# FORMULATIONS OF RIFAXIMIN AND USES THEREOF

## RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/363,609 filed 12 July 2010, and U.S. Provisional Application No. 61/419,056, filed 2 December 2010, the entire contents of each of which are hereby incorporated herein by reference.

## BACKGROUND

Rifaximin (INN; see The Merck Index, XIII Ed., 8304) is an antibiotic belonging to the rifamycin class of antibiotics, e.g., a pyrido-imidazo rifamycin. Rifaximin exerts its broad antibacterial activity, for example, in the gastrointestinal tract against localized gastrointestinal bacteria that cause infectious diarrhea, irritable bowel syndrome, small intestinal bacterial overgrowth, Crohn's disease, and pancreatic insufficiency among other diseases. It has been reported that rifaximin is characterized by a 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. Int J Clin Pharmacol Res, 14 (2), 51-56, (1994)*).

Rifaximin is described in Italian Patent IT 1154655 and EP 0161534, both of which are incorporated herein by reference in their entirety for all purposes. EP 0161534 discloses a process for rifaximin production using rifamycin O as the starting material (The Merck Index, XIII Ed., 8301). U.S. Patent No. 7,045,620 B1 and PCT Publication WO 2006/094662 A1 disclose polymorphic forms of rifaximin. There is a need in the art for formulations of rifaximin to better treat gastrointestinal and other diseases.

## SUMMARY

Provided herein are solid dispersion forms of rifaximin with a variety of polymers and polymer concentrations.

In one aspect, provided herein are forms solid dispersion of rifaximin.

In one embodiment, the form solid dispersion of rifaximin is characterized by an XRPD substantially similar to one or more of the XRPDs of Figures 2, 7, 12, 17, 22, 31, and 36.

In one embodiment, the form solid dispersion of rifaximin is characterized by a Thermogram substantially similar to Figures 3-6, 8-11, 13-16, 18-21, 23-26, 27-30, and 32.

In one embodiment, the form has the appearance of a single glass transition temperature (Tg).

In one embodiment, a Tg of a form increases with an increased rifaximin concentration

In one embodiment, a form stressed at 70°C/ 75%RH for 1 week, solids are still x-ray amorphous according to XRPD.

In one embodiment, a form stressed at 70°C/ 75%RH for 3 weeks, solids are still x-ray amorphous according to XRPD.

In one embodiment, a form stressed at 70°C/ 75%RH for 6 weeks, solids are still x-ray amorphous according to XRPD.

In one embodiment, a form stressed at 70°C/ 75%RH for 12 weeks, solids are still x-ray amorphous according to XRPD.

In one aspect, provided herein are microgranules comprising one or more of the solid dispersion forms of rifaximin described herein.

In one embodiment, the microgranules further comprise a polymer.

In one embodiment, the polymer comprises one or more of polyvinylpyrrolidone (PVP) grade K-90, hydroxypropyl methylcellulose phthalate (HPMC-P) grade 55, hydroxypropyl methylcellulose acetate succinate (HPMC-AS) grades HG and MG, or a polymethacrylate (Eudragit® L100-55).

In specific embodiments, the microgranules comprises 25-75% polymer, 40-60% polymer, or 40-50% polymer. In an exemplary embodiment, the microgranules comprises 42-44% polymer.

In one embodiment, the microgranules comprise equal amounts of rifaximin and polymer.

In another embodiment, the microgranules further comprising an intragranular release controlling agent. In exemplary embodiments, the intragranular release controlling agent comprises a pharmaceutically acceptable excepient, disintegrant,

crosprovidone, sodium starch glycolate, corn starch, microcrystalline cellulose, cellulosic derivatives, sodium bicarbonate, and sodium alginate.

In one embodiment, the intragranular release controlling agent comprises between about 2 wt% to about 40 wt% of the microgranule, about 5 wt% to about 20 wt% of the microgranule, or about 10 wt% of the microgranule.

In another embodiment, the intragranular release controlling agent comprises a pharmaceutically acceptable disintegrant, e.g., one selected from the group consisting of crosprovidone, sodium starch glycolate, corn starch, microcrystalline cellulose, cellulosic derivatives, sodium bicarbonate, and sodium alginate.

In another embodiment, the microgranules further comprise a wetting agent or surfactant, e.g., a non-ionic surfactant.

In one embodiment, the non-ionic surfactant comprises between about 2 wt% to about 10 wt% of the microgranule, between about 4 wt% to about 8 wt% of the microgranule, or about 5.0 wt% of the microgranule .

In one embodiment, the non-ionic surfactant comprises a poloxamer, e.g., poloxamer 407 also known as Pluronic F-127.

In another embodiment, the microgranules further comprise an antioxidant.

In exemplary embodiments, the antioxidant is butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) or propyl gallate (PG).

In another embodiment, the antioxidant comprises between about 0.1 wt% to about 3 wt% of the microgranule or between about 0.5 wt% to about 1 wt% of the microgranule.

In another aspect, provided herein are pharmaceutical compositions comprising the microgranules described herein.

In one embodiment, the pharmaceutical compositions further comprise one or more pharmaceutically acceptable excepients.

In one embodiment, the pharmaceutical compositions are tablets or capsules.

In one embodiment, the pharmaceutical compositions comprises a disintegrant.

In one embodiment, the polymer comprises one or more of polyvinylpyrrolidone (PVP) grade K-90, hydroxypropyl methylcellulose phthalate (HPMC-P) grade 55, hydroxypropyl methylcellulose acetate succinate (HPMC-AS) grades HG and MG, or a polymethacrylate (Eudragit® L100-55).

In one aspect, provided herein are pharmaceutical solid dispersion formulations comprising: rifaximin, HPMC-AS, at a rifaximin to polymer ratio of 50:50, a non-ionic, surfactant polyol and a intragranular release controlling agent.

In one embodiment, the intragranular release controlling agent comprises about 10 wt% of the formulation.

In one aspect, provided herein are processes for producing a solid dispersion of rifaximin comprising: making a slurry of methanol, rifaximin, a polymer and a surfactant; spray drying the slurry; and blending the spray dried slurry with a intragranular release controlling agent.

In one aspect, provided herein are processes for producing a solid dispersion of rifaximin comprising: making a slurry of methanol, rifaximin, HPMC-AS MG and Pluronic F-127; spray drying the slurry; and blending the spray dried slurry with a intragranular release controlling agent.

In one embodiment, the intragranular release controlling agent comprises croscarmellose sodium.

A process for producing form solid dispersion of rifaximin comprising one or more of the methods listed in Tables 1-5.

In one embodiment, pharmaceutical compositions comprising SD rifaximin, a polymer, a surfactant, and a release controlling agent are provided. In one embodiment, provided are pharmaceutical compositions comprising SD rifaximin, HPMC-AS, pluronic F127, and croscarmellose Na (CS). In one embodiment, the pharmaceutical compositions are tablets or pills.

In additional embodiments, the pharmaceutical compositions further comprise fillers, glidants or lubricants.

In specific embodiments, the pharmaceutical compositions comprise the ratios of components set forth in Table 37.

Other embodiment and aspects are disclosed *infra*.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Chemical structure of Rifaximin.

Figure 2. Overlay of XRPD patterns for Rifaximin/PVP K-90 dispersions obtained from methanol by spray drying.

Figure 3. mDSC thermogram for 25:75 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying.

Figure 4. mDSC thermogram for 50:50 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying .

Figure 5. mDSC thermogram for 75:25 (w/w) Rifaximin/PVP K-90 dispersion obtained from methanol by spray drying .

Figure 6. Overlay of mDSC thermogram for Rifaximin/PVP K-90 dispersions obtained from methanol by spray drying.

Figure 7. Overlay of XRPD patterns for Rifaximin/HPMC-P dispersions obtained from methanol by spray drying.

Figure 8. mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying.

Figure 9. mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying.

Figure 10. mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-P dispersion obtained from methanol by spray drying .

Figure 11. Overlay of mDSC thermogram for Rifaximin/HPMC-P dispersions obtained from methanol by spray drying.

Figure 12. Overlay of XRPD patterns for Rifaximin/HPMC-AS HG dispersions obtained from methanol by spray drying.

Figure 13. mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying .

Figure 14. mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying.

Figure 15. mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-AS HG dispersion obtained from methanol by spray drying.

Figure 16. Overlay of mDSC thermogram for Rifaximin/HPMC-AS HG dispersions obtained from methanol by spray drying.

Figure 17. Overlay of XRPD patterns for Rifaximin/HPMC-AS MG dispersions obtained from methanol by spray drying.

Figure 18. mDSC thermogram for 25:75 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying.

Figure 19. mDSC thermogram for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying.

Figure 20. mDSC thermogram for 75:25 (w/w) Rifaximin/HPMC-AS MG dispersion obtained from methanol by spray drying.

Figure 21. Overlay of mDSC thermogram for Rifaximin/HPMC-AS MG dispersions obtained from methanol by spray drying.

Figure 22. Overlay of XRPD patterns for Rifaximin/Eudragit L100-55 dispersions obtained from methanol by spray drying.

Figure 23. mDSC thermogram for 25:75 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying.

Figure 24. mDSC thermogram for 50:50 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying.

Figure 25. mDSC thermogram for 75:25 (w/w) Rifaximin/Eudragit L100-55 dispersion obtained from methanol by spray drying.

Figure 26. Overlay of mDSC thermogram for Rifaximin/Eudragit L100-55 dispersions obtained from methanol by spray drying.

Figure 27. mDSC thergram for 25:75 (w/w) Rifaximin/HPMC-P dispersion stressed at 40 ºC/75% RH for 7 d.

Figure 28. mDSC thergram for 75:25 (w/w) Rifaximin/HPMC-AS HG dispersion stressed at 40 ºC/75% RH for 7 d.

Figure 29. mDSC thergram for 75:25 (w/w) Rifaximin/HPMC-AS MG dispersion stressed at 40 ºC/75% RH for 7 d.

Figure 30. mDSC thergram for 25:75 (w/w) Rifaximin/Eudragit L100-55 dispersion stressed at 40 ºC/75% RH for 7 d.

Figure 31. XRPD pattern for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion.

Figure 32. Modulate DSC thermograms for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion.

Figure 33. TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion– TGA data.

Figure 34. TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion– Gram-Schmidt plot and waterfall plot.

Figure 35. TG-IR analysis for 50:50 (w/w) Rifaximin/HPMC-AS MG dispersion.

Figure 36. XRPD pattern for 25:75 (w/w) Rifaximin/HPMC-P dispersion.

Figure 37. Modulate DSC thermograms for 25:75 (w/w) Rifaximin/HPMC-P dispersion.

Figure 38. TG-IR analysis for 25:75 (w/w) Rifaximin/HPMC-P dispersion – TGA data.

Figure 39. TG-IR analysis for 25:75 (w/w) Rifaximin/HPMC-P dispersion – Gram-Schmidt plot and waterfall plot.

Figure 40. TG-IR analysis for 25:75 (w/w) Rifaximin/HPMC-P dispersion.

Figure 41. Overlay of pre-processed XRPD patterns in multivariate mixture analysis.

Figure 42. Estimated Concentrations of Rifaximin (blue) and HPMC-AS MG (red) using Unscrambler MCR analysis.

Figure 43. Estimated XRPD patterns of Rifaximin (blue) and HPMC-AS MG (red) using Unscrambler MCR analysis.

Figure 44. Overlay of estimated XRPD pattern of pure rifaximin using MCR and measured XRPD pattern of 100% rifaximin.

Figure 45. Overlay of estimated XRPD pattern of pure HPMC-AS MG using MCR and measured XRPD pattern of 100% HPMC-AS MG.

Figure 46. An exemplary XRPD pattern for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 47. A modulate DSC thermogram for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 48. A TG-IR analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion – TGA thermogram.

Figure 49. An exemplary TG-IR analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 50. An exemplary overlay of IR spectra for X-ray amorphous Rifaximin and combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 51. An exemplary overlay of Ramam spectra for X-ray amorphous Rifaximin and combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 52. A particle size analysis report for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 53. An exemplary dynamic vapor sorption (DVS) analysis for combined solids of Rifaximin/HPMC-AS MG/Pluronic ternary dispersion.

Figure 54. An exemplary overlay of XRPD patterns for Rifaximin/HPMC-AS MG/Pluronic ternary dispersion post-DVS solids and solids as-prepared.

Figure 55. An exemplary overlay of XRPD patterns for Rifaximin ternary dispersion post-stressed samples and as-prepared sample.

Figure 56. An exemplary mDSC thermgram for Rifaximin ternary dispersion after 70 ºC/75% RH 1week.

Figure 57. An exemplary mDSC thermgram for Rifaximin ternary dispersion after 70 ºC/75% RH 3weeks.

Figure 58. An exemplary mDSC thermgram for Rifaximin ternary dispersion after 40 ºC/75% RH 6 weeks.

Figure 59. An exemplary mDSC thermgram for Rifaximin ternary dispersion after 40 ºC/75% RH 12 weeks.

Figure 60. Pharmacokinetic data of solid dispersion in dogs.

Figure 61. Rifaximin SD capsules dissolution; acid phase: 0.1 N HCl with variable exposure time. Buffer phase: pH 6.8 with 0.45% SDS.

Figure 62. Rifaximin SD capsules dissolution; acid phase: 2 hours; buffer phase: pH 6.8.

Figure 63. Rifaximin capsule dissolution; phosphate buffer pH 6.8 with 0.45% SDS.

Figure 64. Rifaximin spray dried dispersion (SDD) capsule dissolution. (a) acid phase 2 hours, buffer phase: P. Buffer, pH. 7.4. (b) acid phase: 0.1N HCl with various exposure times, buffer phase: P. buffer, pH 7.4 with 0.45% SDS.

Figure 65. Rifamixin SDD with 10%CS formulation. (a) kinetic solubility Rifamixin SD granules. 10% wt% CS sodium FaSSIF, 10% wt% CS sodium FeSSIF. (b) dissolution profiles SDD tablet 10% CS. 0.2% SLS, pH4.5; 0.2% SLS, pH5.5; 0.2% SLS, pH 7.4; FaSSIF.

Figure 66. Rifaximin SDD with 10% CS formulation. Rifaxamin SDD capsules dissolution: (a) acid phase 2 hours, buffer phase: P. Buffer, pH. 7.4. With 0.45% SDS; without SDS. (b) acid phase: 0.1N HCl with variable exposure times, buffer phase: P. buffer, pH 7.4 with 0.45% SDS.

Figure 67. Effects of media pH on dissolution. (a) Rifaxamin SDD tablet dissolution. Acid phase: 2 hours, pH 2.0, (b) Dissolution profiles 0.2% SDS at pH 4.5, SDD tablet dissolution at various levels of CS: 0%, 2.5%,5%, and 10% CS.

Figure 68. Effects of media pH on dissolution. (a) Rifaxamin SDD tablet dissolution at various levels of CS: 0%, 2.5%,5%, and 10% CS, 0.2% SDS at pH 5.5. (b) Dissolution profiles SDD tablet dissolution at various levels of CS: 0%, 2.5%,5%, and 10% CS, 0.2% SDS at pH 7.4.

Figure 69. Effects of media pH on dissolution. (a) Rifaxamin SDD tablet dissolution 2.5% CS, 0.2% SLS, pH4.5, 0.2% SLS, pH 5.5, 0.2% SLS, pH 7.4. (b) Rifaxamin SDD tablet dissolution 0% CS, 0.2% SLS, pH4.5, 0.2% SLS, pH 5.5, 0.2% SLS, pH 7.4.

Figure 70. Effects of media pH on dissolution. (a) Rifaxamin SDD tablet dissolution 10% CS, 0.2% SLS, pH4.5, 0.2% SLS, pH 5.5, 0.2% SLS, pH 7.4. (b) Rifaxamin SDD tablet dissolution 5% CS, 0.2% SLS, pH4.5, 0.2% SLS, pH 5.5, 0.2% SLS, pH 7.4.

Figure 71. CS release mechanism. (a) Kinetic solubility in FaSSIF media, pH 6.5, (b) slope vs. time point.

Figure 72 depicts an overlay of XRPD patterns of rifaximin quaternary samples spray dried from methanol. The top is a rifaximin quaternary sample containing 0.063 wt% BHA. The second is rifaximin quaternary sample containing 0.063 wt% BHT. The third: is rifaximin quaternary sample containing 0.094 wt% PG, and the bottom is a spray dried rifaximin ternary dispersion.

