

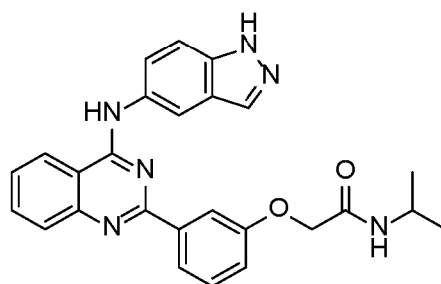
SOLID DISPERSION COMPRISING AMORPHOUS 2-[3-[4-(1H-INDAZOL-5-YLAMINO)QUINAZOLIN-2-YL]PHENOXY]-N-PROPAN-2-YL-ACETAMIDE

TECHNICAL FIELD

[0001] The present disclosure relates to a solid dispersion comprising amorphous 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-*N*-(propan-2-yl) acetamide (otherwise known as belumosudil and KD025). The present disclosure further relates to methods of preparing a solid dispersion comprising amorphous belumosudil, to pharmaceutical compositions comprising one or more of said solid dispersions, and to methods of using the pharmaceutical compositions to treat diseases and conditions regulated by Rho-associated coiled-coil kinase (ROCK), as described herein.

BACKGROUND

[0002] Belumosudil, chemically known as 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazolinyl]phenoxy}-*N*-(propan-2-yl) acetamide, is represented by Formula I below:



2-(3-(4-((1*H*-indazol-5-yl)amino)quinazolin-2-yl)phenoxy)-*N*-isopropylacetamide (I)

[0003] Belumosudil (also known as KD025) is an inhibitor of Rho-associated coiled-coil kinase (ROCK). Belumosudil binds to and inhibits the serine/threonine kinase activity of ROCK1 and ROCK2 and is therefore useful in treating diseases, disorders and conditions regulated by ROCK, including autoimmune and fibrotic disorders, acute and chronic graft versus host disease (GVHD), idiopathic pulmonary fibrosis, and moderate to severe psoriasis, among other indications. The mesylate salt of belumosudil is presently marketed in the United States and other countries under the tradename REZUROCK® (Kadmon Corp./Sanofi), for the treatment of patients with chronic GVHD (cGVHD), in some instances after failure of at least two prior lines of systemic therapy.

[0004] A process for preparing belumosudil is disclosed in US Patent 8,357,693 (the '693 patent), specifically, in Example 82 thereof. The process disclosed in the '693 patent provides belumosudil as a crude product that was purified by high performance liquid chromatograph (HPLC). Belumosudil and processes for making the compound are also described in US Patent No. 9,815,820, US Patent No. 10,183,931, and US Patent No. 10,696,660.

[0005] Belumosudil is a weakly basic compound that is practically insoluble in water. Present methods of administering belumosudil involve formulating the mesylate salt of belumosudil into pharmaceutically acceptable capsules and tablets for oral administration. Given belumosudil's low water solubility, the compound tends to precipitate-out when transitioning from the acidic gastric environment of the stomach and early digestive pathway to the more neutral pH of the intestinal environment. The low solubility of belumosudil may thus impact the manner and timing of its bioabsorption and pharmacokinetic properties. In addition, the low solubility of belumosudil may limit the use of traditional excipients and wet granulation methods.

[0006] Belumosudil's low solubility and variable pharmacokinetic properties present challenges in developing alternate formulations. To illustrate, formulations of belumosudil having enhanced solubility would offer more flexibility and wider options in developing different dosing regimens, formulations, and modes for delivering the compound to a subject.

[0007] Therefore, there remains a need for formulations comprising belumosudil that can address these challenges.

SUMMARY

[0008] In one aspect, the present disclosure provides a solid dispersion comprising an amorphous form of belumosudil. In some embodiments, an amorphous form of belumosudil is disposed in a solid dispersion comprising a matrix carrier material. The use of amorphous belumosudil in the solid dispersion enhances its solubility and improves its bio-performance to provide for expanded methods for formulating and delivering the drug.

[0009] In some embodiments, the present disclosure provides an amorphous solid dispersion comprising belumosudil, optionally prepared using a spray-drying technique.

[0010] In some embodiments, an amorphous form of belumosudil is provided as an amorphous solid dispersion of belumosudil formulated with at least one polymer, optionally, for example, with a pharmaceutically acceptable polymer.

[0011] Another aspect of the present disclosure provides a process for preparing a solid dispersion comprising amorphous belumosudil. Solvent evaporation methods, such as spray-drying may be used for preparing the solid dispersion comprising amorphous belumosudil. A solid dispersion comprising amorphous belumosudil may be prepared by dissolving belumosudil in a suitable solvent; adding one or more carrier matrix materials; and removing the solvent by spray-drying, thereby providing the solid dispersion comprising amorphous belumosudil in the carrier matrix material.

[0012] The solid dispersion comprising amorphous belumosudil may be used in preparing solid pharmaceutical dosage forms, such as tablets and capsules. The pharmaceutical compositions comprising an effective amount the amorphous form of belumosudil are useful for treating diseases, disorders and conditions regulated by ROCK, as further described herein.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 shows scanning electron microscopy (SEM) images of the solid dispersions of Example 1 (specifically, Nos. 1.1, 1.2 and 1.3 in Table 5) captured at 1500x and 5000x magnification.

[0014] Figure 2 shows XRPD results for the six, spray-dried formulations prepared as in Example 1.

[0015] Figure 3 shows two-stage dissolution data for the six, spray-dried belumosudil formulations of Example 1 as compared to the crystalline mesylate salt form of belumosudil.

[0016] Figure 4 is an expanded view of a portion of the data of Figure 3.

[0017] Figure 5 shows XRPD results for the three solid dispersions of Example 3.

[0018] Figure 6 shows SEM images for the three solid dispersions of Example 3 (Formulations F1, F2 and F3), captured at 1500x and 5000x magnification.

[0019] Figure 7 shows particle size data for the three solid dispersions of Example 3 (Formulations F1, F2 and F3).

[0020] Figure 8 shows the modulated differential scanning calorimetry (mDSC) evaluation of T_g for homogeneous determination following one cooling cycle (upper contours) and one heating cycle (lower contours) for the three solid dispersions of Example 3 (Formulations F1, F2 and F3).

[0021] Figure 9 shows non-sink dissolution data for the three solid dispersions of Example 3 (Formulations F1, F2 and F3), as compared to the crystalline mesylate salt form of belumosudil.

[0022] Figure 10 shows assay and impurity data for the three solid dispersions of Example 3 (Formulations F1, F2 and F3), as compared to the crystalline mesylate salt form of belumosudil and diluent as described in Example 4.

[0023] Figures 11A-11C show XRPD diffractograms for the three solid dispersions of Example 3 after an 8 week stability study, as described in Example 5 (Figure 11A: F1 [20:80 KD025:PPPEG]; Figure 11B: F2 [20:80 KD025:PVPVA]; and Figure 11C: F3 [40:60 KD025:PPPEG]).

[0024] Figure 12 shows the polarized light microscopy images of the solid dispersions of Example 3 (F1, F2 and F3), in 0.5 wt.% Methocel A4M (aq.) suspensions at 25 mgA/mL (5X magnification).

[0025] Figure 13 shows the *in vivo* plasma concentration (ng/mL) of belumosudil vs time profile following administration of belumosudil as described in Example 6 for: (a) the tablet formulation - fasted; (b) F2 (20:80 KD025:PVPVA) – fasted; (c) Tablet formulation – fed; and (d) F2 (20:80 KD025:PVPVA) - fed.

