifaximin was dispersed with a homogenizer in soyabean oil and hydrogenated castor oil.
- 2) The dispersed mass was encapsulated in the soft gel capsules.
- 5 3) The soft gel capsules obtained in step (2) were further dried.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has
10 been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of
15 description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular
20 forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a propellant" includes a single propellant as well as two or more different propellants; reference to a "cosolvent" refers to a single cosolvent or to combinations of two or more cosolvents, and the like.

Claims

1. A pharmaceutical composition comprising rifaximin in the form of a suppository dosage form.

5

2. A pharmaceutical composition according to claim 1, wherein the rifaximin has an effective particle less than or equal to 2 micrometres.

3. A pharmaceutical composition according to claim 1, wherein the rifaximin has an effective particle less than or equal to 1 micrometre.

10

4. A pharmaceutical composition according to claim 1, 2 or 3, comprising rifaximin dispersed in and one or more suppository vehicle.

5. A pharmaceutical composition according to claim 1, 2 or 3, comprising rifaximin suppository in the form of a soft capsule.

15

6. A pharmaceutical composition according to claim 1, 2 or 3, comprising rifaximin and one or more suppository vehicle dispersed in a soft capsule.

20

7. A pharmaceutical composition according to claim 4, 5 or 6, wherein the suppository vehicle is an aqueous base that has hydrophilic properties.

8. A pharmaceutical composition according to claim 4, 5 or 6, wherein the suppository vehicle comprises a fatty base material that has hydrophobic properties.

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9. A process for making a pharmaceutical composition comprising mixing rifaximin with a liquid suppository base material to disperse the rifaximin in the base material, then solidifying the base material to produce a suppository containing rifaximin.

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10. A process for making a pharmaceutical composition comprising encapsulating rifaximin in a suppository capsule to produce a suppository containing rifaximin.

11. A composition according to any one of claims 1 to 8, for use in treating a bacterial infection.

5 12. The use of a composition according to any one of claims 1 to 8 in the manufacture of a medicament for treating a bacterial infection.

13. A method of treating a bacterial infection comprising administering a therapeutically effective amount of a composition according to any one of claims 1 to 8 to a patient in need
10 thereof.

14. A pharmaceutical composition substantially as herein described with reference to the examples.

15 15. A method of making a pharmaceutical composition substantially as herein described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/000786

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/02 A61K31/437 A61P31/04
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 A61P

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)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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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

7 July 2011

Date of mailing of the international search report

15/07/2011

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/000786

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