Figure 73 depicts an mDSC thermogram of rifaximin quaternary sample containing 0.063 wt% BHA

Figure 74 depicts an mDSC thermogram of rifaximin quaternary sample containing 0.063 wt% BHT.

Figure 75 depicts a mDSC thermogram of rifaximin quaternary sample containing 0.094 wt% PG.

Figure 76 depicts an XRPD pattern comparison of rifaximin solid dispersion powder 42.48% w/w with roller compacted material of rifaximin blend.Top: Rifaximin Solid Dispersion Powder 42.48% w/w; Bottom: roller compacted rifaximin blend.

Figure 77 depicts the pharmacokinetics of rifaximin following administration of varying forms and formulations following a single oral dose of 2200 mg in dogs.

Figure 78 depicts Rifaximin SDD in dogs.

Figure 79 depicts the quotient study design.

Figure 80 summarizes the dose escalation/regional absorption study, part A dose escalation/dose selection.

Figure 81 depicts representative subject data from a dose escalation study.

Figure 82 depicts representative subject data from a dose escalation study.

Figure 83 depicts mean dose escalation data, on a linear scale.

Figure 84 depicts mean dose escalation data, on a log scale.

Figure 85 depicts a summary of Rifaximin SDD dose escalation studies.

Figure 86 is a Table of dose/ dosage form comparison.

Figure 87 is a Table of dose/ dosage form comparison. This table compares SDD at increasing doses to the current crystalline formulation in terms of systemic PK.

## DETAILED DESCRIPTION

Embodiments described herein relate to the discovery of new solid dispersion forms of rifaximin with a variety of polymers and polymer concentrations. In one embodiment the use of one or more of new solid dispersion forms of the antibiotic known as Rifaximin (INN), in the manufacture of medicinal preparations for the oral or topical route is contemplated. For example, the solid dispersion forms of rifaximin are used to create pharmaceutical compositions, e.g.,. tablets or capsules, or microgranules comprising solid dispersion forms of rifaximin. Exemplary methods for producing rifaximin microgranules are set forth in the examples. Rifaximin microgranules can be formulated into pharmaceutical compositions as described herein.

Embodiments described herein also relate to administration of such medicinal preparations to a subject in need of treatment with antibiotics. Provided herein are solid dispersion forms of rifaximin with a variety of polymers and polymer concentrations.

As used herein, the term "intragranular release controlling agent" include agents that cause a pharmaceutical composition, e.g., a microgranule, to breakdown thereby

releasing the active ingredient, e.g., rifaximin. Exemplary intragranular release controlling agent, include disintegrants such as crosprovidone, sodium starch glycolate, corn starch, microcrystalline cellulose, cellulosic derivatives, sodium bicarbonate, and sodium alginate.

In one embodiment, the intragranular release controlling agent comprises between about 2 wt% to about 40 wt% of the microgranule, about 5 wt% to about 20 wt% of the microgranule, about 8-15 wt% or about 10 wt% of the microgranule.

In another embodiment, the microgranule comprises a surfactant, e.g., a non-ionic surfactant. In one embodiment, the non-ionic surfactant comprises between about 2 wt% to about 10 wt% of the microgranule, between about 4 wt% to about 8 wt% of the microgranule, about 6 to about 7 wt % of the microgranule, or about 5.0 wt% of the microgranule .

In another embodiment, the microgranule comprises an antioxidant. In one embodiment, the antioxidant comprises between about 0.1 wt% to about 3 wt% of the microgranule, between 0.3 wt% to about 2 wt% or between about 0.5 wt% to about 1 wt% of the microgranule.

As used herein, the term "intragranular" refers to the components that reside within the microgranule. As used herein, the term "extragranular" refers to the components of the pharmaceutical composition that are not contained within the microgranule.

As used herein, the term polymorph is occasionally used as a general term in reference to the forms of rifaximin and includes within the context, salt, hydrate, polymorph co-crystal and amorphous forms of rifaximin. This use depends on context and will be clear to one of skill in the art.

As used herein, the term "about" when used in reference to x-ray powder diffraction pattern peak positions refers to the inherent variability of the peaks depending on, for example, the calibration of the equipment used, the process used to produce the polymorph, the age of the crystallized material and the like, depending on the instrumentation used. In this case the measure variability of the instrument was about $\pm$0.2 degrees 2-$\theta$. A person skilled in the art, having the benefit of this disclosure, would understand the use of "about" in this context. The term "about" in reference to other defined parameters, e.g., water content, $C_{max}$, $t_{max}$, AUC, intrinsic dissolution rates, temperature, and time, indicates the inherent variability in, for example, measuring the parameter or achieving the parameter. A

person skilled in the art, having the benefit of this disclosure, would understand the variability of a parameter as connoted by the use of the word about.

As used herein, "similar" in reference to a form exhibiting characteristics similar to, for example, an XRPD, an IR, a Raman spectrum, a DSC, TGA, NMR, SSNMR, etc, indicates that the polymorph or cocrystal is identifiable by that method and could range from similar to substantially similar, so long as the material is identified by the method with variations expected by one of skill in the art according to the experimental variations, including, for example, instruments used, time of day, humidity, season, pressure, room temperature, etc.

As used herein, "rifaximin solid dispersion," "rifaximin ternary dispersion," "solid dispersion of rifaximin," "solid dispersion", "solid dispersion forms of rifaximin", "SD", "SDD", and "form solid dispersion of rifaximin" are intended to have equivalent meanings and include rifaximin polymer dispersion composition. These compositions are XRPD amorphous, but distinguishable from XRPD of amorphous rifaximin. As shown in the Examples and Figures, the rifaximin polymer dispersion compositions are physically chemically distinguishable from amorphous rifaximin, including different Tg, different XRPD profiles and different dissolution profiles.

Polymorphism, as used herein, refers to the occurrence of different crystalline forms of a single compound in distinct hydrate status, e.g., a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as solubility profiles, melting point temperatures, hygroscopicity, particle shape, density, flowability, compactibility and/or x-ray diffraction peaks. The solubility of each polymorph may vary, thus, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. For a general review of polymorphs and the pharmaceutical applications of polymorphs see G. M. Wall, Pharm Manuf. 3, 33 (1986); J. K. Haleblian and W. McCrone, J Pharm. Sci., 58, 911 (1969); and J. K. Haleblian, J. Pharm. Sci., 64, 1269 (1975), all of which are incorporated herein by reference.

As used herein, "subject" includes organisms which are capable of suffering from a bowel disorder or other disorder treatable by rifaximin or who could otherwise benefit from the administration of rifaximin solid dispersion compositions as described herein, such as human and non-human animals. The term "non-human animals" includes all vertebrates, e.g., mammals, e.g., rodents, e.g., mice, and non-mammals, such as non-human primates, e.g., sheep, dog, cow, chickens, amphibians, reptiles, etc. Susceptible to a bowel disorder is meant to include subjects at risk of developing a bowel disorder infection, e.g., subjects suffering from one or more of an immune suppression, subjects that have been exposed to other subjects with a bacterial infection, physicians, nurses, subjects traveling to remote areas known to harbor bacteria that causes travelers' diarrhea, subjects who drink amounts of alcohol that damage the liver, subjects with a history of hepatic dysfunction, etc.

The language "a prophylactically effective amount" of a composition refers to an amount of a rifaximin solid dispersion formulation or otherwise described herein which is effective, upon single or multiple dose administration to the subject, in preventing or treating a bacterial infection.

The language "therapeutically effective amount" of a composition refers to an amount of a rifaximin solid dispersion effective, upon single or multiple dose administration to the subject to provide a therapeutic benefit to the subject. In one embodiment, the therapeutic benefit is wounding or killing a bacterium, or in prolonging the survivability of a subject with such a bowel or skin disorder. In another embodiment, the therapeutic benefit is inhibiting a bacterial infection or prolonging the survival of a subject with such a bacterial infection beyond that expected in the absence of such treatment.

Rifaximin exerts a broad antibacterial activity in the gastrointestinal tract against localized gastrointestinal bacteria that cause infectious diarrhea, including anaerobic strains. It has been reported that rifaximin is characterized by a 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. Int J Clin Pharmacol Res, 14 (2), 51-56, (1994)*).

In respect to possible adverse events coupled to the therapeutic use of rifaximin, the induction of bacterial resistance to the antibiotics is of particular relevance.

From this point of view, any differences found in the systemic absorption of the forms of rifaximin disclosed herein may be significant, because at sub-inhibitory concentration of rifaximin, such as in the range from 0.1 to 1 μg/ml, selection of resistant mutants has been demonstrated to be possible (*Marchese A. et al. In vitro activity of rifaximin, metronidazole and vancomycin against clostridium difficile and the rate of*

*selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy, 46(4), 253-266,(2000)).*

Forms, formulations and compositions of rifaximin have been found to have differing *in vivo* bioavailability properties. Thus, the polymorphs disclosed herein would be useful in the preparation of pharmaceuticals with different characteristics for the treatment of infections. This would allow generation of rifaximin preparations that have significantly different levels of adsorption with $C_{max}$ values from about 0.0 ng/ml to 5.0 µg/ml. This leads to preparation of rifaximin compositions that are from negligibly to significantly adsorbed by subjects undergoing treatment. One embodiment described herein is modulating the therapeutic action of rifaximin by selecting the proper form, formulation and/or composition, or mixture thereof, for treatment of a subject. For example, in the case of invasive bacteria, the most bioavailable form, formulation and/or composition can be selected from those disclosed herein, whereas in case of non-invasive pathogens less adsorbed forms, formulations and/or compositions of rifaximin can be selected, since they may be safer for the subject undergoing treatment. A form, formulation and/or composition of rifaximin may determine solubility, which may also determine bioavailability.

For XRPD analysis, accuracy and precision associated with third party measurements on independently prepared samples on different instruments may lead to variability which is greater than ±0.1° 2θ. For d-space listings, the wavelength used to calculate d-spacings was 1.541874 Å, a weighted average of the Cu-Kα1 and Cu-Kα2 wavelengths. Variability associated with d-spacing estimates was calculated from the USP recommendation, at each d-spacing, and provided in the respective data tables and peak lists.

**Methods of Treatment**

Provided herein are methods of treating, preventing, or alleviating bowel related disorders comprising administering to a subject in need thereof an effective amount of one or more of the solid dispersion compositions of rifaximin. Bowel related disorders include one or more of irritable bowel syndrome, diarrhea, microbe associated diarrhea, Clostridium difficile associated diarrhea, travelers' diarrhea, small intestinal bacterial overgrowth, Crohn's disease, diverticular disease, chronic pancreatitis, pancreatic insufficiency, enteritis, colitis, hepatic encephalopathy, minimal hepatic encephalopathy or pouchitis.

The length of treatment for a particular bowel disorder will depend in part on the disorder. For example, travelers' diarrhea may only require treatment duration of 12 to about 72 hours, while Crohn's disease may require treatment durations from about 2 days to 3 months. Dosages of rifaximin will also vary depending on the diseases state. Proper

dosage ranges are provided herein infra. The polymorphs and cocrystals described herein may also be used to treat or prevent apathology in a subject suspected of being exposed to a biological warfare agent.

The identification of those subjects who are in need of prophylactic treatment for bowel disorder is well within the ability and knowledge of one skilled in the art. Certain of the methods for identification of subjects which are at risk of developing a bowel disorder which can be treated by the subject method are appreciated in the medical arts, such as family history, travel history and expected travel plans, the presence of risk factors associated with the development of that disease state in the subject. A clinician skilled in the art can readily identify such candidate subjects, by the use of, for example, clinical tests, physical examination and medical/family/travel history.

Topical skin infections and vaginal infections may also be treated with the rifaximin compositions described herein. Thus, described herein are methods of using a solid dispersion composition of rifaximin (SD rifaximin compositions) to treat vaginal infections, ear infections, lung infections, periodontal conditions, rosacea, and other infections of the skin and/or other related conditions. Provided herein are vaginal pharmaceutical compositions to treat vaginal infection, particularly bacterial vaginosis, to be administered topically, including vaginal foams and creams, containing a therapeutically effective amount of SD rifaximin compositions, preferably between about 50 mg and 2500 mg. Pharmaceutical compositions known to those of skill in the art for the treatment of vaginal pathological conditions by the topical route may be advantageously used with SD rifaximin compositions. For example, vaginal foams, ointments, creams, gels, ovules, capsules, tablets and effervescent tablets may be effectively used as pharmaceutical compositions containing SD rifaximin compositions, which may be administered topically for the treatment of vaginal infections, including bacterial vaginosis. Also provided herein are method of using SD rifaximin compositions to treat gastric dyspepsia, including gastritis, gastroduodenitis, antral gastritis, antral erosions, erosive duodenitis and peptic ulcers. These conditions may be caused by the Helicobacter pylori. Pharmaceutical formulations known by those of skill in the art with the benefit of this disclosure to be used for oral administration of a drug may be used. Provided herein are methods of treating ear infections with SD rifaximin compositions. Ear infections include external ear infection, or a middle and inner ear infection. Also provided herein are methods of using SD rifaximin compositions to treat or prevent aspiration pneumonia and/or sepsis, including the prevention of aspiration pneumonia and/or sepsis in patients undergoing acid suppression or undergoing artificial enteral feedings via a Gastrostomy/Jejunostomy or naso/oro gastric

tubes; prevention of aspiration pneumonia in patients with impairment of mental status, for example, for any reason, for subjects undergoing anesthesia or mechanical ventilation that are at high risk for aspiration pneumonia. Provided herein are methods to treat or to prevent periodontal conditions, including plaque, tooth decay and gingivitis. Provided herein are methods of treating rosacea, which is a chronic skin condition involving inflammation of the cheeks, nose, chin, forehead, or eyelids.

**Pharmaceutical Preparations**

Embodiments also provide pharmaceutical compositions, comprising an effective amount of one or more SD rifaximin compositions, or microgranules comprising SD forms of rifaximin described herein (e.g., described herein and a pharmaceutically acceptable carrier). In a further embodiment, the effective amount is effective to treat a bacterial infection, e.g., small intestinal bacterial overgrowth, Crohn's disease, hepatic encephalopathy, antibiotic associated colitis, and/or diverticular disease. Embodiments also provide pharmaceutical compositions, comprising an effective amount of rifaximin SD compositions.

For examples of the use of rifaximin to treat Travelers' diarrhea, see Infante RM, Ericsson CD, Zhi-Dong J, Ke S, Steffen R, Riopel L, Sack DA, DuPont, HL., Enteroaggregative *Escherichia coli* Diarrhea in Travelers: Response to Rifaximin Therapy. *Clinical Gastroenterology and Hepatology.* 2004;2:135-138; and Steffen R, M.D., Sack DA, M.D., Riopel L, Ph.D., Zhi-Dong J, Ph.D., Sturchler M, M.D., Ericsson CD, M.D., Lowe B, M.Phil., Waiyaki P, Ph.D., White M, Ph.D., DuPont HL, M.D. Therapy of Travelers' Diarrhea With Rifaximin on Various Continents. *The American Journal of Gastroenterology.* May 2003, Volume 98, Number 5, all of which are incorporated herein by reference in their entirety. Examples of treating hepatic encephalopathy with rifaximin see, for example, N. Engl J Med. 2010_362_1071-1081.

Embodiments also provide pharmaceutical compositions comprising rifaximin SD compositions and a pharmaceutically acceptable carrier. Embodiments of the pharmaceutical composition further comprise excipients, for example, one or more of a diluting agent, binding agent, lubricating agent, intragranular release controlling agent, e.g., a disintegrating agent, coloring agent, flavoring agent or sweetening agent. One composition may be formulated for selected coated and uncoated tablets, hard and soft gelatin capsules, sugar-coated pills, lozenges, wafer sheets, pellets and powders in sealed packet. For example, compositions may be formulated for topical use, for example, ointments, pomades, creams, gels and lotions.

In an embodiment, the rifaximin SD composition is administered to the subject using a pharmaceutically-acceptable formulation, *e.g.,* a pharmaceutically-acceptable formulation that provides sustained or delayed delivery of the SD rifaximin composition to a subject for at least 2, 4, 6, 8, 10, 12 hours, 24 hours, 36 hours, 48 hours, one week, two weeks, three weeks, or four weeks after the pharmaceutically-acceptable formulation is administered to the subject. The pharmaceutically-acceptable formulations may contain microgranules comprising rifaximin as described herein.