DETAILED DESCRIPTION

[0026] The present disclosure provides a solid dispersion comprising an amorphous form of belumosudil that enhances the solubility and improves the bio-performance of the compound. Reliable dosing and absorption of belumosudil is important to ensure consistent systemic exposure. Therefore, the development of a reproducible drug delivery system and the characterization of its associated dissolution profile provides advantages in ensuring consistent and effective dosing of belumosudil

[0027] Solvent evaporation methods, such as spray drying, may be used to prepare a solid dispersion comprising amorphous belumosudil. This technique comprises dissolving or

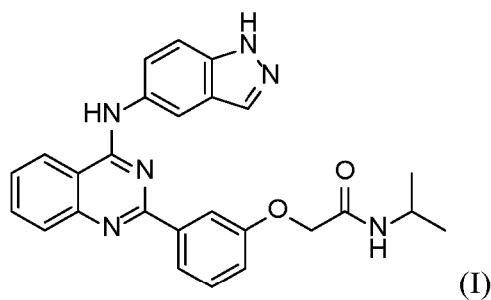
suspending belumosudil in a polymer matrix carrier followed by spraying the mixture stream. The spray-drying removes the solvent resulting in a solid dispersion comprising amorphous belumosudil dispersed in a polymer matrix carrier.

[0028] Applying the spray-drying technique, the belumosudil is transformed into an amorphous state dispersed in a polymeric matrix carrier. The amorphous belumosudil prepared by the methods disclosed herein provides dissolution enhancement by particle size reduction and removal of crystalline lattice. The absence of crystallinity results in no crystal lattice energy to be overcome for the belumosudil to dissolve. The carrier material may additionally assist in the dissolution by improving the wetting, solubility, and stability characteristics of the belumosudil in super-saturation solutions. The spray-dried, solid dispersion comprising amorphous belumosudil provides good physiochemical properties such as controlled particle size and flow-ability, which are useful for downstream processing, such as tablet compression.

[0029] Additionally, the pharmaceutical composition comprising the solid dispersion comprising amorphous belumosudil demonstrate an increase in the dissolution rate as compared with compositions comprising crystalline forms of belumosudil; in some embodiments, a significant increase in the dissolution rate is obtained with the solid dispersion herein. The enhanced solubility of the solid dispersion comprising amorphous belumosudil provides advantages and greater flexibility with formulation development and drug delivery.

Definitions

[0030] The term belumosudil (or KD025) as used herein refers to 2-{3-[4-(1*H*-indazol-5-ylamino)-2-quinazoliny]phenoxy}-*N*-(propan-2-yl) acetamide, represented by Formula I below:



[0031] In some embodiments, the amorphous belumosudil is in the free-base form.

[0032] When the term “belumosudil” is used herein, it should be understood that, unless the context clearly indicates otherwise, the term may cover the compound belumosudil in any form as well as pharmaceutically acceptable salts thereof. The term “belumosudil” refers both to the compound belumosudil (for example, in the free base form, amorphous form, or crystalline form), to pharmaceutically acceptable salts of belumosudil, for example, the mesylate salt form as used in as REZUROCK,TM and to any form of belumosudil that may be used in a formulation or pharmaceutical composition for administering the compound to a patient.

[0033] The term “pharmaceutically-acceptable salts” refers to non-toxic, inorganic, and organic acid addition salts of belumosudil. In some embodiments, the pharmaceutically-acceptable salt of belumosudil herein is the mesylate salt.

[0034] “About” as used herein includes the exact amount modified by the term, about, as well as an amount that would be expected to be within experimental error, such as for example, within 15%, 10%, or 5%. For example, “about 5 mg” means “5 mg” and also a range of mgs that is within experimental error, *e.g.*, plus or minus 15%, 10%, or 5% of 5 mg. As used herein, the term “about” may be used to modify a range and also, a particular value.

[0035] The acronym, API, refers to “active pharmaceutical ingredient” which as used herein is synonymous with the definition of belumosudil (or KD025) and pharmaceutically-acceptable salts thereof, optionally, the mesylate salt of belumosudil.

[0036] “Administering” or “administered to” as used herein refers to the act of prescribing medicine(s) containing the API for the subject to take during treatment, the act of dispensing the medicine(s) to the subject, and/or the act of physically receiving or ingesting the medicine(s). Thus, the API (belumosudil), can be “administered” by a physician or other medical professional who writes prescriptions for medicine(s); and/or by a pharmacist who fills said prescriptions and/or dispenses the medicine(s) to the subject; and/or by the patient or subject who ingests the medicine and/or his or her partner or caretaker who provides the medicine to a subject.

[0037] The term “solid dispersion” as used herein, refers to a system in which the API is diffused throughout a solid carrier, in some embodiments, a solid matrix carrier. In some embodiments, the carrier comprises a small molecule and/or polymer or copolymer,

optionally, a polymer. Thus, a solid dispersion will include at least two components wherein one component is the API, and the other component(s) is a carrier. Further additives may optionally be included (*e.g.*, surfactants). Optionally, in the solid dispersion, the API is homogenously, or evenly, dispersed throughout the carrier matrix.

[0038] The term “amorphous solid dispersion” as used herein, refers to a single-phase amorphous system where the API is molecularly dispersed, or dissolved, in the carrier matrix, optionally, a polymer matrix.

[0039] In some embodiments herein, the ratio of belumosudil to the carrier matrix material(s) in the solid dispersion may be from about 10:90 to 90:10 by weight; or from about 20:80 to 80:20 by weight; or from about 25:75 to 75:25 by weight; or from 40:60 to 60:40 by weight.

[0040] Unless otherwise specified, the term "amorphous" or "amorphous form" means that the substance or component is not substantially crystalline, and is a disordered solid form, *i.e.*, a solid form substantially lacking long range crystalline order, as determined by XRPD data. A substantially amorphous state includes at least about 50% by weight, optionally at least about 60% by weight, optionally at least about 70% by weight, optionally at least about 80% by weight, optionally at least about 90% by weight, optionally at least 95% by weight, or optionally at least 99% by weight of the API in an amorphous form, as compared with other forms of the substance or component.

[0041] In some embodiments, the amorphous belumosudil is a solid-state form of belumosudil that is substantially amorphous; in some embodiments, in a form that includes at least about 95% of the belumosudil in an amorphous form; in some embodiments, at least 98% of the belumosudil in an amorphous form. Whether the belumosudil is in an amorphous form can be characterized, for example, by XRPD techniques as described herein, or as otherwise known to those skilled in the art.

[0042] “Carrier matrix” or “carrier matrix materials” as used herein refers to components that stabilize, suspend and/or transport the amorphous form of belumosudil when in the solid state. Optionally, carrier matrix materials are amorphous polymeric materials. The polymer selection for the solid dispersion may play an important role on the overall final product attributes. Polymers for use as the carrier matrix material may include povidone derivatives such as polyvinylpyrrolidone (PVP), and polyvinylpyrrolidone-vinyl acetate

copolymers (PVPVA) (such as those sold under the tradename Kollidon VA 64®), polymethacrylates derivatives (such as Eudragit® series), polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (PPPEG) (such as those presently sold under the tradename Soluplus®), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl methylcellulose acetate succinate (HPMCAS). Optional carrier matrix materials herein are PVPVA and PPPEG.

[0043] The term “effective amount” in connection with an amorphous form of belumosudil means an amount capable of treating or preventing a disorder, disease or condition, or symptoms thereof, as disclosed herein. The effective amount of an amorphous form of belumosudil, for example, in a pharmaceutical composition, may be at a level that will provide the desired effect; for example, about 0.5 to 15 mg/kg of a subject’s body weight, optionally about 1 to 5 mg/kg of a subject’s body weight, optionally about 3 mg/kg of a patient’s body weight in unit dosage for oral administration. For example, the dose of belumosudil may be the current therapeutic dose of 200 mg administered daily, or alternatively, a dose in the range of 10 mg to up to 1000 mg, optionally, for adult patients, in the range of 100 mg to 400 mg; optionally, in the range of 100 mg to 200 mg.