In certain embodiments, these pharmaceutical compositions are suitable for topical or oral administration to a subject. In other embodiments, as described in detail below, the pharmaceutical compositions described herein may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; or (5) aerosol, for example, as an aqueous aerosol, liposomal preparation or solid particles containing the compound.

The phrase "pharmaceutically acceptable" refers to those SD rifaximin compositions and cocrystals presented herein, compositions containing such compounds, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" includes pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ, or portion of the body, to another organ, or portion of the body. Each carrier is preferably "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil,

olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Methods of preparing these compositions include the step of bringing into association a SD rifaximin composition(s) or microgranules containing the SD rifaximin compositions with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a SD rifaximin composition with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a SD rifaximin composition(s) as an active ingredient. A compound may also be administered as a bolus, electuary or paste.

The SD compositions of rifaximin disclosed herein can be advantageously used in the production of medicinal preparations having antibiotic activity, containing rifaximin, for both oral and topical use. The medicinal preparations for oral use will contain an SD composition of rifaximin together with the usual excipients, for example diluting agents

such as mannitol, lactose and sorbitol; binding agents such as starches, gelatines, sugars, cellulose derivatives, natural gums and polyvinylpyrrolidone; lubricating agents such as talc, stearates, hydrogenated vegetable oils, polyethylenglycol and colloidal silicon dioxide; disintegrating agents such as starches, celluloses, alginates, gums and reticulated polymers; coloring, flavoring, disintegrants, and sweetening agents.

Embodiments described herein include SD rifaximin composition administrable by the oral route, for instance coated and uncoated tablets, of soft and hard gelatin capsules, sugar-coated pills, lozenges, wafer sheets, pellets and powders in sealed packets or other containers.

Pharmaceutical compositions for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more SD rifaximin composition(s) with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent. Compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a SD rifaximin composition(s) include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active SD rifaximin composition(s) may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

Ointments, pastes, creams and gels may contain, in addition to SD rifaximin composition(s), excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a SD rifaximin composition(s), excipients such as lactose, talc, silicic acid, aluminium hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

The SD rifaximin composition(s) can be alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (*e.g.,* fluorocarbon propellant) suspension could

be used. Sonic nebulizers are preferred because they minimize exposing the agent to shear, which can result in degradation of the compound.

An aqueous aerosol is made, for example, by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically-acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular compound, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Transdermal patches have the added advantage of providing controlled delivery of a SD rifaximin composition(s) to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the active ingredient across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active ingredient in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of the invention.

Pharmaceutical compositions suitable for parenteral administration may comprise one or more SD rifaximin composition(s) in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

When the SD rifaximin composition(s) are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically-acceptable carrier.

Regardless of the route of administration selected, the SD rifaximin composition(s) are formulated into pharmaceutically-acceptable dosage forms by methods known to those of skill in the art.

Actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject. An exemplary dose range is from 25 to 3000 mg per day. Other doses include, for example, 600mg/day, 1100mg/day and 1650mg/day. Other exemplary doses include, for example, 1000mg/day, 1500mg/day, from between 500mg to about 1800mg/day or any value in-between.

A preferred dose of the SD rifaximin composition disclosed herein is the maximum that a subject can tolerate without developing serious side effects. Preferably, the SD rifaximin composition is administered at a concentration of about 1 mg to about 200 mg per kilogram of body weight, about 10 to about 100 mg/kg or about 40 mg to about 80 mg/kg of body weight. Ranges intermediate to the above-recited values are also intended to be part. For example, doses may range from 50mg to about 2000mg/day.

In combination therapy treatment, the other drug agent(s) are administered to mammals (*e.g.*, humans, male or female) by conventional methods. The agents may be administered in a single dosage form or in separate dosage forms. Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment in which another therapeutic agent is administered to an animal, the effective amount of the rifaximin SD composition is less than its effective amount in case the other therapeutic agent is not administered. In another embodiment, the effective amount of the conventional agent is less than its effective amount in case the rifaximin SD composition is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those skilled in the art.

In various embodiments, the therapies (*e.g.*, prophylactic or therapeutic agents) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8

hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours part. In preferred embodiments, two or more therapies are administered within the same subject's visit.

In certain embodiments, one or more compounds and one or more other therapies (*e.g.*, prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agent) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agent) for a period of time, optionally, followed by the administration of a third therapy (*e.g.*, prophylactic or therapeutic agent) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the therapies, to avoid or reduce the side effects of one of the therapies, and/or to improve the efficacy of the therapies.

In certain embodiments, the administration of the same compounds may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months. In other embodiments, the administration of the same therapy (*e.g.*, prophylactic or therapeutic agent) other than a SD rifaximin composition may be repeated and the administration may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months.

Certain indications may require longer treatment times. For example, travelers' diarrhea treatment may only last from between about 12 hours to about 72 hours, while a treatment for Crohn's disease may be from between about 1 day to about 3 months. A treatment for hepatic encephalopathy may be, for example, for the remainder of the subject's life span. A treatment for IBS may be intermittent for weeks or months at a time or for the remainder of the subject's life.

**Compositions and Formulations**

Rifaximin solid dispersions, pharmaceutical compositions comprising SD rifaximin or microgranules comprising rifaxmin solid dispersions, can be made from, for example, polymers including polyvinylpyrrolidone (PVP) grade K-90, hydroxypropyl methylcellulose phthalate (HPMC-P) grade 55, hydroxypropyl methylcellulose acetate succinate (HPMC-

AS) grades HG and MG, and a polymethacrylate (Eudragit® L100-55). Rifaximin solid dispersion compositions are comprised of, for example, 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50 60:40, 70:30, 75:25, 80:20, 85:15, and 90:10 (Rifaximin/polymer, by weight). Preferred solid dispersions are comprised of 25:75, 50:50 and 75:25 (Rifaximin/polymer, by weight). In addition to rifaximin and polymer, solid dispersions may also comprise surfactants, for example, non-ionic, surfactant polyols.

An example of a formulation comprises about 50:50 (w/w) Rifaximin:HPMC-AS MG with from between about 2 wt% to about 10 wt% of a non-ionic, surfactant polyol, for example, Pluronic F-127.

One example of a formulation comprises 50:50 (w/w) Rifaximin:HPMC-AS MG with about 5.9 wt%) of a non-ionic, surfactant polyol, for example, Pluronic F-127. Spray dried rifaximin ternary dispersion (50:50 (w/w) rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127) was blended with 10 wt% croscarmellose sodium and then filled into gelatin capsules. Each capsule contains 275 mg of rifaximin and the blend formulation is 85:5:10 of 50:50 (w/w) Rifaximin:HPMC-AS MG : Pluronic : croscarmellose sodium (calculated in total solids). Other examples of microgranules and pharmaceutical compositions comprising SD rifaximin are described in the examples.

To form the rifaximin solid dispersion, the components, e.g., rifaximin, polymer and methanol are mixed and then spray dried. Exemplary conditions are summarized in Table 9 and the procedure outlined below and in Examples 3 and 4.

Exemplary Spray Drying Process Parameters, include for example:

- Spray Dryer – e.g., PSD 1;
- Single or multi-fluid nozzle: e.g., a two Fluid Niro Nozzle;
- Nozzle orifice – 0.1 – 10 mm;
- Inlet gas temperature – 75 - 150±5 deg C;
- Process gas flow (mmH2O) – 20 – 70, preferred 44;
- Atomizing gas pressure – 0.7 - 1 bar;
- Feed rate – 2 - 7 kg/Hr;
- Outlet temperature – 30 – 70 ± 3 deg C;
- Solution temperature – 20 – 50 deg C; and
- Post spray drying vacuum dry at 20 - 60 deg C, for between about 2 and 72 hrs.

**Article of Manufacture**

Another embodiment includes articles of manufacture that comprise, for example, a container holding a rifaximin SD pharmaceutical composition suitable for oral or topical administration of rifaximin in combination with printed labeling instructions providing a discussion of when a particular dosage form should be administered with food and when it should be taken on an empty stomach. Exemplary dosage forms and administration protocols are described infra. The composition will be contained in any suitable container capable of holding and dispensing the dosage form and which will not significantly interact with the composition and will further be in physical relation with the appropriate labeling. The labeling instructions will be consistent with the methods of treatment as described hereinbefore. The labeling may be associated with the container by any means that maintain a physical proximity of the two, by way of non-limiting example, they may both be contained in a packaging material such as a box or plastic shrink wrap or may be associated with the instructions being bonded to the container such as with glue that does not obscure the labeling instructions or other bonding or holding means.

Another aspect is an article of manufacture that comprises a container containing a pharmaceutical composition comprising SD rifaximin composition or formulation wherein the container holds preferably rifaximin composition in unit dosage form and is associated with printed labeling instructions advising of the differing absorption when the pharmaceutical composition is taken with and without food.

Packaged compositions are also provided, and may comprise a therapeutically effective amount of rifaximin. Rifaximin SD composition and a pharmaceutically acceptable carrier or diluent, wherein the composition is formulated for treating a subject suffering from or susceptible to a bowel disorder, and packaged with instructions to treat a subject suffering from or susceptible to a bowel disorder.

Kits are also provided herein, for example, kits for treating a bowel disorder in a subject. The kits may contain, for example, one or more of the solid dispersion forms of rifaximin and instructions for use. The instructions for use may contain proscribing information, dosage information, storage information, and the like.

Packaged compositions are also provided, and may comprise a therapeutically effective amount of an SD rifaximin composition and a pharmaceutically acceptable carrier or diluent, wherein the composition is formulated for treating a subject suffering from or susceptible to a bowel disorder, and packaged with instructions to treat a subject suffering from or susceptible to a bowel disorder.

The present invention is further illustrated by the following examples, which should not be construed as further limiting. The contents of all figures and all references, patents and published patent applications cited throughout this application, as well as the Figures, are expressly incorporated herein by reference in their entirety.

## EXAMPLES

The chemical structure of Rifaximin is shown below in Figure 1.

### Example 1. Solid Dispersions of Rifaximin

Various polymers were formulated with rifaximin into solids prepared by methanol and spray drying at small scale (~ 1g). Polymers, including polyvinylpyrrolidone (PVP) grade K-90, hydroxypropyl methylcellulose phthalate (HPMC-P) grade 55, hydroxypropyl methylcellulose acetate succinate (HPMC-AS) grades HG and MG, and a polymethacrylate (Eudragit® L100-55) were used. Solids have compositions of 25:75, 50:50 and 75:25 (Rifaximin/polymer, by weight).

Samples generated were observed under polarized light microscope after preparation and were characterized by XRPD. The results are included in Table 1 through Table 5. Birefringence with extinction (B/E) was not observed for any of the samples, indicating solids without crystalline order were obtained. No sharp peaks were evident by visual inspection of XRPD patterns of these samples, consistent with non-crystalline materials, as shown in Figure 2 (with PVP K-90), Figure 7 (with HPMC-P), Figure 12 (with HMPC-AS HG), Figure 12 (with HMPC-AS MG), and Figure 17 (with Eudragit L100-55).

Materials were characterized by mDSC where the appearance of a single glass transition temperature (Tg), provides support for a non-crystalline fully miscible dispersion. All the dispersions prepared with PVP K-90 display a single apparent Tg at approximately 185 °C (Figure 3, 25:75 w/w), 193 °C (Figure 4, 50:50 w/w), and 197 °C (Figure 5, 75:25) respectively. The change in heat capacity ($\Delta Cp$) at Tg is approximately 0.3 J/g·°C for each dispersion. A non-reversible endotherm, which is likely due to the residual solvent in the materials, was observed in each of Rifaximin /PVP K-90 dispersions centered at approximately 78 °C, 59 °C and 61 °C.

From Figure 6, Tg of Rifaximin/PVP K-90 dispersions increases with the increased Rifaximin concentration, which is due to the higher Tg of Rifaximin (199 °C) than PVP K-90 (174 °C). Evidence of a single Tg may suggest that the components of the dispersion are intimately mixed, or miscible.

Dispersions prepared with other polymers also display a single apparent Tg, as a step change in the reversing heat flow signal by mDSC. Dispersions prepared with HPMC-P exhibit Tg at 153 ºC (Figure 8, 25:75 w/w), 161 ºC (Figure 9, 50:50 w/w) and 174 ºC (Figure 10, 75:25 w/w) respectively, with ΔCp at Tg approximately 0.4 J/g·ºC.

With HPMC-AS HG, dispersions display Tg at 137 ºC (Figure 13, 25:75 w/w), 154 ºC (Figure 14, 50:50 w/w) and 177 ºC (Figure 15, 75:25 w/w) respectively; ΔCp at Tg is approximately 0.4 or 0.3 J/g·ºC.

With HPMC-AS MG, dispersions display Tg at 140 ºC (Figure 18, 25:75 w/w), 159 ºC (Figure 19, 50:50 w/w) and 177 ºC (Figure 10, 75:25 w/w) respectively; ΔCp at Tg is approximately 0.4 or 0.3 J/g·ºC.

Dispersions prepared with Eudragit L100-55 exhibit Tg at 141 ºC with ΔCp approximately 0.5 J/g·ºC (Figure 23, 25:75 w/w), 159 ºC with ΔCp approximately 0.3 J/g·ºC (Figure 24, 50:50 w/w), and 176 ºC with ΔCp at Tg approximately 0.2 J/g·ºC (Figure 25, 75:25 w/w) respectively.

Similarly, as shown in Figure 11 (with HPMC-P), Figure 16 (with HPMC-AS HG), Figure 21 (with HPMC-AS MG, and Figure 26 (with Eudragit L100-55), Tg of material in each set of Rifaximin/polymer dispersions increases with the increased Rifaximin concentration due to the higher Tg of Rifaximin.

**Physical Stability Assessment**

An assessment of physical stability for rifaximin/polymer dispersions was conducted under stress conditions of aqueous solutions at different biologically relevant conditions, including 0.1N HCl solution at 37 ºC and pH 6.5 FASSIF buffer at 37 ºC, elevated temperature/relative humidity (40 ºC/75% RH), and elevated temperature/dry (60 ºC). The x-ray amorphous rifaximin – only sample prepared from methanol by spray drying was also stressed under the same conditions for comparison.

**Stress in 0.1N HCl solution at 37 ºC**

For the assessment of physical stability for samples in a 0.1N HCl solution maintained at 37 ºC, observations were made and microscopy images were acquired using polarized light at different time points including 0, 6 and 24 hrs, as summarized in Table 6. Based on the absence of birefringent particles when samples were observed by PLM, dispersions prepared with HPMC-AS HG and HPMC-AS MG display the highest physical stability under this particular stress condition. The results of this study for each of samples are discussed below.

X-ray amorphous Rifaximin stressed in 0.1N HCl solution at 37 ºC at 0, 6, and 24 hrs showed evidence of birefringence/extinctions was observed at 6hrs, indicating the occurrence of devitrification of the material.

Samples at compositions of 25:75 and 50:50 (w/w) crystallized at 6 hrs; sample at 75:25 (w/w) composition crystallized within 24 hrs while no evidence of crystallization was observed at 6 hrs or earlier. The decreased stability of Rifaximin/PVP K-90 dispersions in 0.1N HCl solution with increased PVP K-90 concentration may due to the high solubility of PVP K-90 in the solution.

Irregular aggregates without birefringence/extinctions were observed for dispersion prepared with HPMC-P at t = 0 hr, the initial time point when 0.1N HCl solution was just added into solids. After 24 hrs, samples at compositions of 25:75 and 50:50 (w/w) remained as non-birefringent aggregates, indicating no occurrence of devitrification under the conditions examined. Evidence of crystallization was observed for sample of 75:25 (w/w) composition at 6 hrs. No birefringence/extinctions were observed for all of dispersions prepared with HPMC-AS HG and HPMC-AS MG after 24 hrs, suggesting these samples are resistant to devitrification upon exposure to 0.1N HCl solution for 24 hrs.