[0044] Additionally, optionally for pediatric patients, a dose of belumosudil may be in the range of 10 mg to 200 mg. The dose of belumosudil may be adjusted depending upon the body weight of the patient. For example, for a pediatric patient having a body weight in the range of about 6 kg to less than 20 kg, the dose may be in the range of about 10 to 50 mg administered once daily; in another embodiment, for a pediatric patient having a body weight in the range of about 10 kg to less than 20 kg, a dose may be about 50 mg administered once daily; for a pediatric patient having a body weight in the range of about 20 kg to less than 40 kg, the dose may be about 100 mg once daily; and for pediatric patients having a body weight of equal to or greater than 40 kg, the dose may be 200 mg once daily.

[0045] As will be apparent to those skilled in the art, it is to be expected that the effective amount of an amorphous form of belumosudil disclosed herein may vary depending on the severity of the indication being treated, the route of administration, and/or other drugs administered to the subject considering drug-drug interactions, for example, proton pump inhibitors or CYP3A inducers.

[0046] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a solid filler, diluent,

excipient, manufacturing aid (*e.g.*, lubricant, talc, magnesium, calcium or zinc stearate, or steric acid). Each carrier must be "acceptable" in the sense of being compatible with, and maintaining the stability of the other ingredients of, the formulation (*e.g.*, including the API, so as not to allow for slow crystallization over time), and not injurious to the patient.

[0047] A “suitable solvent” as used herein, for example, as used to dissolve belumosudil in a solvent system with carrier matrix material, means a solvent, or mixture of one or more solvents, that is compatible with belumosudil and carrier matrix material(s) and capable of sufficiently dissolving belumosudil and the one or more carrier matrix materials to enable use of a spray-drying technique. The term “suitable solvent” may include a mixture of solvents and is thus interchangeable with “suitable solvent system.” The solubility of API and/or carrier matrix materials may be confirmed by filtration and HPLC analysis or through visual observation (*e.g.*, produces a clear or substantially clear solution upon visual observation). For a solvent to be “suitable” also means that the solvent(s) do not present unacceptable toxicities or environmental hazards and are acceptable for use in the manufacture of pharmaceuticals for human consumption.

[0048] “Or” is used in the inclusive sense (equivalent to “and/or”) unless the context requires otherwise.

General Methods of Preparation and Use

[0049] A solid dispersion comprising amorphous belumosudil may be prepared by dissolving belumosudil in a suitable solvent; adding one or more carrier matrix materials to the belumosudil solution; and removing the solvent, or substantially removing the solvent, to provide amorphous belumosudil dispersed in the carrier matrix.

[0050] In the first step of the process involving adding belumosudil to a suitable solvent, the belumosudil may be in a variety of forms, for example, any polymorphic crystalline form or as a solvate. The belumosudil may be in a salt form or may be in the free-base form. If the belumosudil is in the form of an acid addition salt and an amorphous belumosudil in the free-base form is desired, a sufficient amount of base may be added to the solvent to form the belumosudil free-base. The base may be an inorganic base, such as an alkali metal hydroxide, or the base may be an amine such as diethylamine, triethyl amine, or the like.

[0051] Within the context of this method, the choice of the solvent is an important consideration in preparing the amorphous solid dispersion and a combination of solvents optionally may be used to obtain the desired solvent parameters. As set forth in Example 1 herein, extensive solvent screening experiments were performed to arrive at a solvent system useful for dissolving belumosudil and a carrier matrix material to enable use of the spray-drying technique. Following these solubility experiments, it was discovered that a suitable solvent system for preparing amorphous belumosudil via spray-drying comprises a mixture of triethylamine (TEA) and acetone. In comparison, solvent systems comprising acetone, ethyl acetate, acetonitrile (ACN), tetrahydrofuran, methanol, dichloromethane (DCM), dimethyl formamide (DMF), isopropanol (IPA), methyl ethyl ketone, methyl isobutyl ketone (MIBK), methyl tert-butyl ether (MTBD), n-heptane, toluene, mixtures of DCM and methanol, mixtures of ethanol and hexanes, and mixtures of aqueous solution and acetone or ACN were not effective to dissolve belumosudil and/or belumosudil was determined to be practically insoluble or slightly soluble in these solvent(s) such that these solvents and/or solvent systems are not “suitable solvents” as defined herein.

[0052] For example, WO 2021/129589A1 reportedly identifies solvents claimed to be “good solvents” for use in dissolving belumosudil to produce amorphous forms thereof. WO 2021/129589A1 provides one working example (Example 22 thereof), relating to preparation of amorphous KD025 which comprises use of DMF as solvent. However, applicant has discovered that belumosudil is only slightly soluble in DMF which is therefore not a suitable solvent. WO 2021/129589A1 further identifies solvents recommended for use in preparing amorphous forms of belumosudil as allegedly selected from one or more of methanol, acetone, methyl ethyl ketone, DMF, dimethyl sulfoxide (DMSO), n-methylpyrrolidone and ethylene glycol dimethyl ether. However, WO 2021/129589A1 does not provide working examples describing use of those solvents. Applicant has discovered through actual working examples as described herein that solvents identified in WO 2021/129589A1 are not suitable solvents as defined herein due to either the low solubility of belumosudil and/or carrier matrix in the solvents and/or their incompatibility in the spray-drying and/or drug development process.

[0053] The amorphous solid dispersion comprising belumosudil may be used in preparing solid pharmaceutical dosage forms, such as tablets and capsules.

[0054] In one aspect, the present disclosure provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of an amorphous form of belumosudil formulated with one or more pharmaceutically excipients. The pharmaceutical compositions may be specially formulated for administration in solid form and adapted for administration to a patient via methods amenable to use of solid forms of API, such as via oral administration, for example, with tablets or capsules.

[0055] In some embodiments, the present disclosure provides solid pharmaceutical dosage forms comprising an amorphous solid dispersion of belumosudil for oral administration (capsules, tablets, pills, powders, granules, and the like), which are mixed with one or more pharmaceutically-acceptable excipients including a pharmaceutically-acceptable carrier, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0056] A tablet may be made by compression or molding (including melt extrusion), optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropyl methyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be

made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0057] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present disclosure, such as capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, *e.g.*, freeze-dried. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or optionally, in a certain portion of the gastrointestinal tract, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0058] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0059] The pharmaceutical compositions comprising an effective amount of the amorphous form of belumosudil are useful for inhibiting ROCK1 and ROCK2, preferentially ROCK2, and are therefore useful in treating diseases regulated by ROCK enzymes such as autoimmune disorders and/or fibrotic disorders including GVHD (chronic and acute), pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, radiation induced fibrosis, or arterial, cardiac, endomyocardial, renal, or liver fibrosis; moderate to severe psoriasis, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), Crohn's disease, dermatitis (*e.g.*, atopic dermatitis), and eczema, among other indications.

[0060] The compositions provided herein may further be useful in treating bronchiolitis obliterans syndrome (BOS), a potentially severe complication after lung transplantation or allogeneic hematopoietic stem cell transplantation (allo-HSCT).

EXAMPLES

[0061] The following abbreviations may be useful as a reference in consideration of the disclosures herein.

Abbreviations:

ACN	Acetonitrile
API	Active pharmaceutical ingredient (here, KD025)
DCM	Dichloromethane
DSC/TGA	Differential scanning calorimetry/Thermogravimetric analysis
FaSSIF	Fasted-state simulated intestinal fluid
GC-HS	Gas Chromatography-Head Space
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
h/hr	Hour(s)
MDSC	Modulated differential scanning calorimetry
MEK	Methyl ethyl ketone
PK	Pharmacokinetics
PLM	Polarized light microscopy
PMA	Polymethacrylate
PO	By mouth; orally
PPPEG	Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol
PSD	Particle size distribution
PVP	Polyvinylpyrrolidone
PVPVA	Polyvinylpyrrolidone-vinyl acetate
RCS	Refrigerated cooling system
RH	Relative humidity
RRT	Relative retention time
RT	Room temperature
SDD	Spray-dried dispersion
SEM	Scanning electron microscopy
TEA	Triethylamine
Temp.	Temperature
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
XRPD	X-ray powder diffraction

Instrumentation:

[0062] The following instrumentation and procedures may be used to collect data as set forth in the Examples herein, unless other instrumentation details are set forth in the

following Examples. One skilled in the field can appreciate that alternate instrumentation and procedures optionally may be used to collect characterization data such as PLM, XRPD, TGA, DSC/TGA, and PSD.

[0063] XRPD, PSD, and MDSC data was collected using the instrumentation and procedures set forth below in Tables 1, 2 and 3, respectively:

Table 1

XRPD Parameters	
Instrument:	Rigaku Miniflex 6G
Radiation Source:	Cu-K α (1.5406 Å)
Scan Mode:	Coupled 2 θ / θ
Scan Range:	5°- 40°
Scan Speed:	5°/min
Step Increment:	0.0005°
Voltage:	40 kV
Current:	15 mA
Rotation:	30 rpm
Divergence Slit:	0.625 mm
Sample Holder:	Zero-Background Cup

Table 2

PSD Parameters	
Instrument:	Malvern Mastersizer 3000
Dispersion Unit:	Aero S (Dry)
Hopper Height:	1.5 mm
Dispersion Gas:	Nitrogen
Gas Pressure:	1.5 bar
Feed Rate:	20-40%
Obscuration Limits:	0.1%-10%
Refractive Index Name:	Drug and Polymer Dispersion
Refractive Index:	1.6
Density	0.5 g/mL
Measurement Duration:	30 s
Measurement Replicates	n=3

Table 3

MDSC Parameters	
Instrument:	TA Discovery DSC2500 with RCS90 chiller
Scan Mode:	Modulated
Temp. Range:	0°C-240°C
Heating Rate:	2.0°C/min
Mod. Period:	60 s
Mod. Amplitude:	±1.0°C
Pan/Lid type	Non-Hermetic
Replicates	n=3

Example 1

1.1 Solvent Screening

[0064] The objective of the experiments set forth in this Example was to explore amorphous solid dispersions utilizing the spray-drying technique to enhance the solubility and improve the bio-performance of belumosudil. However, the spray drying technique requires a suitable solvent system compatible with belumosudil and a polymer matrix material.

[0065] To investigate a suitable solvent system for use with belumosudil and a polymer matrix material, the organic solvent systems set forth in this Section (and in Tables 4A, 4B, and 4C) were prepared and evaluated.

A. Solubility Assessments Using HPLC

[0066] The solubility (w/v) of belumosudil in various solvents was determined using HPLC. Saturated solutions of belumosudil were prepared with approximately 99-105 mg of belumosudil and 2.0 mL of solvent in a 5 mL amber color vial as set forth below in Table 4A. The solutions were shaken well and loaded to a laboratory rotator at 200 rpm for constant rotation at 24 h. The resulting sample was filtered through a 0.45µm filter and the filtrate was used for the quantification of belumosudil by HPLC using a linearity method. Samples of IPA, acetonitrile, ethyl acetate, DCM, toluene, MIBK, acetone, n-heptane, and methyl tert-butyl ether (MTBE) were injected into HPLC without any further dilution; samples with methanol, DMF, and DMSO, were further diluted prior to injection into HPLC; for the

methanol, DMF, and DMSO solutions, 0.1 mL of the filtered solution was transferred into a 100 mL volumetric flask and diluted to volume with diluent prior to injection. The solubilities are reported in Table 4A in mg/mL.

Table 4A: Results of Solubility Experiments with HPLC

Solvent	Sample wt. (mg/2 mL solvent)	Solubility (mg/mL)	Result
Water	101.75	0.01	Practically insoluble
Methanol	102.46	3.85	Slightly soluble
Acetonitrile	99.89	0.00	Practically insoluble
Toluene	101.51	NA	Practically insoluble
Ethyl acetate	102.94	0.00	Practically insoluble
DCM	100.81	0.00	Practically insoluble
MIBK	102.74	0.02	Practically insoluble
Acetone	102.64	0.01	Practically insoluble
MTBE	103.20	0.00	Practically insoluble
IPA	103.44	0.03	Practically insoluble
n-Heptane	101.05	NA	Practically insoluble
DMF	100.94	2.15	Slightly soluble
DMSO	105.58	23.41	Soluble

B. pH-Based Solubility Assessments

[0067] The solubility of belumosudil was examined in various pH buffer solutions, *i.e.*, in buffer solutions at pH 1.2, 3.5, 4.5, 6.8, 7.4, and 10. To prepare the buffer solutions, stock solutions were prepared for pH adjustment as follows: a 0.2M HCl solution was prepared by transferring 17.0 mL of 35% HCl in 500 mL of water, mixing well and diluting the solution to 1000 mL with water; a 2M acetic acid solution was prepared by transferring 116.0 mL of acetic acid in 500 mL of water, mixing well and diluting to 1000 mL with water; a 0.2M NaOH solution was prepared by transferring 4.01492 g of sodium hydroxide pellets into 250 mL of water, dissolving and diluting to 500 mL with water; and a phosphate buffer stock solution was prepared by transferring about 2.72 g of potassium hydrogen phosphate buffer into a 100 mL volumetric flask, dissolving and diluting to the volume with water.

[0068] Buffer solutions containing sample (belumosudil) were prepared as follows.

[0069] **Sample pH 1.2 buffer solution.** 1.53145 g of potassium chloride was transferred into a 100 mL volumetric flask, dissolved, and diluted to volume with water. 25.0 mL of this solution was transferred into a 100 mL volumetric flask; 42.5 mL of the 0.2M hydrochloric acid solution was added and the solution diluted to volume with water. 2.0 mL

of this pH 1.2 buffer solution was added to a 5 mL amber color vial containing 100.15 mg of belumosudil.

[0070] **Sample pH 3.5 buffer solution.** 4.11871 g of potassium phthalate was transferred into a 100 mL volumetric flask, dissolved, and diluted to volume with water. 25.0 mL of this solution was transferred into a 100 mL volumetric flask to which 8.3 mL of 0.2M hydrochloric acid was added, and the solution diluted to volume with water. 2.0 mL of this buffer solution was added to a 5 mL amber color vial containing 100.52 mg of belumosudil.

[0071] **Sample pH 4.5 buffer solution.** 25.0 mL of the pH 3.5 buffer solution (from the preceding paragraph) was added into a 100 mL volumetric flask. Another 10 mL of 0.2M sodium hydroxide was added and the solution diluted to volume with water. 2.0 mL of this pH 4.5 buffer solution was added to a 5 mL amber color vial containing 101.53 mg of belumosudil.

[0072] **Sample pH 6.8 buffer solution.** 25.0 mL of the phosphate buffer stock was transferred into a 100 mL volumetric flask; 23 mL of 0.2M sodium hydroxide was added and the solution diluted to volume with water. 2.0 mL of this pH 6.8 buffer solution was added to a 5 mL amber color vial containing 100.18 mg of belumosudil.