For dispersions prepared with Eudragit L100-55, upon exposure to 0.1N HCl solution for 24 hrs, birefringent particles with extinctions were observed only in the sample at 50:50 (w/w) composition. Considered that no evidence of crystallization was observed for dispersions of compositions at 25:75 and 75:25 (w/w), it is unknown whether such birefringence was caused by some foreign materials or by crystalline solids indicating the occurrence of devitrification.

**Stress in pH 6.5 FASSIF buffer at 37 ºC**

An assessment of physical stability of dispersions prepared was also performed in pH 6.5 FASSIF buffer maintained at 37 ºC. X-ray amorphous Rifaximin material was also stressed under same condition for comparison. PLM observations indicated that dispersions prepared from HPMC-AS HG and HPMC-AS MG display the highest physical stability under this stress condition. X-ray amorphous rifaximin-only material crystallized within 6 hrs, so did all rifaximin/PVP K-90 dispersions. For dispersions prepared with HPMC-P, birefringent particles with extinctions were observed in samples at 50:50 and 75:25 (w/w) compositions within 6 hrs, indicating the occurrence of devitrification in materials. No evidence of any birefringence/extinctions was observed in 25:75 (w/w) rifaximin/HPMC-P dispersion material after 24 hrs. No birefringence/extinctions were observed for all of dispersions prepared with HPMC-AS HG and HPMC-AS MG after 24 hrs, suggesting these

samples are resistant to devitrification upon exposure to pH 6.5 FASSIF buffer for 24 hrs. Rifaximin/Eudragit L100-55 dispersions at 50:50 and 75:25 (w/w) compositions crystallized with 6 hrs while no evidence of crystallization was observed in the sample at 25:75 (w/w) composition after 24 hrs.

**Stress at 40 °C/ 75% RH condition**

The samples including all the dispersions and x-ray amorphous rifaximin-only material were assessed for evidence of crystallization based on observations by microscopy using polarized light. Each of the samples remained as irregular aggregates without birefringence/extinctions after stressed at 40 °C/ 75% RH condition for 7 days.

Modulated DSC analyses were carried out on selected samples including 25:75 (w/w) rifaximin/HPMC-P, 75:25 (w/w) rifaximin/HPMC-AS HG, 75:25 (w/w) rifaximin/HPMC-AS MG, and 25:75 (w/w) Rifaximin/Eudragit L100-55 to inspect for evidence of phase separation after exposure to 40 °C/ 75% RH for 7 days. All of samples display a single apparent Tg at approximately 148 °C (Figure 27 , 25:75 (w/w) HPMC-P), 177 °C (Figure 28, 75:25 (w/w) HPMC-AS HG) 152 °C (Figure 29, 75:25 (w/w) HPMC-AS MG) and 140 °C (Figure 30, 25:75 (w/w) Eudragit L100-55) respectively, indicating the components of each dispersion remained intimately miscible after stress. Although crimped with manual pin-hole DSC pan was used, the release of moisture from sample upon heating can still be observed from non-reversible heat flow signals.

**Stress at 60 °C/ dry condition**

All the dispersions and x-ray amorphous rifaximin-only material were also stressed at 60 °C/ dry condition for 7 days and were assessed for evidence of crystallization based on observations by microscopy using polarized light. Each of the samples remained as irregular aggregates without birefringence/extinctions after stressed at this condition for 7 days.

**Rifaximin Solid Dispersions by Spray Drying**

Based on the experimental results from screen, HPMC-AS MG and HPMC-P were used to prepare additional quantities of solid dispersions at gram-scale by spray drying. The operating parameters used for processing are presented in Table 9. Based on visual inspection, both dispersions were x-ray amorphous by XRPD (Figure 31 and Figure 36).

**Characterization of 50:50 (w/w) Rifaximin/HPMC-AS MG Dispersion**

Characterization and results for the 50% API loading HPMC-AS MG are summarized in Table 10. The sample was x-ray amorphous based on high resolution XRPD. A single Tg at approximately 154 ºC was observed from the apparent step change in the reversing heat flow signal in mDSC with the change of heat capacity 0.4 J/ g ºC. A non-reversible endotherm was observed at approximately 39 °C which is likely due to the residual solvent in the materials (Figure 32). TG-IR analysis was carried out in order to determine volatile content on heating. TGA data for this material is shown in Figure 34. There was a 0.5% weight loss up to ~100 °C. A Gram-Schmidt plot corresponding to the overall IR intensity associated with volatiles released by solids upon heating at 20 °C/min is shown in Figure 33. There was a dramatic increase of intensity of released volatiles after ~8 minutes, with a maximum at ~ 11.5 minutes. The waterfall plot (Figure 34) and the linked IR spectrum (Figure 35) are indicative of the loss of water loss up to ~8 minutes then methanol and some unknown volatiles thereafter. This is consistent with the dramatic change in the slope in the TGA and may indicate decomposition of material.

**Characterization of 25:75 (w/w) Rifaximin/HPMC-P Dispersion**

Characterization and results for the 25% API loading dispersion of HPMC-P are summarized in Table 11. Solids were x-ray amorphous based on high resolution XRPD (Figure 36). By mDSC, there is a single Tg at approximately 152 ºC from the apparent step change in the reversing heat flow signal. The change of heat capacity is 0.4 J/ g ºC (Figure 37). A non-reversible endotherm, which is likely due to the residual solvent in the materials, was observed at approximately 46 °C. Volatiles generated on heating were analyzed by TG-IR. The total weight loss of sample was approximately 1.5 wt% to 100 °C and the dramatic change in the slope occurs at approximately 178 °C (Figure 38). The Gram-Schmidt plot (Figure 39) shows a small increase of intensity upon heating after ~ 2 minutes, followed by negligible change of intensity until ~ 9 minutes. Then dramatic change of intensity can be observed with a maximum at ~ 11 minutes, followed by a final increase of intensity above ~12 minutes. As seen in the waterfall plot (Figure 39), some volatiles were released during entire heating period (data is shown in Figure 40 using the linked IR spectrum at different time points as an example). The sample released water during entire heating period and methanol after ~ 9 minutes.

**Dispersions Miscibility Study by Multivariate Mixture Analysis**

For Rifaximin/HPMC-AS MG dispersions prepared by spray drying, a multivariate mixture analysis was performed using the XRPD data to examine the physical state of the components and inspect for evidence of miscibility. The analysis was done with MATLAB (v7.6.0) and Unscrambler (v 9.8) and it was not performed under cGMP guidelines. XRPD patterns of all the samples were truncated with their baseline corrected, and unit area normalized before analysis. The pre-possessed XRPD patterns are shown in Figure 41.

In the analysis, Rifaximin and HPMC-AS MG were assumed to be separated phases (no miscibility) and the compositions of Rifaximin and HPMC-AS MG in each sample were estimated based on this assumption. As shown in Figure 42, the estimated ratios of Rifaximin to HPMC-AS MG based on pure separated phases did not agree with samples actual compositions, especially for the samples with high compositions of HPMC-AS MG (low Rifaximin loading). Also, the calculated XRPD patterns for Rifaximin and HMPC-AS MG based on the assumption of separated phases (Figure 43) compared to actual experimental XRPD patterns for Rifaximin (Figure 44) and HPMC-AS MG (Figure 45) were generated. Although the calculated Rifaximin pattern is similar to its experimental pattern, the calculated HMPC-AS MG pattern is quite different from its experimental pattern. Both results suggest that Rifaximin and HPMC-AS MG are not separated phases but miscible in the dispersions. The differences in the estimated and actual compositions are likely due to the interaction between Rifaximin and HPMC-AS MG.

**Table 1. Solid Dispersion Attempts for Rifaximin/PVP K-90 by Spray Drying**

| Description (a, b) | Habit/Description | Analysis | Result (c) |
|---|---|---|---|
| (25:75) PVP K-90 | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 185 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |
| (50:50) PVP K-90 | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 193 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |
| (75:25) PVP K-90 | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 197 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |

(a): approximate ratio of Rifaximin to polymer, by weight;
(b): samples stored in freezer over desiccant after prepared.

**Table 2. Solid Dispersion Attempts for Rifaximin/HPMC-P by Spray Drying**

| Description (a, b) | Habit/Description | Analysis | Result (c) |
|---|---|---|---|
| (25:75) HPMC-P | solids light orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 153 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (50:50) HPMC-P | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 161 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (75:25) HPMC-P | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 174 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |

(a): approximate ratio of Rifaximin to polymer, by weight;
(b): samples stored in freezer over desiccant after prepared.

**Table 3. Solid Dispersion Attempts for Rifaximin/HPMC-AS HG by Spray Drying**

| Description (a, b) | Habit/Description | Analysis | Result (c) |
|---|---|---|---|
| (25:75) HPMC-AS HG | solids light orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 137 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (50:50) HPMC-AS HG | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 154 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (75:25) HPMC-AS HG | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 177 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |

(a): approximate ratio of Rifaximin to polymer, by weight;
(b): samples stored in freezer over desiccant after prepared.

**Table 4. Solid Dispersion Attempts for Rifaximin/HPMC-AS MG by Spray Drying**

| Description (a, b) | Habit/Description | Analysis | Result (c) |
|---|---|---|---|
| (25:75) HPMC-AS MG | solids light orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 140 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (50:50) HPMC-AS MG | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 159 °C ($T_g$, midpoint); 0.4 J/g·°C ($\Delta C_p$) |
| (75:25) HPMC-AS MG | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 177 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |

(a): approximate ratio of Rifaximin to polymer, by weight;
(b): samples stored in freezer over desiccant after prepared.

**Table 5. Solid Dispersion Attempts for Rifaximin/Eudragit L100-55 by Spray Drying**

| Description (a, b) | Habit/Description | Analysis | Result (c) |
|---|---|---|---|
| (25:75) Eudragit L100-55 | solids light orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 141 °C ($T_g$, midpoint); 0.5 J/g·°C ($\Delta C_p$) |
| (50:50) Eudragit L100-55 | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 159 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |
| (75:25) Eudragit L100-55 | solids orange; aggregates, irregular, no B/E | XRPD | x-ray amorph. |
| | | mDSC | 176 °C ($T_g$, midpoint); 0.2 J/g·°C ($\Delta C_p$) |

(a): approximate ratio of Rifaximin to polymer, by weight;
(b): samples stored in freezer over desiccant after prepared.

**Table 6. Physical Stability Assessment in 0.1N HCl at 37 °C for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Time (b) | Habit/Description | Analysis | Results |
|---|---|---|---|---|
| (100:0) Rifaximin-only | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, no liquid left | PLM | agg., no B/E + a few B/E particles |
| | | | | clear view of B/E particles |
| | 24 hrs | orange solids, solution cloudy | PLM | agg., no B/E + a few B/E particles |
| (25:75) PVP K-90 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, solution slightly yellow | PLM | agg., no B/E + B/E particles |
| | | | | clear view of B/E particles |
| | 24 hrs | orange solids, solution slightly yellow | PLM | agg., no B/E + B/E particles |
| (50:50) PVP K-90 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, solution slightly yellow | PLM | agg., no B/E + a few B/E particles |
| | | | | clear view of B/E particles |
| | 24 hrs | orange solids, small amount of liquid left | PLM | majority agg., no B/E + a few B/E particles |
| | | | | clear view of B/E particles |
| (75:25) PVP K-90 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, solution slightly yellow | PLM | agg., no B/E |
| | | | | agg., no B/E |
| | 24 hrs | orange solids, small amount of liquid left | PLM | agg., no B/E |
| | | | | a few B/E particles in view field |

(a): approximate ratio of Rifaximin to polymer, by weight.
(b): time is cumulative and approximate; 100 μL of 0.1 N HCl solution added into samples at t = 0.
(c): 100 μL of 0.1 N HCl solution added into the sample after PLM analysis at 6 hrs.

**Table 6 (cont'd) Physical Stability Assessment in 0.1N HCl at 37 °C for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Time (b) | Habit/Description | Analysis | Results |
|---|---|---|---|---|
| (25:75) HPMC-P | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | light orange solids, liquid turbid | PLM | agg., no B/E |
| | | | | agg., no B/E |
| | 24 hrs | orange solids, liquid turbid | PLM | agg., no B/E |
| | | | | agg., no B/E |
| (50:50) HPMC-P | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | agg., no B/E |
| | | | | agg., no B/E |
| | 24 hrs | orange solids, solution cloudy | PLM | agg., no B/E |
| | | | | agg., no B/E |
| (75:25) HPMC-P | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | agg., no B/E + some B/E particles |
| | | | | clear view of B/E particles |
| | 24 hrs | orange solids, small amount of liquid left | PLM | B/E particles observed |
| | | | | clear view of B/E particles |
| (25:75) HPMC-AS HG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | light orange solids in cloudy liquid | PLM | no B/E observed |
| | | | | no B/E observed |
| | 24 hrs | orange solids in cloudy solution | PLM | no B/E observed |
| | | | | no B/E observed |
| (50:50) HPMC-AS HG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid cloudy | PLM | no B/E observed |
| | | | | no B/E observed |
| | 24 hrs | orange solids in cloudy solution | PLM | no B/E observed |
| (75:25) HPMC-AS HG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | no B/E observed |
| | | | | no B/E observed |
| | 24 hrs | orange solids + cloudy solution | PLM | agg., no B/E |
| | | | | agg., no B/E |

**Table 6 (cont'd) Physical Stability Assessment in 0.1N HCl at 37 °C for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Time (b) | Habit/Description | Analysis | Results |
|---|---|---|---|---|
| (25:75) HPMC-AS MG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | light orange solids in cloudy liquid | PLM | no B/E observed |
| | 24 hrs | orange solids in cloudy liquid | PLM | majority no B/E, a few B/E particles |
| | | | | B/E particles seems fiber-like, may due to foreign materials |
| (50:50) HPMC-AS MG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | agg., no B/E + a few B/E particles seems due to foreign material |
| | | | | clear view of B/E particles |
| | 24 hrs | orange solids in cloudy solution | PLM | no B/E observed |
| | | | | no B/E observed |
| (75:25) HPMC-AS MG | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | no B/E observed |
| | | | | no B/E observed |
| | 24 hrs | orange solids in cloudy liquid | PLM | no B/E observed |
| | | | | agg., no B/E |

**Table 6 (cont'd) Physical Stability Assessment in 0.1N HCl at 37 °C for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Time (b) | Habit/Description | Analysis | Results |
|---|---|---|---|---|
| (25:75) Eudragit L100-55 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | light orange solids in cloudy liquid | PLM | no B/E observed |
| | 24 hrs | orange solids in cloudy solution | PLM | no B/E observed |
| (50:50) Eudragit L100-55 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids in cloudy liquid | PLM | no B/E observed except 2 particles |
| | 24 hrs | orange solids in cloudy solurion | PLM | majority no B/E, a few B/E particles in center |
| | | | | clear view of B/E particles |
| (75:25) Eudragit L100-55 | 0 | - | PLM | agg., irr., no B/E |
| | | | | agg., irr., no B/E |
| | 6 hrs | orange solids, liquid turbid | PLM | agg., no B/E |
| | | | | agg., no B/E |
| | 24 hrs | orange solids in cloudy liquid | PLM | agg., no B/E |

**Table 7. Physical Stability Assessment at 40 °C/75 % RH/ 7 d Condition for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Habit/Description | Analysis | Results |
|---|---|---|---|
| (100:0) Rifaximin-only | orange solids, dry | PLM | agg., irr., no B/E |
| (25:75) PVP K-90 | dark yellow solids, dry | PLM | agg., irr., no B/E |
| (50:50) PVP K-90 | orange solids, dry | PLM | agg., irr., no B/E |
| (75:25) PVP K-90 | orange solids, dry | PLM | agg., irr., no B/E |
| (25:75) HPMC-P | light orange solids, dry | PLM | agg., irr., no B/E |
| | | mDSC | 148 °C ($T_g$, midpoint); 0.3 J/g·°C ($\Delta C_p$) |
| (50:50) HPMC-P | orange solids, dry | PLM | agg., irr., no B/E |
| (75:25) HPMC-P | orange solids, dry | PLM | agg., irr., no B/E |
| (25:75) HPMC-AS HG | light orange solids, dry | PLM | agg., irr., no B/E |
| (50:50) HPMC-AS HG | orange solids, dry | PLM | agg., irr., no B/E |
| (75:25) HPMC-AS HG | orange solids, dry | PLM | agg., irr., no B/E |
| | | mDSC | 177 °C ($T_g$, midpoint); 0.5 J/g·°C ($\Delta C_p$) |
| (25:75) HPMC-AS MG | light orange solids, dry | PLM | agg., irr., no B/E |
| (50:50) HPMC-AS MG | orange solids, dry | PLM | agg., irr., no B/E |
| (75:25) HPMC-AS MG | orange solids, dry | PLM | agg., irr., no B/E |
| | | mDSC | 152 °C ($T_g$, midpoint) |
| (25:75) Eudragit L100-55 | light orange solids, dry | PLM | agg., irr., no B/E |
| | | mDSC | 140 °C ($T_g$, midpoint); 0.5 J/g·°C ($\Delta C_p$) |
| (50:50) Eudragit L100-55 | orange solids, dry | PLM | agg., irr., no B/E |
| (75:25) Eudragit L100-55 | orange solids, dry | PLM | agg., irr., no B/E |

(a): approximate ratio of Rifaximin to polymer, by weight.
(b): analysis treated as non-cGMP.

**Table 8. Physical Stability Assessment at 60 °C/Dry/ 7 d Condition for Rifaximin and Rifaximin Dispersions Prepared in Methanol by Spray Drying**

| Description (a) | Habit/Description | Analysis | Results |
|---|---|---|---|
| (100:0) Rifaximin-only | orange solids | PLM | agg., irr., no B/E |
| (25:75) PVP K-90 | orange solids | PLM | agg., irr., no B/E |
| (50:50) PVP K-90 | orange solids | PLM | agg., irr., no B/E |
| (75:25) PVP K-90 | orange solids | PLM | agg., irr., no B/E |
| (25:75) HPMC-P | light orange solids | PLM | agg., irr., no B/E |
| (50:50) HPMC-P | orange solids | PLM | agg., irr., no B/E |
| (75:25) HPMC-P | orange solids | PLM | agg., irr., no B/E |
| (25:75) HPMC-AS HG | light orange solids | PLM | agg., irr., no B/E |
| (50:50) HPMC-AS HG | orange solids | PLM | agg., irr., no B/E |
| (75:25) HPMC-AS HG | orange solids | PLM | agg., irr., no B/E |
| (25:75) HPMC-AS MG | light orange solids | PLM | agg., irr., no B/E |
| (50:50) HPMC-AS MG | orange solids | PLM | agg., irr., no B/E |
| (75:25) HPMC-AS MG | orange solids | PLM | agg., irr., no B/E |
| (25:75) Eudragit L100-55 | light orange solids | PLM | agg., irr., no B/E |
| (50:50) Eudragit L100-55 | orange solids | PLM | agg., irr., no B/E |
| (75:25) Eudragit L100-55 | orange solids | PLM | agg., irr., no B/E |

(a): approximate ratio of Rifaximin to polymer, by weight.

**Table 9. Parameters for Rifaximin Solid Dispersions by Spray Drying**

| Description (a) | Inlet temp. (set, °C) | Aspirator% | Pump % | Inlet temp. (measured, °C) | Outlet temp. (measured, °C) | Spray rate (b) mL/min |
|---|---|---|---|---|---|---|
| (50:50) HPMC-AS MG, ~10g scale | 120 | 95 | 40-30 | 120-119 | 60-45 | 9.6 |
| (25:75) HPMC-P, ~10g scale | 120 | 95 | 45-30 | 120-119 | 55-43 | 9.7 |

(a): approximate ratio of Rifaximin to polymer, by weight.
(b): flow rates are estimated at 30% pump.

**Table 10. Characterizations of 50:50 (w/w) Rifaximin/HPMC-AS MG Dispersion by Spray Drying**

| Analysis | Results |
|---|---|
| XRPD | x-ray amorphous |
| mDSC | 154 °C (midpoint, $T_g$)<br>0.4 J/g·°C (ΔCp) |
| TG-IR | 0.5 wt%<br>(loss up to 100 °C)<br>199°C<br>(onset, apparent decomp.) |
| | water, methanol and unknown volatiles |

**Table 11. Characterizations of 25:75 (w/w) Rifaximin/HPMC-P Dispersion by Spray Drying**

| Analysis | Results |
|---|---|
| XRPD | x-ray amorphous |
| mDSC | 152 °C (midpoint, $T_g$)<br>0.4 J/g·°C (ΔCp) |
| TG-IR | 1.5 wt%<br>(loss up to 100 °C)<br>178°C<br>(onset, apparent decomp.) |
| | water and methanol |

**Table 12. Sample Information of Rifaximin Dispersions for Dissolution Test in pH 6.52 FASSIF Buffer at 37 °C**

| Description (a) | Sample ID | Dissolution Vessel No | Solids Weight (mg) | Volume of Buffer (mL) |
|---|---|---|---|---|
| (50:50) HPMC-AS MG | 4042-97-01 | 1 | 122.1 | 300 |
| | | 2 | 120.5 | |
| | | 3 | 121.4 | |
| (25:75) HPMC-P | 4103-01-01 | 4 | 242.5 | 300 |
| | | 5 | 239.2 | |
| | | 6 | 242.4 | |

(a): approximate ratio of Rifaximin to polymer, by weight.

**Table 13. Rifaximin Concentrations of 50:50 (w/w) Rifaximin/HPMC-AS MG Dispersion in pH 6.52 FASSIF Buffer at 37 °C**

| Dissolution Vessel No | Time (min.) | Dilution (c) | Absorbance (d) | Concentration (µg/mL) |
|---|---|---|---|---|
| 1 | 5 | - | 0.0159 | 0.34 |
| | 10 | - | 0.0346 | 2.53 |
| | 15 | - | 0.0569 | 5.13 |
| | 30 | - | 0.09655 | 9.75 |
| | 60 | - | 0.1626 | 17.46 |
| | 90 | - | 0.2216 | 24.35 |
| | 120 | - | 0.25625 | 28.39 |
| | 1440 | 4 | 0.4093 | 184.99 |
| 2 | 5 | 2 | 0.02895 | 3.73 |
| | 10 | - | 0.0304 | 2.04 |
| | 15 | - | 0.04655 | 3.92 |
| | 30 | - | 0.104 | 10.62 |
| | 60 | - | 0.17755 | 19.21 |
| | 90 | - | 0.248 | 27.43 |
| | 120 | - | 0.3065 | 34.25 |
| | 1440 | 4 | 0.3944 | 178.04 |
| 3 | 5 | - | 0.0107 | -0.26 |
| | 10 | - | 0.02555 | 1.47 |
| | 15 | - | 0.03975 | 3.13 |
| | 30 | - | 0.08735 | 8.68 |
| | 60 | - | 0.1766 | 19.10 |
| | 90 | - | 0.25815 | 28.61 |
| | 120 | - | 0.32055 | 35.89 |
| | 1440 | 4 | 0.4202 | 190.08 |

(c): certain samples were diluted before analyzed to avoid the possibility of falling outside the linearity range of the instrument.
(d): absorbance data less than 0.05 is below instrument detection limit and therefore concentration calculated from such absorbance is an approximate value.

**Table 14. Rifaximin Concentrations of 25:75 (w/w) Rifaximin/HPMC-P Dispersion in pH 6.52 FASSIF Buffer at 37 °C**

| Dissolution Vessel No | Time (min.) | Dilution (d) | Absorbance (e) | Concentration (µg/mL) |
|---|---|---|---|---|
| 4 | 5 | - | 0.01555 | 0.30 |
| | 10 | - | 0.03395 | 2.45 |
| | 15 | - | 0.0528 | 4.65 |
| | 30 | - | 0.12235 | 12.77 |
| | 60 | - | 0.2643 | 29.33 |
| | 90 | - | 0.37355 | 42.08 |
| | 120 | - | 0.455 | 51.58 |
| | 1440 | 4 | 0.39465 | 178.16 |
| 5 | 5 | - | 0.0329 | 2.33 |
| | 10 | - | 0.06805 | 6.43 |
| | 15 | - | 0.07905 | 7.71 |
| | 30 | - | 0.13745 | 14.53 |
| | 60 | - | 0.242 | 26.73 |
| | 90 | - | 0.32595 | 36.52 |
| | 120 | - | 0.40555 | 45.81 |
| | 1440 | 4 | 0.38525 | 173.77 |
| 6 | 5 | - | 0.0155 | 0.30 |
| | 10 | - | 0.057 | 5.14 |
| | 15 | - | 0.09415 | 9.47 |
| | 30 | - | 0.17145 | 18.49 |
| | 60 | - | 0.2724 | 30.27 |
| | 90 | - | 0.36815 | 41.45 |
| | 120 | - | 0.43155 | 48.84 |
| | 1440 | 4 | 0.3838 | 173.09 |

(d): certain samples were diluted before analyzed to avoid the possibility of falling outside the linearity range of the instrument.
(e): absorbance data less than 0.05 is below instrument detection limit and therefore concentration calculated from such absorbance is an approximate value.

**Table 15. Averaged Concentrations of 50:50 (w/w) Rifaximin/HPMC-AS MG Dispersions in pH 6.52 FASSIF Buffer at 37 °C**

| Description (a) | Dissolution Vessel No | Time (min.) | Concentration (µg/mL) | Average Concentration (µg/mL) | Standard Deviation |
|---|---|---|---|---|---|
| (50:50) HPMC-AS MG | 1 | 5 | 0.34 | 1.27[b] | 2.154 |
| | 2 | | 3.73 | | |
| | 3 | | -0.26 | | |
| | 1 | 10 | 2.53 | 2.01[b] | 0.5284 |
| | 2 | | 2.04 | | |
| | 3 | | 1.47 | | |
| | 1 | 15 | 5.13 | 4.06[b] | 1.008 |
| | 2 | | 3.92 | | |
| | 3 | | 3.13 | | |
| | 1 | 30 | 9.75 | 9.69 | 0.970 |
| | 2 | | 10.62 | | |
| | 3 | | 8.68 | | |
| | 1 | 60 | 17.46 | 18.59 | 0.977 |
| | 2 | | 19.21 | | |
| | 3 | | 19.10 | | |
| | 1 | 90 | 24.35 | 26.80 | 2.202 |
| | 2 | | 27.43 | | |
| | 3 | | 28.61 | | |
| | 1 | 120 | 28.39 | 32.85 | 3.945 |
| | 2 | | 34.25 | | |
| | 3 | | 35.89 | | |
| | 1 | 1440 | 184.99 | 184.37 | 6.0455 |
| | 2 | | 178.04 | | |
| | 3 | | 190.08 | | |

(a): approximate ratio of Rifaximin to polymer, by weight.
(b): absorbance data less than 0.05 is below instrument detection limit and therefore concentration calculated from such absorbance is an approximate value.

**Table 16. Averaged Concentrations of 25:75 (w/w) Rifaximin/HPMC-P Dispersions in pH 6.52 FASSIF Buffer at 37 °C**

| Description (a) | Dissolution Vessel No | Time (min.) | Concentration (µg/mL) | Average Concentration (µg/mL) | Standard Deviation |
|---|---|---|---|---|---|
| (25:75) HPMC-P | 4 | 5 | 0.30 | 0.98[b] | 1.171 |
| | 5 | | 2.33 | | |
| | 6 | | 0.30 | | |
| | 4 | 10 | 2.45 | 4.67[b] | 2.030 |
| | 5 | | 6.43 | | |
| | 6 | | 5.14 | | |
| | 4 | 15 | 4.65 | 7.28 | 2.442 |
| | 5 | | 7.71 | | |
| | 6 | | 9.47 | | |
| | 4 | 30 | 12.77 | 15.26 | 2.935 |
| | 5 | | 14.53 | | |
| | 6 | | 18.49 | | |
| | 4 | 60 | 29.33 | 28.78 | 1.840 |
| | 5 | | 26.73 | | |
| | 6 | | 30.27 | | |
| | 4 | 90 | 42.08 | 40.02 | 3.041 |
| | 5 | | 36.52 | | |
| | 6 | | 41.45 | | |
| | 4 | 120 | 51.58 | 48.75 | 2.886 |
| | 5 | | 45.81 | | |
| | 6 | | 48.84 | | |
| | 4 | 1440 | 178.16 | 175.01 | 2.749 |
| | 5 | | 173.77 | | |
| | 6 | | 173.09 | | |

(a): approximate ratio of Rifaximin to polymer, by weight.
(b): absorbance data less than 0.05 is below instrument detection limit and therefore concentration calculated from such absorbance is an approximate value.

**Table 17. Analysis of Rifaximin Dispersions after Dissolution Test in pH 6.52 FASSIF Buffer at 37 °C**

| Description (a) | Dissolution Vessel No | Analysis | Results |
|---|---|---|---|
| (50:50) HPMC-AS MG | 1 | PLM | no B/E observed |
| | | | change view field, no B/E |
| | 2 | PLM | no B/E observed |
| | | | change view field, no B/E |
| | 3 | PLM | no B/E observed |
| | | | majority no B/E, only 1 B/E particle in view field |
| (25:75) HPMC-P | 4 | PLM | B/E flakes and blades |
| | 5 | PLM | no B/E material + B/E flakes |
| | 6 | PLM | no B/E material + B/E flakes & blades |

(a): approximate ratio of Rifaximin to polymer, by weight.

## Abbreviations

| Type | Abbreviation | Full Name / Description |
|---|---|---|
| INSTRUMENTAL | XRPD | x-ray powder diffractometry |
| | mDSC | modulated differential scanning calorimetry |
| | TG-IR | thermogravimetric infrared |
| | PLM | polarized light microscopy |
| | UV | ultraviolet spectroscopy |
| POLYMER | HPMC-AS | hydroxypropylmethyl cellulose acetate succinate |
| | HPMC-P | hydroxypropylmethyl cellulose phthalate |
| | Eudragit L100 | anionic polymers with methacrylic acid as a functional group, dissolution at pH > 6.0 |
| | PVP K-90 | polyvinylpyrrolidone, grade K-90 |
| RESULTS | $T_g$ | glass transition temperature |
| | $\Delta C_p$ | heat of capacity change |
| | amorph. | amorphous |
| | agg. | aggregates |
| | irr. | irregular |
| | decomp. | decomposition |
| | B | birefringence |
| | E | extinction |

**Example 2. Ternary Dispersion of 50:50 (w/w) Rifaximin:HPMC-AS MG**

A ternary dispersion of 50:50 (w/w) Rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127 was prepared in large quantity (containing approximately 110 g of Rifaximin) by spray drying. Disclosed herein are the analytical characterizations for Rifaximin ternary dispersion as-prepared and post-stress samples at 70 °C/75% RH for 1 week and 3 week, and post-stress sample at 40 °C/75% RH for 6 weeks and 12 weeks.

**Characterization of Rifaximin Ternary Dispersion**

Characterizations of the spray dried Rifaximin ternary dispersion (50:50 (w/w) rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127) are described in Table 18.

**Table 18. Characterizations of Combined Rifaximin Ternary Dispersion Solids - Spray Drying**

| Sample ID | Analysis | Results (b) |
|---|---|---|
| 4103-74-01a | XRPD | x-ray amorphous |
| | mDSC | 136 °C (midpoint, $T_g$)<br>0.4 J/g·°C (ΔCp) |
| | TG-IR | 0.7 wt%<br>(loss up to 100 °C)<br>202°C<br>(onset, volatilization and apparent decomp.) |
| | | methanol and possible acetic acid |
| | IR-ATR | consistent with structure |
| | Raman | consistent with structure |
| | SEM | agglomerates of collapsed spheres |
| | PLM | irregularly-shaped equant particles |
| | PSA | d10 (μm): 3.627, d50 (μm): 8.233,<br>d90 (μm): 17.530 |
| | DVS | 0.13 wt% (loss at 5%RH)<br>11.14 wt% (gain, 5-95% RH)<br>10.80 wt% (loss, 95-5% RH) |
| 4074-89-01 (c) | XRPD | x-ray amorphous |

(b): temperatures are round to the nearest degree; ΔCp is rounded to one decimal places and wt% is rounded to one decimal place.

A high resolution XRPD pattern was acquired and material is x-ray amorphous (Figure 46). By mDSC (Figure 47), a single apparent $T_g$ is observed from the step change in the reversing heat flow signal at approximately 136 ºC with a heat capacity change at $T_g$ of approximately 0.4 J/g·ºC.