[0073] **Sample pH 7.4 buffer solution.** 25.0 mL of phosphate buffer stock was transferred into a 100 mL volumetric flask; 41 mL of 0.2M sodium hydroxide was added and the solution diluted to volume with water. 2.0 mL of this pH 7.4 buffer solution was added to a 5 mL amber color vial containing 100.52 mg of belumosudil.

[0074] **Sample pH 10.0 buffer solution.** 1.52493 g of potassium chloride and 1.21879 g of boric acid were added to 100 mL volumetric flask, dissolved, and diluted to volume with water. 25.0 mL of this solution was transferred to a 100 mL volumetric flask; 22 mL of 0.2M sodium hydroxide was added and the solution diluted to volume with water. 2.0 mL of this pH 10.0 buffer solution was added to a 5 mL amber color vial containing 103.8 mg of belumosudil.

[0075] The sample pH buffered solutions prepared according to the preceding paragraphs were each shaken well and loaded to a laboratory rotator at 200 rpm for constant rotation at 24 h. In each case, undissolved sample was observed in the vial after 24 h. The resulting sample solution was filtered through a 0.45 μ syringe filter, filtrate was collected and injected into HPLC without any further dilution. The pH was observed after equilibrium with 24 hours at 25°C. Results were as shown in Table 4B.

Table 4B: Solubility of Belumosudil in pH Buffered Solutions

pH of the buffer used	pH observed after equilibration for 24 hr at 25°C	Solubility (mg/mL)	Result
1.2	1.42	NA	Practically insoluble
3.5	3.22	NA	Practically insoluble
4.5	4.32	NA	Practically insoluble
6.8	4.45	NA	Practically insoluble
7.4	4.84	NA	Practically insoluble
10	5.64	NA	Practically insoluble

C. Solubility Assessments - Visual Observation

[0076] Solubility assessments were further conducted with each of the solvent systems listed in Table 4C with 25 mg of belumosudil used for each sample.

Table 4C: Solvent Systems Used in Solubility Experiments

Solvent System
Acetone
Tetrahydrofuran (THF)
Methanol
Dichloromethane (DCM)
Methyl Ethyl Ketone (MEK)
90:10 DCM:Methanol
80:20 DCM:Methanol
50:50 DCM:Methanol
95:5 Acetone:Water
Acetonitrile (ACN)
90:10 ACN:Water
50:50 Ethanol:Hexanes

[0077] All solutions were prepared at 10 wt. % of belumosudil and then diluted down to 1 wt.% of belumosudil. Under those conditions, belumosudil was not soluble in any of the solvent systems listed in Table 4C. All solutions were then heated to 40 degrees C, but no improvement was observed with heating. Accordingly, the solvent systems listed in Table 4C were not suitable for dissolving belumosudil and polymer carrier matrix materials to enable techniques toward preparing an amorphous form. Following further experimentation, a mixture of belumosudil, triethylamine (TEA) and acetone at a ratio of 3:1 (moles equivalent of TEA:acetone) provided a clear solution at 5 wt.% belumosudil. Therefore, a mixture of

TEA and acetone was nominated for the solvent system for formulating the solid dispersions used in the following examples.

1.2 *Polymer Carrier Matrix and Ratio Selection*

[0078] The following three polymers were selected to prepare six formulations: (1) vinylpyrrolidone-vinyl acetate copolymer (PVPVA) (sold under the tradename Kollidon® VA 64); (2) polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (PCL-PVAc-PEG, or herein, “PPPEG”) (sold under the tradename Soluplus® and available from BASF); and (3) hypromellose acetate succinate (HPMCAS-M, or HPMC) (available from Shin Etsu Chemical Co.).

[0079] Ratios of belumosudil to polymer carrier matrix (by weight) were selected for assessments as follows:

Table 5: Belumosudil (KD025): Polymer Ratios for Six Formulations

Example No.	Polymer Carrier	Ratio: API to Polymer
1.1	HPMC	20:80
1.2	PVPVA	20:80
1.3	PPPEG	20:80
1.4	HPMC	40:60
1.5	PVPVA	40:60
1.6	PPPEG	40:60

1.3 *Spray Drying Dispersion Preparation*

[0080] Acetone suspensions of belumosudil and TEA were prepared first, and then the three polymer carrier matrix materials of Table 5 were added, using the ratio of belumosudil: polymer as set forth in Table 5. Spray-drying of the suspensions then proceeded as follows.

[0081] A Buchi B-290 spray dryer was used in this study. Nitrogen was used as the drying gas. The solution feed rate (mL/min) and atomization pressure (Psi) were adjusted to 17.5 and 26, respectively. The inlet temperature ranged between 84-101°C and the outlet temperature was adjusted to range between 49-51°C. The spray-dried formulations were oven dried at 50°C for 24h to remove residual solvent utilizing a convection tray dryer.

Example 2

[0082] All six formulations of Example 1 were characterized for surface morphology, crystallinity, and dissolution as described in this Example 2. All six formulations resulted in solid products considered acceptable for further evaluation according to their morphology and amorphous state. However, following analysis and characterization for surface morphology, crystallinity, and dissolution as set forth below in Sections 2.1-2.3, Example 1.2 (20:80 KD025: PVPVA), Example 1.3 (20:80 KD025: PPPEG), and Example 1.6 (40:60 KD025: PPPEG), were selected as preferred candidates for further evaluation as described in Examples 3 through 6.

2.1 *Scanning Electron Microscopy*

[0083] The dispersions of Examples 1.1, 1.2, and 1.3 were selected for visual observation using scanning electron microscopy (SEM). Samples were prepared by dispensing them onto an adhesive carbon-coated sample stub and coating with a thin conductive layer of gold using a Cressington 108 Auto. Samples were analyzed using a FEI Quanta 200 SEM fitted with an Everhart-Thornley (secondary electron) detector operating in high vacuum mode. Results are shown in Figure 1 hereof. Typical morphology characteristic of solid dispersions was observed consisting of whole and collapsed spheres with smooth surfaces. However, from this assessment, use of polymer carrier matrixes comprising PVPVA and PPPEG emerged as having advantages over HPMC, as the dispersion comprising HPMC appeared to have some long filaments, and dispersions comprising PVPVA and PPPEG produced more homogenous matrixes of belumosudil suspended in the polymer matrix.

2.2 *Powder x-ray Diffraction*

[0084] Powder x-ray diffraction (XRPD) was used to evaluate the crystalline form of the six dispersions of Example 1 (using a Rigaku Miniflex 6G X-ray diffractometer). The samples were irradiated with monochromatized Cu K α radiation and analyzed between 5° and 40° with a continuous scanning mode. Samples were rotated during analysis to minimize preferred orientation effect. Figure 2 shows the XRPD results for each of Examples 1.1 to 1.6. These results confirm that each solid dispersion of Example 1 was present in an amorphous state as reflected by the lack of crystalline peaks.

2.3 Dissolution Assessments

[0085] The initial steps of the dissolution evaluation were to determine the solubility of belumosudil directly in biorelevant media, either 0.1N HCl or FaSSIF, found to be >1000µg/mL and 5µg/mL respectively. The dissolution performance of the six dispersions of Example 1 and the crystalline mesylate salt form of belumosudil were tested by non-sink dissolution (results are shown in Figure 3). The dissolution test was used to measure the enhancement in solubility above the bulk crystalline belumosudil solubility in biorelevant FaSSIF media after 30 minutes exposure to a low-pH environment. During the test, samples were transitioned from 0.1N HCl [theoretical C_{max} = 1000 µgA/mL] to FaSSIF [theoretical C_{max} = 500 µgA/mL] via dilution. The drug concentrations measured in this test were a composite of SDI free drug, drug in micelles, and drug in drug-polymer colloids. The objective of this experiment was to rank order and select lead formulations. Table 6 summarizes the overall two-stage dissolution data.

Table 6: Two-Stage Dissolution Data

Example	Formulation Ratio API:carrier/ Carrier	C _{max} in SGF µgA/mL	C _{max} after transfer to FaSSIF (µgA/mL)	Drug conc. at C ₂₁₀ (µgA/mL)	AUC ₃₅₋₂₁₀ FaSSIF (min*µgA/ mL)	AUC _{Formulation} increase over AUC _{API}
1.1	20:80/HPMC	1028	10.2	7.0	1300	1.9
1.2	20:80/PVPVA	899	99.9	20.8	5200	7.4
1.3	20:80/PPPEG	932	369.6	369.6	58000	82.9
1.4	40:60/HPMC	1015	22.6	6.6	1400	2.0
1.5	40:60/PVPVA	990	15.3	11.3	1900	2.7
1.6	40:60/PPPEG	977	79.7	50.4	9800	14.0
	API	932	6.1	6.1	700	NA

[0086] In general, the C_{max} in low pH at the gastric environment was much higher compared to the C_{max} in higher pH for most formulations. However, as shown in Table 6, Examples 1.3 and 1.6 (both PPPEG dispersions, at 20:80 and 40:60), along with Example 1.2 (the 20:80 KD025:PVPVA dispersion), outperformed the other three formulations with C_{max}

of 369.6, 79.7 and 99.9 $\mu\text{gA/mL}$ respectively. Additionally, the drug concentration at the end of the dissolution runs (210 minute) was found higher for these formulations as compared with crystalline KD025 with values reported of 20.8 $\mu\text{gA/mL}$ (Example 1.2 [20:80 KD025:PVPVA]), 369.6 $\mu\text{gA/mL}$ (Example 1.3 [20:80 KD025: PPPEG]), 50.4 $\mu\text{gA/mL}$ (Example 1.6 [40:60 KD025: PPPEG]), as compared to 6.1 for the crystalline KD025. In summary, an increase of area under the curve (AUC) for Example 1.2 (20:80 KD025:PVPVA), Example 1.3 (20:80 KD025:PPPEG), and Example 1.6 (40:60 KD025: PPPEG), compared to belumosudil (KD025) was observed.

Example 3

[0087] Based on the surface morphology, crystallinity and the dissolution studies of Example 2, three formulations were selected for additional characterization and *in vivo* assessments and experimentation, *i.e.*: Example 1.2 (20:80 KD025:PVPVA); Example 1.3 (20:80 KD025:PPPEG); and Example 1.6 (40:60 KD025:PPPEG). For ease of reference, these selected formulations are identified hereinafter as: Formulation 1 [**F1**]: 20:80 KD025:PPPEG (Ex. 1.3); Formulation 2 [**F2**]: 20:80 KD025:PVPVA (Ex. 1.2); and Formulation 3 [**F3**]: 40:60 KD025:PPPEG (Ex. 1.6).

[0088] For this Example, F1, F2 and F3 were prepared following the processing conditions set forth below in Table 7 and then analyzed as to their amorphous state, surface morphology, residual solvents, particle size distribution, and thermal evaluation.

Table 7: Process for Preparing Amorphous Dispersion Formulations F1, F2 and F3

	Formulation (Ratio API:Carrier/carrier)		
Process condition	<u>F1</u> 20:80/PPPEG	<u>F2</u> 20:80/PVPVA	<u>F3</u> 40:60/PPPEG
Batch Size, solids (g)	71.65	71.65	34.15
Spray Solvent	Acetone:TEA	Acetone:TEA	Acetone:TEA
Spray Solution (wt% total solids)	7.4%	7.4%	3.5%
Nozzle Type	Two-Fluid -1.5 mm Air Cap, 0.7 mm Liquid Tip		
Drying Gas Mode	Recycle		
Cyclone Type	High Efficiency Cyclone		
Solution Flow Rate (mL/min)	~17.5	~17.5	~17.5

Atomization Pressure (psi)	26	26	26
Inlet Temp. (°C)	93-97	84-86	86-101
Outlet Temp. (°C)	49-50	50-51	49-51
Condenser Temp. (°C)	(-17) - (-22)	(-17) - (-22)	(-17) - (-22)
Secondary Drying Temp./Time	50	50	50
Wet SDD Yield (%)	83.9	90.3	71.2
Dry SDD Yield (%)	81.5	90.3	70.6
Residual solvent (wt%)	Acetone: ND TEA: <LOQ	Acetone: ND TEA: 1631	Acetone: ND TEA: <LOQ
Appearance	Yellow powder	Off-white powder	Bright yellow powder

3.1 *Amorphous Dispersions*

[0089] XRPD results were obtained for the three formulations produced according to the procedures described in Table 7 applying instrumentation conditions set forth above in Table 1. The results are shown in Figure 5. All solid dispersions were confirmed to be amorphous (Fig. 5). SEM images for F1, F2 and F3 were also obtained at 1500x and 5000x magnification (following procedures as in Example 2.1), and results are shown in Figure 6. No crystals were observed in any of the three solid dispersions. Formulations F1 and F2 (the 20:80 dispersions), were inflated with collapsed spheres, and F3 formed mostly inflated spheres fused in clusters.

3.2 *Residual Solvent Content Evaluation*

[0090] After the secondary drying step set forth in Table 7, a GC-HS was used to measure the residual acetone and TEA remaining in the three solid dispersions (F1, F2 and F3). Measurements were made using an HP 6890 series GC equipped with an Agilent 7697A headspace sampler. A 30 m x 0.32 mm x 1.8 µ capillary column with 6% cyanopropylphenyl 94% dimethylpolysiloxane GC column was used for the testing.

[0091] The residual solvents detected in all formulations are reported below in Table 8. For all three formulations (F1, F2 and F3), acetone levels were not detected. The TEA levels were below the limit of quantitation (LOQ) for F1 and F3 (the PPPEG formulations) and 1631 ppm for F2 (the PVPVA formulation). These levels are below the acetone and TEA limit (5000 ppm) set forth by the International Conference on Harmonization (ICH).

Table 8: Residual Solvent Evaluation of F1, F2 and F3

Formulation	Residual Acetone (ppm)	Residual TEA (ppm)	Measured Tg °C
F1	ND	<LOQ	73
F2	ND	1631	90
F3	ND	<LOQ	67

ND= not detected

3.3 Particle Size Distribution

[0092] Particle size distribution (PSD) of F1, F2 and F3 was measured using the parameters summarized in Table 2 and laser diffraction methods (Mastersizer 3000 with an Aero S unit). 200 mg samples were added to the standard venture disperser with a hopper gap of 1.5 mm and then fed into the dispersion system. The feed rate of (20-40%) was adjusted to keep the laser obscuration level at 0.1-15%. Compressed air at 1.5 bar was used to transport and suspend the sample particles through the optical cell. A measurement time of 10 seconds was used, and background measurements were made using air for 10 seconds. Dv10, Dv50 and Dv90 diameters were used to characterize the particle size distribution of the powders.

[0093] The results of the PSD study are shown in Table 9 and Figure 7. F1 and F2 (20:80 belumosudil dispersions) were shown to have fairly similar particle sizes with the Dv50 less than 10 µm and a fairly narrow range of sizes for both formulations (with values for Dv10-Dv90 at ~3 to ~28 for F1 and ~2 to ~17 for F2). The F3 (the 40% belumosudil dispersion) was found to have a bimodal distribution with larger overall particles (Dv10 = 6.54, Dv90 = 187). These results were consistent with observations by SEM (Figure 6), which showed particles fused together into clusters for F3.