Thermogravimetric analysis coupled with infra-red spectroscopy (TG-IR) was performed to analyze volatiles generated upon heating. The total weight loss of sample was approximately 0.7 wt% to 100 °C and the dramatic change in the slope occurs at approximately 202 °C (Figure 48). The Gram-Schmidt plot corresponds to the overall IR intensity associated with volatiles released by a sample upon heating at 20 °C/min. By Gram-Schmidt, a negligible increase of intensity upon heating is observed before ~ 7 minutes followed by a dramatic increase of intensity with the maximum at ~ 11.8 min. The waterfall plot (data not shown) of this sample indicates volatile are released upon heating after ~ 7 min (data is shown in Figure 49 using the linked IR spectrum at different time

points as an example) and volatiles were identified as residual methanol from the processing solvent in spray drying and possible acetic acid from HPMC-AS MG.

Vibrational spectroscopy techniques, including IR and Raman were employed to further characterize this ternary dispersion. The overlay of IR spectra for the dispersion and X-ray amorphous Rifaximin is shown in Figure 50. Based on visual inspection, two spectra are very similar. Similar observations can be drawn from the comparison of Raman analysis (Figure 51). The sample is composed of agglomerates of collapsed spheres. Particles sizes of spheres are not uniform, ranging from slightly larger to much less than 10 μm.

PLM images (data not shown) of solids dispersed in mineral oil were collected, which indicate sample primarily is composed of irregularly-shaped equant particles approximately 5-15 μm in length with some agglomerates 20-50 μm in length. Particle size analysis (Figure 52) indicates that 50% of particles have size less than 8.233 μm and 90% of particles have size less than 17.530 μm. Data was acquired in 2% (w/v) Lecithin in Isopar G.

The DVS isotherm of solids is shown in Figure 53. The material exhibits a 0.13 wt% loss upon equilibration at 5% RH. Solids then gain 11.14 wt% between 5% and 95% RH and exhibits some hysteresis with 10.80 wt% loss upon desorption from 95% to 5% RH. XRPD analysis of the solids recovered after completion of the desorption step showed no evidence of sharp peaks indicative of a crystalline solid (Figure 54).

**Physical Stability Assessment on Rifaximin Ternary Dispersion**

An assessment of physical stability of this rifaximin ternary dispersion is currently in progress by exposing solids to varied elevated temperature/relative humidity conditions, including 25ºC/ 60%RH, 40ºC/ 75%RH and 70ºC/ 75%RH for extended period of time. At designated time interval, such as at 1 week, 3 week, 6 week, and 12 weeks, selected samples were removed from stress conditions for characterization.

Table 19 summarized characterization results for the samples that stressed at 70ºC/ 75%RH condition 1 week and 3 weeks, and the sample that stressed at 40ºC/ 75%RH condition 6 weeks.

**Table 19. Physical Stability Evaluation on Rifaximin Ternary Dispersion**

| Condition | Time | Habit/ Description | Analysis | Results (a) |
|---|---|---|---|---|
| 70 ºC/75% RH | 1 week | orange solids, aggregates, no B/E | XRPD | x-ray amorphous |
| | | | mDSC | 134 °C (midpoint, $T_g$)<br>0.4 J/g·ºC (ΔCp) |
| | | | SEM | agglomerates of collapsed spheres |
| | | | KF | 3.80% |
| 70 ºC/75% RH | 3 weeks | dark orange solids, aggregates, no B/E | XRPD | x-ray amorphous |
| | | | mDSC | 134 °C (midpoint, $T_g$)<br>0.4 J/g·ºC (ΔCp) |
| | | | SEM | agglomerates of collapsed spheres |
| | | | KF | 3.19% |
| 40 ºC/75% RH | 6 weeks | orange solids, aggregates, no B/E | XRPD | x-ray amorphous |
| | | | mDSC | 133 °C (midpoint, $T_g$)<br>0.4 J/g·ºC (ΔCp) |
| | | | SEM | agglomerates of collapsed spheres |
| | | | KF | 4.05% |
| 40 ºC/75% RH | 12 weeks | orange solids, aggregates, no B/E | XRPD | x-ray amorphous |
| | | | mDSC | 132 °C (midpoint, $T_g$)<br>0.5 J/g·ºC (ΔCp) |
| | | | SEM | agglomerates of collapsed spheres |
| | | | KF | 3.37% |

(a): temperatures are round to the nearest degree; ΔCp is rounded to one decimal places.

For a sample that was stressed at 70ºC/ 75%RH for 1 week, solids are still x-ray amorphous according to XRPD (Figure 55). A single $T_g$ at approximately 134 ºC was observed from the apparent step change in the reversing heat flow signal in mDSC with the change of heat capacity 0.4 J/ g ºC, indicating the components of each dispersion remained intimately miscible after stress (Figure 56). A non-reversible endotherm was observed at approximately 54 °C which is likely due to the residual solvent from spray drying and moisture that materials absorbed during stress, which is confirmed by KF analysis that sample contains 3.80 wt% of water (KF analysis for Rifaximin ternary dispersion after 70 ºC/75% RH 1week; 1.2855 g – R1=3.72 and .988 g – R1= 3.87%). The sample is composed of agglomerates of collapsed spheres and particles sizes of spheres are not uniform, which is similar to the as-prepared material.

For the sample that was stressed at 70ºC/ 75%RH for 3 weeks, although the color of the material appeared to be darker than the 1-week sample, characterization results for 3-week sample are similar to that for 1-week sample. Solids are also x-ray amorphous by XRPD (Figure 55) and display a single $T_g$ at approximately 134 ºC by mDSC (Figure 57). KF analysis indicates it contains 3.19 wt% of water (KF analysis for rifaximin ternary dispersion after 70 ºC/75% RH 3weeks; 1.2254g – R1 = 3.45 and 1.1313g – R1 = 2.93). By SEM (data not shown), the material has morphology similar to the as-prepared dispersion

and 1-week stress sample, which is composed of agglomerates of collapsed spheres and particles sizes of spheres are not uniform.

For the sample that was stressed at 40ºC/ 75%RH for 6 weeks, solids are still x-ray amorphous according to XRPD (Figure 55). It has a single $T_g$ at approximately 133 ºC by mDSC with the change of heat capacity 0.4 J/ g ºC (Figure 58). It contains 4.05 wt% of water by KF (KF analysis for rifaximin ternary dispersion after 40 ºC/75% RH 6 weeks; 1.0947g – R1 = 3.47 and 1.2030 – R1= 4.63). By SEM (data not shown), the sample is composed of agglomerates of collapsed spheres and particles sizes of spheres are not uniform, which is similar to the as-prepared material.

For the sample that was stressed at 40ºC/ 75%RH for 12 weeks, solids are x-ray amorphous (Figure 55) and display a single $T_g$ at approximately 132 ºC with the change of heat capacity 0.5 J/ g ºC (Figure 59). It contains 3.37 wt% of water by KF (KF analysis for Rifaximin ternary dispersion after 40 ºC/75% RH 12 weeks; 1.3687 g - R1= 3.06 and 1.1630 g – R1= 3.67). SEM analysis (data not shown) indicates that the sample is composed of agglomerates of collapsed spheres and particles sizes of spheres are not uniform, which is similar to the as-prepared material.

**Example 3. Rifaximin Solid Dispersion Composition and Procedures**

Rifaximin Ternary Dispersion Ingredients:

Rifaximin ternary dispersions (50:50 w/w Rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127) were prepared from methanol using spray drying in closed mode suitable for processing organic solvents. Ingredients are listed as below in Table 20:

**Table 20. Components of Rifaximin Solid Dispersion**

| Component | mg/g | Purpose |
|---|---|---|
| Rifaximin | 472 | active pharmaceutical ingredient |
| Hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), Type MG | 472 | stabilizing agent |
| Pluronic F-127 | 56 | wetting agent |
| Methanol | -- | volatile; removed during process |

Spray Drying Procedures:

Rifaximin ternary dispersions were prepared by spray drying in both small scale (~1 g API) and large scale (≥ 34 g API in a single batch).

For the small-scale sample, rifaximin and then the methanol were added to a flask. The mixture was stirred at ambient temperature for ~ 5 min to give a clear solution. HPMC-

AS MG and Pluronic F-127 were added in succession and the sample was stirred for ~ 1hr. An orange solution was obtained.

For large-scale samples, a solution was prepared at ~40 ºC. Rifaximin and then methanol were added to a flask and the mixture was stirred at ~40 ºC for ~ 5min until clear. HPMC-AS MG, and then Pluronic F-127 were added into the rifaximin solution under stirring at ~40 ºC. The sample continued to stir for ~ 1.5 hr to 2 hr at this temperature. A dark red solution was obtained. The sample was removed from the hot plate and left at ambient to cool.

Experimental conditions to prepare Rifaximin ternary solutions are summarized in Table 21 below:

**Table 21. Experimental Conditions to Prepare Rifaximin Ternary Solutions**

| Solvent | weight (API/HPMC AS MG/Pluronic F127, g) | Temperature | Concentration (g/L) |
|---|---|---|---|
| methanol, 100 mL | 1.0535/1.0529/0.1249 | ambient | 22.3 |
| methanol, 1000 mL | 34.07/34.07/4.02 | ~ 40 ºC | 72.2 |
| methanol, 1250 mL | 50.34/50.32/5.94 | ~ 40 ºC | 85.3 |
| methanol, 1250 mL | 50.16/50.14/5.92 | ~ 40 ºC | 85 |
| methanol, 1250 mL | 50.05/50.06/5.91 | ~ 40 ºC | 85 |

During the spray drying process, both the small and large scale rifaximin ternary solutions were kept at ambient temperature. The pump % was decreased during the process in an attempt to control outlet temperature above 40 ºC. The operating parameters used for processing are presented in Table 22 below.

**Table 22. Operating Parameters Used For Processing Rifaximin SD**

| Description (a) | Inlet temp. (set, ºC) | Aspirator % | Pump % | Inlet temp. (measured, ºC) | Outlet temp. (measured, ºC) | Spray rate (b) mL/min |
|---|---|---|---|---|---|---|
| 50:50 Rifaximin:HPMC-AS MG 5.9 wt% Pluronic F-127 | 120 | 95 | 35 | 120 | 60-55 | 10.4 |
| | 120 | 95 | 65-30 | 120-119 | 61-42 | 23 |
| | 120 | 95 | 50-30 | 120-119 | 67-43 | 16 |
| | 120 | 95 | 50-30 | 120-119 | 65-43 | 16 |
| | 120 | 95 | 50-30 | 120-119 | 67-43 | 16 |

(a): 50:50 is approximate ratio of Rifaximin to polymer, by weight; 5.9 wt% Pluronic is weight fraction to 50:50 rifaximin:HPMC-AS MG dispersion.
(b): Flow rates are estimated. Flow rate for 4103-41-01 was measured at pump 35%; for 4103-56-01 was measured at pump 65%, while for others were measured at pump 50%.

Solids recovered after spray drying were dried at 40 ºC under vacuum for 24 hours and then stored at sub-ambient temperatures over desiccant.

Spray Drying Process Parameters:

- Spray Dryer – PSD 1
- Two Fluid Niro Nozzle
- Nozzle orifice – 1mm
- Inlet gas temperature - 125±5 deg C
- Process gas flow (mmH2O) – 44
- Atomizing gas pressure – 0.7 - 1 bar
- Feed rate – 4.7 kg/Hr
- Outlet temperature - 55± 3 deg C
- Solution temperature – 36 deg C
- Post spray drying vacuum dry at 40 deg C for 48 hrs

**Example 4.**

Exemplary formulations for micronized, API, amorphous, solid dispersion and micronized capsules are below in Table 23. These capsules were used in the dog study of Example 5.

**Table 23. Capsule Formulation composition (Solid Dispersion (SD) Capsules)**

| Ingredients | Micronized Capsules | | API Capsules | | Amorphous Capsules | | SD Capsules | | Micronized Tablets | |
|---|---|---|---|---|---|---|---|---|---|---|
| | % | g/dose | % | g/dose | % | g/dose | % | g/dose | % | g/dose |
| **Rifaximin** | 95.5 | 2.2 | 47.2 | 2.2 | 51.7 | 2.2 | 42.47 | 2.2 | 50 | 2.2 |
| **Ac-di-sol** | 4.5 | 0.1 | 5 | 0.23 | 5 | 0.21 | 10.02 | 0.52 | 7.5 | 0.33 |
| **Mannitol 160C** | | | 47.8 | 2.23 | 43.3 | 1.84 | | | | |
| **Pluronic 188** | | | | | | | 5.04 | 0.26 | | |
| **HPMC AS** | | | | | | | 42.47 | 2.2 | | |
| **Avicel 113** | | | | | | | | | 26 | 1.14 |
| **Avicel 112** | | | | | | | | | 15 | 0.66 |
| **Magnesium Stearate** | | | | | | | | | 1 | 0.04 |
| **Cab-o-sil** | | | | | | | | | 0.5 | 0.02 |
| **Avicel CL-611** | | | | | | | | | | |
| **Mannitol 160C** | | | | | | | | | | |
| **Total** | 100 | 2.3 | 100 | 4.66 | 100 | 4.26 | 100 | 5.18 | 100 | 4.4 |

**Table 24. Manufacture of rifaximin/HPMC-AS /Pluronic 275mg Capsules**

| Component | % Formula | mg/caps | Theo. Qty (g) | Actual Qty (g) |
|---|---|---|---|---|
| Rifaximin | 42.47 | 275 | 113.7 | 113.7 |
| HPMC-AS (type MG) | 42.47 | 275 | 113.7 | 113.7 |
| Pluronic F-127 | 5.04 | 32.63 | 13.49 | 13.49 |
| Sodium Croscarmellose | 10.02 | 64.87 | 26.82 | 26.82 |
| Hard Gelatin Capsule (size 000) Clear | 1 | N/A | 300 | 300 |
| Total | 100 | 647.5 | 267.7 g | |

**Blending/Encapsulation Procedure:**

To form the capsules sodium croscarmellose was added to the bag of SD rifaximin dispersion and bag blend for 1 minute, and then the material was added to the V-blender and blended for 10 minutes at 24 rpm.

The material was then discharged into a stainless steel pan and record the height of material in the pan. Empty capsules were tared using an analytical balance, then the capsules were filled by depressing into the bed of material. The weight is adjusted within + or – 5% of target fill weight of 647.5mg (acceptable fill range 615.13 - 679.88 mg).

Figures 61 – 63 show the rifaximin solid dispersion (SD) capsules in various buffers; with and without SDS; and compared to amorphous rifaximin. Figure 61 shows results of dissolution studies of rifaximin SD capsules in acid phase: 0.1 N HCl with variable exposure times in a buffer containing 0.45% SDS at pH 6.8. Figure 62 shows results of dissolution studies of rifaximin SD capsules in acid phase for 2 hours buffered at pH 6.8 with and without SDS. Figure 63 shows results of dissolution studies of rifaximin SD capsules in acid phase in a phosphate buffer at pH 6.8 with 0.45% SDS compared to amorphous rifaximin. As shown in the Figures 61 – 63 rifaximin SD near 100% dissolution is achieved in 0.45% SDS and the SD formulation dissolves more slowly than the amorphous rifaximin.

**Example 5. Pharmacokinetic (PK) studies** of **solid dispersion in capsules**

Presented herein are dog pharmacokinetics (PK) studies comparing various forms of rifaximin. PK following administration of rifaximin API in capsule, micronized API in capsule, nanocrystal API in capsule (containing surfactant), amorphous in capsule, and solid dispersion (SD) in capsule were tested.

In the SD dosage form, the polymer used was HPMC-AS at a drug to polymer ratio of 50:50. The formulation also comprised pluronic F127 and crosscarmellose sodium (see Example 4).

A brief study design: male beagle dogs (N=6, approximately 10 kg) received rifaximin 2200 mg in the dosage forms described above as a single dose (capsules, 275 mg, 8 capsules administered in rapid succession), in a cross-over design with one week washout between phases. Blood was collected at timed intervals for 24 h after dosage administration, and plasma was harvested for LC-MS/MS analysis. The mean concentrations are shown in Figure 60.

Table 25 shows the PK parameters. From the table it can be seen that systemic exposure of the solid dispersion formulation is greater than that of amorphous or crystalline form (API) of rifaximin.

**Table 25. PK Parameters of API, Amorphous and Solid Dispersion to Dogs**

| ID | Half-life* | Tmax | Cmax | AUClast | AUCINF_obs | AUC_0-24 |
|---|---|---|---|---|---|---|
| | h | h | ng/mL | h*ng/mL | h*ng/mL | h*ng/mL |
| | | | | | | |
| 901_API | 16.76 | 0.5 | 65.5 | 101 | 118 | 101 |
| 902_API | 9.41 | 1 | 3.83 | 25 | 29 | 25 |
| 903_API | 10.03 | 1 | 197 | 344 | 360 | 344 |
| 904_API | 3.56 | 1 | 1.21 | 5 | 6 | 6 |
| 905_API | 2.94 | 1 | 1.53 | 5 | 6 | 6 |
| 906_API | | 24 | 0.52 | 7 | | 7 |
| **mean** | **6.98** | **1** | **44.93** | **81** | **104** | **82** |
| **SD** | | [0.5-24] | 78.75 | 134 | 150 | 134 |
| | | | | | | |
| 901_amorph | 5.38 | 1 | 536 | 1407 | 1421 | 1407 |
| 902_amorph | 5.93 | 2 | 4100 | 12258 | 12762 | 12258 |
| 903_amorph | 6.25 | 2 | 1050 | 3375 | 3523 | 3375 |
| 904_amorph | 4.77 | 2 | 763 | 2291 | 2306 | 2291 |
| 905_amorph | 7.72 | 1 | 1200 | 2041 | 2059 | 2041 |
| 906_amorph | 5.63 | 2 | 704 | 2076 | 2090 | 2076 |
| **mean** | **5.88** | **2** | **1392.17** | **3908** | **4027** | **3908** |
| **SD** | | [1-2] | 1348.24 | 4141 | 4334 | 4141 |
| | | | | | | |
| 901_SD amorph | 6.66 | 2 | 491 | 1354 | 1394 | 1354 |
| 902_SD amorph | 2.04 | 2 | 6550 | 25140 | 25149 | 25140 |
| 903_SD amorph | 2.8 | 4 | 2410 | 10490 | 10508 | 10490 |
| 904_SD amorph | 2.24 | 1 | 1410 | 6343 | 6350 | 6343 |
| 905_SD amorph | 3.97 | 2 | 2860 | 7885 | 7895 | 7885 |
| 906_SD amorph | 4.89 | 2 | 1900 | 4532 | 4558 | 4532 |
| **mean** | **3.01** | **2** | **3026** | **10878** | **10892** | **10878** |
| **SD** | | [1-4] | 2043.58 | 8267 | 8264 | 8267 |

*geometric mean **median and range

API exposures were low, in keeping with what has been previously observed for rifaximin. In contrast, mean exposures (AUCinf) following amorphous and SD rifaximin administration were substantially higher, with ~40-and ~100-fold greater exposure, respectively, as compared with API. Variability was high in all three dose groups. In

general, the shapes of all three profiles were similar, suggesting effects of the dosage forms on bioavailability without effects on clearance or volume of distribution.

**Example 6. Human Clinical Studies**

Rifaximin SDD with 10% CS formulation was used in human clinical studies. Figure 65 shows the kinetic solubility of rifaximin SD granules 10% wt CS FaSSIF or 10% wt CS FeSSIF (a) and the dissolution profiles of SDD tablet 10% CS in 0.2% SLS at pH 4.5, 5.5 and 7.4. As shown in the Figure 65, rifaximin SDD 100%, or near 100%, dissolution is achieved in 0.2% SLS, pH 4.5, 5.5 and 7.4. Figure 66 shows that release can be delayed up to two hours and extended up to three hours.

**Example 7. Effects of Media pH on Dissolution**

Figures 67 - 70 show the effects of media pH on Rifaximin SDD tablet SDD tablet dissolution at various levels of CS: 0%, 2.5%,5%, and 10% CS. Figures 67 and 68 show dissolution profiles of SDD tablet with 0%, 2.5%, 5% or 10% CS in 0.2%SDS at 2 hours pH 2.0, pH 4.5, 0.2% SDS pH 5.5, or 0.2% SDS, pH 7.4. Figures 69 and 70 show the dissolution profiles of SDD tablet 2.5% CS, 0% CS, 10% CS and 5% CS in 0.2% SLS, pH4.5, 0.2% SLS, pH 5.5 and 0.2% SLS, pH 7.4. Figure 71 shows CS release mechanism.

**Example 8.**

Described herein are the preparation and characterization of rifaximin quaternary dispersions with antioxidants. Antioxidants used were butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate (PG).

**Sample preparation and Characterization**

Three rifaximin quaternary samples were prepared by spray drying from methanol. Spray drying parameters are summarized in Table 26. Table 2 Parameters for Samples Prepared by Spray Drying

Table 26

| Sample ID | Inlet temp. (set, °C) | Aspirator % | Pump% | Inlet temp. (measured, °C) | Outlet temp. (measured, °C) | Spray rate (a) mL/min |
|---|---|---|---|---|---|---|
| 0.063 wt% of BHA in the dispersion | 120 | 95 | 45-35 | 120-124 | 61-49 | 19 |
| 0.063 wt% of BHT in the dispersion | 120 | 95 | 45-35 | 120-121 | 60-50 | 20 |
| 0.094 wt% of propyl gallate in the dispersion | 120 | 95 | 45-35 | 119-120 | 60-48 | 20 |

(a): flow rates are estimated based on initial pump% of 45%.

Table 27 Characterization of Rifaximin Quaternary Samples

| Habit/Description | Analysis | Results (b) |
|---|---|---|
| orange solids, irregular aggregates, no B/E | XRPD | x-ray amorphous |
| | mDSC | 133 °C (midpoint, $T_g$)<br>0.3 J/g·°C (ΔCp) |
| orange solids, irregular aggregates, no B/E | XRPD | x-ray amorphous |
| | mDSC | 133 °C (midpoint, $T_g$)<br>0.4 J/g·°C (ΔCp) |
| orange solids, irregular aggregates, no B/E | XRPD | x-ray amorphous |
| | mDSC | 134 °C (midpoint, $T_g$)<br>0.4 J/g·°C (ΔCp) |

A small sub-lot from each of spray dried materials was visually inspected by PLM and then characterized by XRPD and mDSC. Characterization results are summarized in Table 27.

The prepared materials are x-ray amorphous, as shown in Figure 72 the overlay of XRPD patterns, which agree with their PLM observations.

In the mDSC, each of material displays a single apparent $T_g$ in the reversing heat flow signal at approximately 133 °C (Figure 73, with 0.063 wt% BHA), 133 °C (Figure 74, with 0.063 wt% BHT), and 134 °C (Figure 75, with 0.094 wt% PG), which is consistent with the $T_g$ of the spray dried rifaximin ternary dispersion of 47.2:47.2:5.6 w/w/w/ rifaximin/HPMC-AS MG/Pluronic F-127 (135 or 136 °C).

**Example 9: Rifaximin Solid Dispersions**

This example sets forth exemplary microgranules of rifaximin and pharmaceutical compositions comprising the same.

Spray dry dispersion (SDD), solid dispersion, amorphous solid dispersion are used interchangabley herein to refer to the rifaximin formulations.

The complete statement of the components and quantitative composition of Rifaximin Solid Dispersion Formulation (Intermediate) is given in Table 28

**Table 28: Composition of Rifaximin Solid Dispersion Formulation**

| Component | Quantity (%) | Function |
|---|---|---|
| Rifaximin Drug Substance | 42.48 | Active Ingredient |
| Hypromellose Acetate Succinate (HPMC-AS) | 42.48 | Solubility Enhancer |
| Poloxamer 407 | 5.04 | Surfactant |
| Croscarmellose Sodium | 10.00 | Dissolution Enhancer |

Composition of Rifaximin solid dispersion IR capsule

**Table 29: Composition of Rifaximin solid dispersion IR capsule**

| Component | Quantity | Function |
|---|---|---|
| Rifaximin solid dispersion (amorphous) | 75mg-275mg* | Active ingredient |
| Hard Gelatin capsules Coni-Snap, Size 000, Transparent | 1 unit | Capsule |

*Rifaximin dose equivalent

Description of Manufacturing Process and Process Controls

*Manufacturing Process for Rifaximin Solid Dispersion Formulation*

Table 30 sets forth the manufacture of Rifaximin solid dispersion microgranules

Table 30

| Component | Process |
|---|---|
| Methanol<br>Rifaximin<br>HPMC-AS<br>Poloxamer 407 | Dissolve Rifaximin, HPMC-AS and Poloxamer in Methanol with heating and agitation.<br>This is the Feed Solution |
| Feed Solution | Using a Spray Drier, Spray dry the Feed Solution |
| | Vacuum dry the Spray Dried material for 48 hours<br>This is the Rifaximin Solid Dispersion |
| Croscarmellose Sodium | Blend the Rifaximin Solid Dispersion with Croscarmellose Sodium. Screen the blend through a #12 mesh and mix. |
| | Roller compact the screened blend and oscillate through a #14 mesh<br>This is the Rifaximin Solid Dispersion Formulation. |
| | Place the Rifaximin Solid Dispersion Formulation into an appropriate container. |

*Manufacturing Process for Rifaximin solid dispersion IR capsules*

The manufacturing process the Rifaximin solid dispersion IR capsules is given in Table 31.

**Table 31: Manufacture of Rifaximin solid dispersion microgranules in IR capsules**

| Component | Process |
|---|---|
| Rifaximin solid dispersion Formulation | Transfer the required amount of Rifaximin solid dispersion Formulation into each capsule and close the capsule. ↓ Place each capsule individually into appropriate container |

Exemplary spary drying processes are set forth in Table 32.

Table 32: Spray Drying Process:

- Spray Dryer – PSD 1
- Two Fluid Niro Nozzle
- Nozzle orifice – 1mm
- Inlet gas temperature - 125±3 deg C
- Process gas flow (mmH2O) – 44
- Atomizing gas pressure – 1 bar
- Feed rate – 4.7 kg/Hr
- Outlet temperature - 55± 3 deg C
- Solution temperature – 36 deg C
- Post spray drying vacuum dry at 40 deg C for 48 hrs

| Ingredients | Micronized Caps | | API Caps | | Amorphous Caps | | Amorphous SD caps | | Micronized Tab | |
|---|---|---|---|---|---|---|---|---|---|---|
| | % | g/dose | % | g/dose | % | g/dose | % | g/dose | % | g/dose |
| Rifaximin | 95.5 | 2.2 | 47.2 | 2.2 | 51.7 | 2.2 | 42.47 | 2.2 | 50 | 2.2 |
| Ac-di-sol | 4.5 | 0.1 | 5 | 0.23 | 5 | 0.21 | 10.02 | 0.52 | 7.5 | 0.33 |
| Mannitol 160C | | | 47.8 | 2.23 | 43.3 | 1.84 | | | | |
| Pluronic 188 | | | | | | | 5.04 | 0.26 | | |
| HPMC AS | | | | | | | 42.47 | 2.2 | | |
| Avicel 113 | | | | | | | | | 26 | 1.14 |
| Avicel 112 | | | | | | | | | 15 | 0.66 |
| Magnesium Stearate | | | | | | | | | 1 | 0.04 |
| Cab-o-sil | | | | | | | | | 0.5 | 0.02 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Avicel CL-611 | | | | | | | | | | |
| Mannitol 160C | | | | | | | | | | |
| Total | 100 | 2.3 | 100 | 4.66 | 100 | 4.26 | 100 | 5.18 | 100 | 4.4 |

**Example 10: Characterization of Drug Product Samples Containing Rifaximin Solid Dispersion**

Disclosed herein is dissolution data for roller compacted materials of Solid Dispersion Rifaximin with varying levels (0, 2.5%, 5%, and 10%) of croscarmellose sodium.

Three roller compacted material of Amorphous Solid Dispersion Rifaximin with varying levels (0, 2.5%, 5%) of croscarmellose sodium were dissolution tested. Results are compared to dissolution of the rifaximin granules with 10% croscarmellose sodium.

Dissolution Studies with USP Paddle Method

Dissolution tests were performed on as received roller compacted materials of Solid Dispersion Rifaximin with 0, 2.5 wt%, and 5 wt% croscarmellose sodium. Powders of solids were directly added into pH 6.5 FaSSIF buffer with gentle agitation of the media (50 rpm paddle stirrer) at 37 ℃ for 24 hrs.

At designated time points of 5, 10, 20, 30, 60, 90, 120, 240 and 1440 minutes, aliquots were removed from each of the samples. Analysis of the date indicates that an increase in rifaximin concentration is apparent with the rising croscarmellose sodium level in materials, particularly in the early stage of the dissolution. After 24 hrs, the rifaximin concentration from granules containing 5 wt% croscarmellose sodium is similar to granules with 10 wt% croscarmellose sodium.

**Example 11: Characterization of Rifaximin Solid Dispersion Powder 42.48% w/w**

Described herein is the characterization of Rifaximin Solid Dispersion Powder 42.48% w/w. Dissolution testing was also performed on the material at pH 6.5 in FaSSIF at 37 °C.

A sample of rifaximin ternary dispersion was characterized by XRPD, mDSC, TG-IR, SEM and KF.

X-ray powder diffraction (XRPD) analysis using a method for Rifaximin Solid Dispersion Powder 42.48% w/w was conducted. The XRPD pattern by visual inspection is x-ray amorphous with no sharp peaks (Figure 76). By mDSC a single apparent $T_g$ is observed from the step change in the reversing heat flow signal at approximately 134 ºC with a heat capacity change at $T_g$ of approximately 0.36 J/g·ºC.

Thermogravimetric analysis coupled with infra-red spectroscopy (TG-IR) was performed to analyze volatiles generated upon heating. The total weight loss of sample was approximately 0.4 wt% to 100 °C, and a dramatic change in the slope occurs at approximately 190 °C which is likely due to decomposition. The Gram-Schmidt plot corresponds to the overall IR intensity associated with volatiles released by a sample upon heating at 20 °C/min. Gram-Schmidt indicates that volatiles are released upon heating after ~ 8min, and volatiles were identified as residual methanol from the processing solvent in spray drying and possible acetic acid from HPMC-AS MG.

KF analysis indicates that the material contains 1.07 wt% water [(1.00 + 1.13)/2 = 1.07%].

**Example 12: Methods for Spray drying Rifaximin ternary dispersion (50:50 w/w Rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127).**

Provided herein are procedures to spray dry Rifaximin ternary dispersion (50:50 w/w Rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127).

Rifaximin ternary dispersions (50:50 w/w Rifaximin:HPMC-AS MG with 5.9 wt% Pluronic F-127) were prepared from methanol using Büchi B-290 Mini Spray Dryer in closed mode suitable for processing organic solvents. Ingredients are listed in Table 33 below:

Table 33

| No. | Component | mg/g | Purpose |
|---|---|---|---|
| 1 | Rifaximin | 472 | active pharmaceutical ingredient |
| 2 | Hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), Type MG | 472 | stabilizing agent |
| 3 | Pluronic F-127 | 56 | wetting agent |
| 4 | Methanol | -- | volatile; removed during process |

Rifaximin ternary dispersions were prepared by spray drying in both small scale (~1 g API) and large scale (≥ 34 g API in a single batch).

For a small-scale sample, rifaximin and then the methanol were added into a clean flask. The mixture was stirred at ambient for ~ 5 min to give a clear solution. HPMC-AS MG and Pluronic F-127 were added in succession and the sample was stirred for ~ 1hr. An orange solution was obtained.

For a large-scale sample, a solution was prepared at ~40 ℃. Rifaximin and then methanol were added to a clean flask and the mixture was stirred at ~40 ℃ for ~ 5min until clear. HPMC-AS MG, and then Pluronic F-127 were added into the rifaximin solution under stirring at ~40 ℃. The sample continued to stir for ~ 1.5 hr to 2 hr at this temperature. A dark red solution was obtained. The sample was removed from the hot plate and left at ambient to cool.