Table 9: Particle Size Data for F1, F2 and F3

Formulation	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
F1	3.01	8.32	27.9
F2	1.88	4.56	17.2
F3	6.54	32.9	187

3.4 *Differential Scanning Calorimetry*

[0094] DSC of F1, F2 and F3 was performed using the instrumentation set forth above in Table 3. Samples were placed in non-hermetic aluminum pans and heated at a constant rate of 2.0°C/min over a 0-240°C temperature range. The system was purged by nitrogen flow at 50 mL/min to ensure inert atmosphere through the course of measurement.

[0095] The results of this thermal analysis (mDSC) are shown in Figure 8. All three formulations F1, F2 and F3 had a single T_g indicating good homogeneity (T_g (°C) of 73, 90 and 67 for F1, F2 and F3, respectively). F3 (40% KD025 dispersion) showed broad T_g with unclear onset, indicating a higher molecular mobility of the dispersion during spray drying.

Example 4

4.1 *In-Vitro Drug Release*

[0096] In-vitro drug release evaluations of F1, F2 and F3, were conducted using a USP Type II Distek 2100 Dissolution Apparatus. Two-stage dissolution tests were performed. Pre-weighed SDI powder was briefly suspended in media and transferred to a pre-heated (37 °C) volume of 50 mL of 0.1N simulated gastric fluid (SGF), pH ~ 1.0, without pepsin or bile salts) with stirring paddles speed at 100 rpm. After 30 minutes of gastric pH exposure, 2x concentrated (FaSSIF) was added to the SGF, resulting in a final pH of 6.8 in FaSSIF (100mM PBS containing 2.24 mg/mL SIF powder (original) (Biorelevant Inc.)) in a total volume of 100 mL. 1.0 mL samples were taken at pre-determined time-points and were analyzed utilizing a suitable HPLC method.

[0097] Results are shown in Table 10 and Figure 9. As reflected in Figure 9, the *in-vitro* performance results indicated that F1, F2 and F3 demonstrated improved dissolution performance as compared with the crystalline mesylate salt of belumosudil. The data indicate that F1, F2 and F3 are viable options to achieve a higher relative solubility while maintaining acceptable chemical and physical stability.

Table 10: Non-Sink Dissolution Data for F1, F2, F3

Formulation	Total Drug C _{max} GB (µgA/mL)	Total Drug C _{max} FaSSiF (µgA/mL)	Total Drug AUC ₃₅₋₂₁₀ FaSSiF (min*µgA/mL)	Total Drug C ₂₁₀ (µgA/mL)
F1	940	356.6	57800	314.3
F2	929	100.4	9400	28.1
F3	894	79.2	6000	29
Mesylate salt /API	932	6.1	700	6.1

4.2 Assay Evaluation

[0098] Reverse phase high performance liquid chromatography (RPHPLC) (Agilent 1200 series LCs (1220s and 1260s)) was used to determine and assay the impurities in F1, F2 and F3 during processing as compared with the mesylate salt form of belumosudil. The HPLC was equipped with a diode array detector. A gradient method with Zorbax SB-CN column was used. The mobile phase consisted of (A) 50mM potassium phosphate buffer and (B) acetonitrile, pumped at a flow rate of 1.4 mL/min at ambient temperature with the detection wavelength at 250nm. The mobile phase gradient was maintained as follows (minute, %B): (0, 20.0); (20.0,30.0); (30.0, 60); (40.0, 60).

[0099] The results of this assay are reported below in Table 11 and shown in Figure 10. The impurity profiles are similar to the mesylate salt form of belumosudil. No degradation was observed during processing.

Table 11: Assay Evaluation and Impurity Profiles

Formulation RRT	KD025 mesylate salt	F1 20:80 (PPPEG)	F2 20:80 (PVPVA)	F3 40:60 (PPPEG)
0.61	0.10%	0.09%	0.10%	0.10%
0.62	Detected,	Detected, <0.05%	Detected, <0.05%	Detected, <0.05%
0.66	<0.05%	Detected, <0.05%	Detected, <0.05%	Detected, <0.05%
0.82	Detected,	Detected, <0.05%	0.06%	0.08%
1.09	<0.05%	0.31%	0.28%	0.31%
1.17		0.29%	0.27%	0.29%
1.37	0.32%		Detected, <0.05%	
1.44	0.34%			0.07%
Total Impurities	0.75%	0.69%	0.72%	0.85%
Assay (wt%)	--	19.9%	19.1%	40.0%

Example 5

5.1 *Stability Assessments*

[00100] To assess the physical and chemical stability of formulations F1, F2 and F3, the three formulations were aged for up to 8 weeks at 25 °C/60 % relative humidity (RH) in open packaging and 40 °C/75 % RH in open and closed packaging. F1, F2 and F3 were evaluated for physical and chemical stability by appearance and XRPD. The XRPD patterns collected are shown in Figures 11A (F1), Figure 11B (F2), and Figure 11C (F3).

[00101] Overall, F2 (20:80 KD025:PVPVA) formed hard solids at all conditions by eight weeks and dispersion remained amorphous at all conditions even with the observed physical changes shown in Figure 11B. F1 (the 20:80 PPPEG dispersion) remained amorphous at 25 °C/60 % RH open and at 40 °C/75% RH closed as shown in Figure 11A. At 40 °C/75 % RH open, F1 formed hard clumps. F3 remained amorphous at 40 °C/75% RH closed and formed crystals at 25 °C/60 % RH open and 40 °C/75% RH open as shown in Figure 11C. This study was informative as to the time and storage conditions required for pre-manufacturing the final dosage form (*i.e.*, tablet compression, suspension etc.).

Example 6

[00102] The pharmacokinetics (PK) of F1, F2 and F3 were evaluated in male beagle dogs following oral (PO) administration as described in this Example 6.

6.1 *Suspension Formulation for In Vivo Administration*

[00103] Suspension formulations were developed for administering F1, F2 and F3 for the PK dog model. Suspensions were prepared at 25mgA/mL in 0.5 wt.% Methocel A4M with each of F1, F2 and F3 and evaluated for visual appearance, syringeability, and crystallinity by PLM. Methylcellulose A4M was added to purified pre-heated water (65±5°C) until it was fully dispersed in the water. Then, under continuous mixing the mixture was cooled down to room temperature. The amount of solid dispersion (F1, F2, F3), powder was slowly added based on the desired dosing. A wet paste was initially formed and turned into a suspension as the mixing continued. The suspensions were evaluated at T=0, T= 1 hr, and T= 2.5 hr using PLM (5X magnification); the images are shown in Figure 12.

[00104] The F1 dispersion (20:80 KD025:PPPEG) was homogeneous with no agglomerates or crystals and remained unchanged through 2.5 hours. The F1 formulation

remained stable in suspension for at least 4.5 hr with stirring at RT. F2 (20:80 KD025:PVPVA) and F3 (40:60 KD025:PPPEG) both showed agglomerates by PLM at T=0 which grew over time; however, no crystals were observed and the suspension remained syringeable (synergized through a 20 gauge gavage tube).

[00105] The suspension formulations were successfully developed and selected for ease of administration for the dog PK model; however, solid dosage forms are also contemplated. Solid dosage form such as tablets are relatively easy to manufacture, package, and transport, are more stable than liquids, and can be formulated with coatings and shaping to facilitate swallowing. One skilled in the field may therefore contemplate use of solid dosage forms as a substitute for the liquid suspensions used in this dog study.