Experimental conditions to prepare Rifaximin ternary solutions are summarized in Table 34 below:

Table 34

| Solvent | weight (API/HPMC AS MG/Pluronic F127, g) | Temperature | Concentration (g/L) |
|---|---|---|---|
| methanol, 100 mL | 1.0535/1.0529/0.1249 | ambient | 22.3 |
| methanol, 1000 mL | 34.07/34.07/4.02 | ~ 40 ºC | 72.2 |
| methanol, 1250 mL | 50.34/50.32/5.94 | ~ 40 ºC | 85.3 |
| methanol, 1250 mL | 50.16/50.14/5.92 | ~ 40 ºC | 85.0 |
| methanol, 1250 mL | 50.05/50.06/5.91 | ~ 40 ºC | 85.0 |

During spray drying process, both the small and large scale rifaximin ternary solutions were kept at ambient temperature. The Pump% was decreased during process in attempt to control outlet temperature above 40 ºC. The operating parameters used for processing are presented in Table 35 below.

Table 35:

| Description (a) | Inlet temp. (set, °C) | Aspirator % | Pump % | Inlet temp. (measured, °C) | Outlet temp. (measured, °C) | Spray rate (b) mL/min |
|---|---|---|---|---|---|---|
| 50:50 Rifaximin:HPMC-AS MG 5.9 wt% Pluronic F-127 | 120 | 95 | 35 | 120 | 60-55 | 10.4 |
| | 120 | 95 | 65-30 | 120-119 | 61-42 | 23 |
| | 120 | 95 | 50-30 | 120-119 | 67-43 | 16 |
| | 120 | 95 | 50-30 | 120-119 | 65-43 | 16 |
| | 120 | 95 | 50-30 | 120-119 | 67-43 | 16 |

(a): 50:50 is approximate ratio of Rifaximin to polymer, by weight; 5.9 wt% Pluronic is weight fraction to 50:50 Rifaximin:HPMC-AS MG dispersion.
(b): flow rates are estimated. Flow rate for 4103-41-01 was measured at pump 35%; for 4103-56-01 was measured at pump 65%, while for others were measured at pump 50%.

Solids recovered after spray drying were dried at 40 ºC under vacuum for 24 hours and then stored at sub-ambient (freezer) over desiccant.

**Example 13. Non-clinical Data- form/ formulation comparison and dose ranging in dogs**

Described herein is non-clinical data, form/formulation comparison in dogs and SDD dose ranging in dogs. Figure 77 indicates the results of two studies conducted to characterize the pharmacokinetics of rifaximin following administration of varying forms and formulations following a single oral dose. Blood samples were collected at timed intervals over the 24 h after single dose administration (2200 mg total dose in each case) and processed to plasma for analysis of rifaximin concentrations. PK parameters were estimated by noncompartmental methods. The results are shown in Figure 77. Of the forms/formulations shown, the spray-dried dispersion showed that the highest exposure, and therefore the highest bioavailability, resulted from administration of the SDD formulaton (dosed as SDD powder in gelatin capsules). In order of decreasing exposure among forms dosed in gelatin capsule formulation, SDD > amorphous > iota > micronzed > eta>current crystalline API. Lower in systemic exposure than all of those

are the micronized suspension formulation (reconstituted powder for oral suspension) and the current 550 mg Xifaxan tablet. Table 36, below, shows Pk parameters for dog forms.

Table 36

| HL_Lambda_z | Tmax h | Cmax h | AUCall ng/mL | AUCINF_obs h*ng/mL | h*ng/mL |
|---|---|---|---|---|---|
| Eta | 9.70 | 1.5 | 162.28 | 434.14 | 608.14 |
| Iota | 6.56 | 2 | 276.50 | 718.23 | 739.94 |
| Amorphous | 5.82 | 2 | 1392.17 | 3907.84 | 4026.86 |
| API capsules | 5.64 | 1 | 44.93 | 81.20 | 103.83 |
| SDD | 3.16 | 2 | 2603.50 | 9290.71 | 9308.83 |
| Micronized capsules | 8.10 | 1 | 473.43 | 894.65 | 905.97 |
| Micronized suspension | 5.22 | 3 | 0.68 | 5.11 | 8.41 |
| Micronized tablets | 4.77 | 5 | 0.83 | 6.81 | 10.20 |
| Nanocrystal capsules | 5.01 | 5 | 0.99 | 9.05 | 8.70 |

Figure 78 shows the results of the dog dose escalation, in which dogs received single doses of the SDD formulation in capsules, at doses from 150 mg to 2200 mg. The results indicate an essentially linear dose escalation (increases in exposure that are approximately proportional to increase in dose) up to 550 mg, followed by a greater-than-proportional increase at 1100 mg and 2200 mg. This is quite unusual in the linear range in that the current crystalline form of rifaxmin does not dose escalate, generally, exposure does not increase substantially on increasing dose. The greater than dose proportional increase on increasing dose is also remarkable and suggests that, at the higher doses, rifaximin is saturating intestinal P-glycoprotein transport that would otherwise limit systemic absorption, thereby allowing increased absorption.

**Example 14. Human studies**

Described herein are clinical studies carried in ten male human subjects. Figure 79 sets out the quotient study design for rifaximin SDD dose escalation. Figure 80 outlines the dose escalation/ regional absorption study, dose escalation/ dose selection. Figures 81 and 82 show representative subject data from an exemplary dose escalation study. Mean data (linear scale and log scale) is shown in Figures 83 and 84, respectively. Mean profiles, log scale. Terminal phases are parallel, in clearance mechanisms. A summary of rifaximin SDD dose escalation is shown indicating that it is likely that there is not saturation of any metabolic or other systemic Figure 85. To

summarize, there are roughly dose proportional increases in exposure ($C_{max}$ and AUC) with increases in dose, as shown by $C_{max}$ multiple and AUC multiple columns. $T_{max}$ is not delayed by dose increases, further indicating an early absorption window (corroborated by regional absorption data). The percent of dose in urine is remarkable in that it stays low, approximately 0.2% or less of the dose excreted over 24 h. This result is surprising in that this is quite low in spite of the significant increases in systemic exposure as compared with the crystalline formulation. Taken together, the results indicate a considerably increased solubility that presumably leads to increased local/lumenal soluble rifaximin, with accompanying increases in systemic exposure, but without significant increases in urinary excretion that are reflective of percent of rifaximin dose absorbed.

Dose/ dosage form comparisons are shown in Figures 86 and 87. The tables compare SDD at increasing doses to the current crystalline formulation in terms of systemic PK. As noted in Figure 87, as compared to the PK of rifaximin from the current formulation, the SDD formulation at the same dose shows an approximate 6.4-fold increase in $C_{max}$ and an approximate 8.9-fold increase in AUC. Nonetheless, these exposures are less than those observed in any hepatic impaired subject with the current tablet formulation.

## Example 15. Exemplary Tablet Formulations

According to certain exemplary embodiments, microgranules, blends and tablets are formulated as set forth in Table 37, below

Table 37.

Rifaximin SDD Granules

| Component | Function | % w/w (0% CS) | %w/w (2.5% CS) | % w/w (5% CS) | %w/w (10% CS) |
|---|---|---|---|---|---|
| Rifaximin | Drug | 47.2 | 46.02 | 44.84 | 42.48 |
| HPMC-AS | Polymer | 47.2 | 46.02 | 44.84 | 42.48 |
| Pluronic F-127 | Wetting agent | 5.6 | 5.46 | 5.32 | 5.04 |
| Croscarmellose Na (CS) | Rate controlling | 0 | 2.5 | 5 | 10 |
| | Total | 100 | 100 | 100 | 100 |

| Granule Blend | | mg/Tab | mg/Tab | mg/Tab | mg/Tab |
|---|---|---|---|---|---|
| Roller Compacted Granules | Granules | 635.59 | 652.34 | 669.05 | 706.21 |
| Avicel PH102 | Filler | 166 | 149.18 | 132.52 | 95.38 |
| Croscarmellose Na (Extra-granular) | Disintegrant | 42.5 | 42.5 | 42.5 | 42.5 |
| Cab-O-Sil | Glidant | 1.7 | 1.7 | 1.7 | 1.7 |
| Magnesium Stearate | Lubricant | 4.25 | 4.25 | 4.25 | 4.25 |
| | Total | 850.04 | 849.97 | 850.02 | 850.04 |

Overall Rifaximin Tablet Composition

| Component | Function | % w/w (0% CS) | %w/w (2.5% CS) | % w/w (5% CS) | %w/w (10% CS) |
|---|---|---|---|---|---|
| Rifaximin | Drug | 35.29 | 35.32 | 35.29 | 35.29 |
| HPMC-AS | Polymer | 35.29 | 35.32 | 35.29 | 35.29 |
| Pluronic F-127 | Wetting agent | 4.19 | 4.19 | 4.19 | 4.19 |
| Croscarmellose Na (intra granular) | Rate controlling | 0.00 | 1.92 | 3.94 | 8.31 |
| Avicel PH102 | Filler | 19.53 | 17.55 | 15.59 | 11.22 |
| Croscarmellose Na (Extra-granular) | Disintegrant | 5.00 | 5.00 | 5.00 | 5.00 |
| Cab-O-Sil | Glidant | 0.20 | 0.20 | 0.20 | 0.20 |
| Magnesium Stearate | Lubricant | 0.50 | 0.50 | 0.50 | 0.50 |
| | Total | 100 | 100 | 100 | 100 |

[Claims]

[Claim 1]

A solid dispersion of rifaximin comprising rifaximin and at least one polymer selected from among hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and polymethacrylate (Eudragit (registered trademark) L100-55), wherein the weight ratio of rifaximin to polymer is in a range from 10:90 to 90:10.

[Claim 2]

A solid dispersion of rifaximin according to claim 1, wherein HPMC-AS comprises one or more of grades HG and MG.

[Claim 3]

A solid dispersion of rifaximin according to claim 1, wherein HPMC-P comprises grade 55.

[Claim 4]

A solid dispersion of rifaximin according to claim 3, further comprising a poloxamer.

[Claim 5]

A solid dispersion of rifaximin according to claim 4, wherein the poloxamer comprises poloxamer 407 or Pluronic F-127.

[Claim 6]

A solid dispersion of rifaximin according to claim 1, further comprising polyvinylpyrrolidone (PVP) grade K-90.

[Claim 7]

A solid dispersion of rifaximin according to claim 1, wherein the weight ratio of rifaximin to polymer is in a range from 15:85 to 85:15.

[Claim 8]

A solid dispersion of rifaximin according to claim 7, wherein the weight ratio of rifaximin to polymer is in a range from 25:75 to 75:25.

[Claim 9]

A solid dispersion of rifaximin according to claim 8, wherein the weight ratio of rifaximin to polymer is in a range from 40:60 to 60:40.

[Claim 10]

A solid dispersion of rifaximin according to claim 1, wherein the weight ratio of rifaximin to polymer is 50:50.

[Claim 11]

A solid dispersion of rifaximin according to claim 1, wherein the solid dispersion has the appearance of a single glass transition temperature (Tg).

[Claim 12]

A solid dispersion of rifaximin according to claim 1, wherein a Tg of the solid dispersion increases with an increased rifaximin concentration

[Claim 13]

A solid dispersion of rifaximin according to claim 1, wherein the solids are still X-ray amorphous according to XRPD when the solid dispersion has been stressed at 70°C/75% RH for 1 week.

[Claim 14]

A solid dispersion of rifaximin according to claim 1, wherein the solids are still X-ray amorphous according to XRPD when the solid dispersion has been stressed at 70°C/75% RH for 3 weeks.

[Claim 15]

A solid dispersion of rifaximin according to claim 1, wherein the solids are still X-ray amorphous according to XRPD when the solid dispersion has been stressed at 70°C/75% RH for 6 weeks.

[Claim 16]

A solid dispersion of rifaximin according to claim 1, wherein the solids are still X-ray amorphous according to XRPD when the solid dispersion has been stressed at 70°C/75% RH for 12 weeks.

[Claim 17]

A microgranule comprising a solid dispersion of rifaximin as described in any one of claims 1 to 16.

[Claim 18]

A microgranule according to claim 17, further comprising and intragranular release controlling agent.

[Claim 19]

A microgranule according to claim 18, wherein the intragranular release controlling agent comprises a pharmaceutically acceptable excipient and/or disintegrant.

[Claim 20]

A microgranule according to claim 19, wherein the disintegrant is selected from a group consisting of crosprovidone, sodium starch glycolate, corn starch, microcrystalline cellulose, cellulosic derivatives, sodium bicarbonate, and sodium alginate.

[Claim 21]

A microgranule according to claim 17, further comprising a surfactant.

[Claim 22]

A microgranule according to claim 17, further comprising an antioxidant.

[Claim 23]

A pharmaceutical composition comprising the microgranule of any one of claims 17 to 22.

[Claim 24]

A pharmaceutical composition according to claim 23, further comprising one or more pharmaceutically acceptable excipient.

[Claim 25]

A pharmaceutical composition according to claim 23, wherein the composition comprises a tablet or capsule.

[Claim 26]

A pharmaceutical composition according to claim 25, wherein the pharmaceutical composition comprises a disintegrant.

[Claim 27]

A pharmaceutical composition comprising a solid dispersion of rifaximin according to claim 1 and at least one pharmaceutically acceptable excipient.

[Claim 28]

A pharmaceutical composition according to claim 27 comprising a solid dispersion of rifaximin, a polymer, a surfactant, and an intragranular release controlling agent.

[Claim 29]

A pharmaceutical composition according to claim 28 comprising a solid dispersion of rifaximin, HPMC-AS, a poloxamer, and croscarmellose Na (CS).

[Claim 30]

A pharmaceutical composition according to claim 28, wherein the pharmaceutical composition is a tablet or pill.

[Claim 31]

A pharmaceutical composition according to claim 28 further comprising a filler, glidant or lubricant.

[Claim 32]

A pharmaceutical composition according to any one of claims 29 to 31, wherein the composition comprises the ratio of components set forth in the table below.

[Table 1]

| Component | Composition 1 %w/w | Composition 2 %w/w | Composition 3 %w/w | Composition 4 %w/w |
|---|---|---|---|---|
| Rifaximin | 35.29 | 35.32 | 35.29 | 35.29 |
| HPMS-AS | 35.29 | 35.32 | 35.29 | 35.29 |
| Pluronic F-127 | 4.19 | 4.19 | 4.19 | 4.19 |
| Croscarmellose Na (Internal/Granules) | 0.00 | 1.92 | 3.94 | 8.31 |
| Avicel PH102 | 19.53 | 17.55 | 15.59 | 11.22 |
| Croscarmellose Na (Added/Granules) | 5.00 | 5.00 | 5.00 | 5.00 |
| Cab-O-Sil | 0.20 | 0.20 | 0.20 | 0.20 |
| Magnesium Stearate | 0.50 | 0.50 | 0.50 | 0.50 |

[Claim 33]

A process for producing a solid dispersion of rifaximin comprising: preparing a slurry of methanol, rifaximin, HPMC-AS MG and poloxamer 407; and spray drying the slurry.

[Claim 34]

A process for producing a solid dispersion of rifaximin comprising: spray drying rifaximin and Eudragit L100-55 at a weight ratio of 25:75, 50:50, or 75:25.

[Claim 35]

A process for producing a solid dispersion of rifaximin comprising: spray drying rifaximin and HPMC-AS MG at a weight ratio of 50:50 or spray drying rifaximin and HPMC-P at a weight ratio of 25:75.

[Claim 36]

A pharmaceutical composition according to claim 27 for use in the prevention or treatment of a bacterial infection.

[Claim 37]

Use of a pharmaceutical composition according to claim 27 in the manufacture of a medicament for the prevention or treatment of a bacterial infection.

[Claim 38]

A pharmaceutical composition according to claim 27 for use in the prevention or treatment of a bowel-related disorder.

[Claim 39]

Use of a pharmaceutical composition according to claim 27 in the manufacture of a medicament for the prevention or treatment of a bowel-related disorder.

[Claim 40]

The use according to claim 39, wherein the bowel-related disorder includes irritable bowel syndrome, diarrhea, microbe-associated diarrhea, Clostridium difficile-associated diarrhea, travelers' diarrhea, small intestinal bacterial overgrowth, Crohn's disease, diverticular disease, chronic pancreatitis, pancreatic insufficiency, enteritis, colitis, hepatic encephalopathy, minimal hepatic encephalopathy, or pouchitis.

[Claim 41]

The use according to claim 39, wherein the bowel-related disease is hepatic encephalopathy.

[Claim 42]

The use according to claim 39, wherein the bowel-related disease is irritable bowel syndrome.

[Claim 43]

The use according to claim 39, wherein the bowel-related disease is Crohn's disease.