6.2 *In-vivo Canine PK Evaluation*

[00106] Male beagle dogs were selected for the bio-performance evaluation of F1, F2 and F3. Studies were conducted under protocol approved by the Pharmaron Institutional Animal Care and Use Committee. Twenty male beagle dogs aged 1-1.5 years old were assigned dosing and feeding conditions with body weights maintained between 11-12 kg during course of the study. All animals were housed in a 12-hours light/dark cycle environment. F1, F2 and F3 were tested under fasted and fed conditions and compared to belumosudil free base powder and immediate release (IR) tablets containing crystalline mesylate salt of belumosudil which were used as controls. For the fasting group, dogs were fasted overnight, and the drug was administered to the dogs in the morning while in the fasted state. Food was returned to the dogs following the 4 h post-dose plasma collection. For the fed group, dogs were fasted overnight and fed 1 hour prior to dosing. All dogs had access to water throughout the study. All samples were dosed orally (PO); the tablets were administered as is. After tablet administration, 5 mL of vehicle was used to help the dog to swallow the tablets. Formulation 1,2 ,3, and free base samples were dosed using a suspension formulation of 0.5 wt% Methocel A4M via oral gavage. After suspension administration, 5mL of vehicle was given to the dog to make sure all suspensions were flushed to the stomach.

6.3 Study Design

[00107] A total of twenty beagle dogs were dosed via the dosing regimen summarized in Table 12. Four dogs were assigned to each group A-J. Group A/F, B/G, C/H, D/I, and E/J shared the same animals; the animals in groups A-E were dosed first. After a seven day wash out period, the animals in groups F to J were dosed. Dosing in each instance was via PO administration. Four males were dosed in each group.

Table 12: Beagle PK Dosing Information for F1, F2 and F3 and API Controls

Group	Treatment	Dose (~Equiv. 1000 mg KD025)	Food Control
A	KD025 Tablet	1000 mg (5 x 200 mg tablets)	Fasted
B	KD025- Free Base Powder	1000 mg	Fasted
C	F1 (20:80 KD025/PPPEG)	5025 mg of F1 SDD	Fasted
D	F2 (20:80 KD025/PVPVA)	5235 mg of F2 SDD	Fasted
E	F3 (40:60 KD025/PPPEG)	2500 mg of F3 SDD	Fasted
F	KD025- Tablet	1000 mg (5 x 200 mg tablets)	Fed
G	KD025- Free Base Powder	1000 mg	Fed
H	F1 (20:80 KD025/PPPEG)	5025 mg of F1 SDD	Fed
I	F2 (20:80 KD025/PVPVA)	5235 mg of F2 SDD	Fed
J	F3 (40:60 KD025/PPPEG)	2500 mg of F3 SDD	Fed

6.4 Sample Collection

[00108] Blood samples were collected from each animal at pre-determined time-points pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 30, and 36 hours post dose. Blood samples (1 mL) were collected from each animal via jugular veins. These blood samples were placed into tubes containing dipotassium ethylene diamine tetraacetic acid and then centrifuged at 2000 g for 10 minutes at 2 to 8 °C to obtain plasma.

6.5 *LC/MS Conditions*

[00109] KD025 in dog plasma samples were evaluated using LC-MS/MS system that consisted of two Shimadzu LC-30AD pumps, a DGU-20A5R© degasser, a Rack changer II and an AB Sciex Triple Quads 5500 LC/MS/MS mass spectrometer. Chromatographic separation was performed on an Agilent ZORBAX XDB-Phenyl 5 μ m (50 $\times$ 2.1 mm) column at RT. The mobile phase was composed of A: 5% acetonitrile (0.1% formic acid) in water; B: 95% acetonitrile (0.1% formic acid) in water. The flow rate was 0.6 mL/min. The injection volume was 2 μ L with lower limit of quantifications (LLOQ) of 10 ng /mL.

6.6 *Data Collection and Statistical Analysis*

[00110] Data acquisition was performed by Sciex Analyst 1.6.3 software (AB Sciex, Forster City, CA). Pharmacokinetic parameters such as area under the curve (AUC_{0-36h}), maximum plasma concentration (C_{max}), and time of C_{max} (T_{max}) were calculated by non-compartmental analysis (Phoenix TM WinNonlin™ 6.1). The linear trapezoidal algorithm was used for AUC calculation. Data statistics and plasma profiles were performed using Excel 2010 software.

[00111] Table 13 summarizes the mean pharmacokinetics parameters after administration of the tested formulations to the male beagle dogs 40 mg/kg dose (n=4). Figure 13 plots the plasma concentration of KD025 as a function of time over a twenty-four data collection period for the following dog groups: Group A = fasted tablet formulation; Group D = fasted F2 formulation (20:80 KD025: PVPVA); Group F = fed tablet formulation; and Group I = fed F2 (20:80 KD025:PVPVA).

Table 13: The average Plasma Pharmacokinetic Parameters Following PO Administration in Beagle Dogs at 1000 mg/dog

Conditions	Formulation	AUC(0-36h) [h*ng/mL]			Cmax [ng/mL]			T _{max} [h]	Relative Bioavailability	Food Effect
		Mean	StDev	%CV	Mean	StDev	%CV			
Fasted	Tablet	32276	31304	97.0	2842	2358	83.0	8.0±4.9	N/A	N/A
Fasted	Free Base	5699	5347	93.8	683	642	94.0	8.0± 6.7	0.18	N/A
Fasted	F 1	10794	5537	51.3	1883	1032	54.8	5.50±1.00	0.33	N/A
Fasted	F 2	19548	6465	33.1	2915	843	28.9	6.00± 0.00	0.61	N/A
Fasted	F 3	5841	5418	92.8	809	556	68.7	5.50± 2.52	0.18	N/A
Fed	Tablet	43340	13176	30.4	4773	1571	32.9	6.50± 1.00	N/A	1.34
Fed	Free Base	18805	12064	64.2	2103	592	28.2	8.0± 6.7	0.43	3.30
Fed	F 1	29331	5373	18.3	2883	237	8.2	5.00±1.15	0.68	2.72
Fed	F 2	36342	12177	33.5	3100	231	7.5	10.0± 6.3	0.84	1.86
Fed	F 3	27908	4021	14.4	2465	522	21.2	4.50± 1.00	0.64	4.78

[00112] When comparing the solid dispersion formulations F1, F2, and F3 to the tablet, it was surprisingly discovered that F2 (20:80 KD025:PVPVA) out-performed the other (PPPEG) formulations. For F2, the mean C_{max} of the fasted and fed groups were found to be similar, *i.e.*, at 2915.0 ng/mL for the fasted group and 3100 ng/mL for the fed group. In contrast, the mean C_{max} of the fasted state of the reference tablet was significantly different from the fed state, *i.e.*, at 2842 ng/mL for the fasted group and 4773 ng/mL for the fed group. This improved control over C_{max} with the amorphous belumosudil may be advantageous from a pharmacokinetic perspective.

[00113] Additionally, the F2 (KD025:PVPVA) tested group demonstrated lower variability as characterized by the % CV ($100 \times \text{StDev} / \text{Mean}$), as compared to the reference tablet. Under fasting conditions, the % CV of the F2 formulation was found to be 28.9, while for the tablet it was 83.0. When compared to the fasted condition, the percent variability was even lower with 7.5% CV for the F2 formulation and 32.9 for the reference tablet. In summary, in terms of C_{max}, the solid dispersion formulation F2 (20:80 KD025:PVPVA) reduced the subject-to-subject variability and minimized the food effect. The AUC observed with the F2 formulation was slightly lower than the actual reference tablet; however, the variability was better controlled. Under fasting conditions, AUC variability was improved using %CV for F2 (20:80 KD025:PVPVA) (33.1) as compared with the tablet (97.0). In summary, use of the solid dispersion formulation F2 was surprisingly effective in achieving minimal variability, and the food effect for F2 was lower than with the free-base tablet. During the study of this Example, no adverse effects were observed for the animals during or post study.