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(54) Title: SOLID DISPERSIONS AND SOLID FORMS COMPRISING 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE, METHOD OF PREPARATION AND USE THEREOF

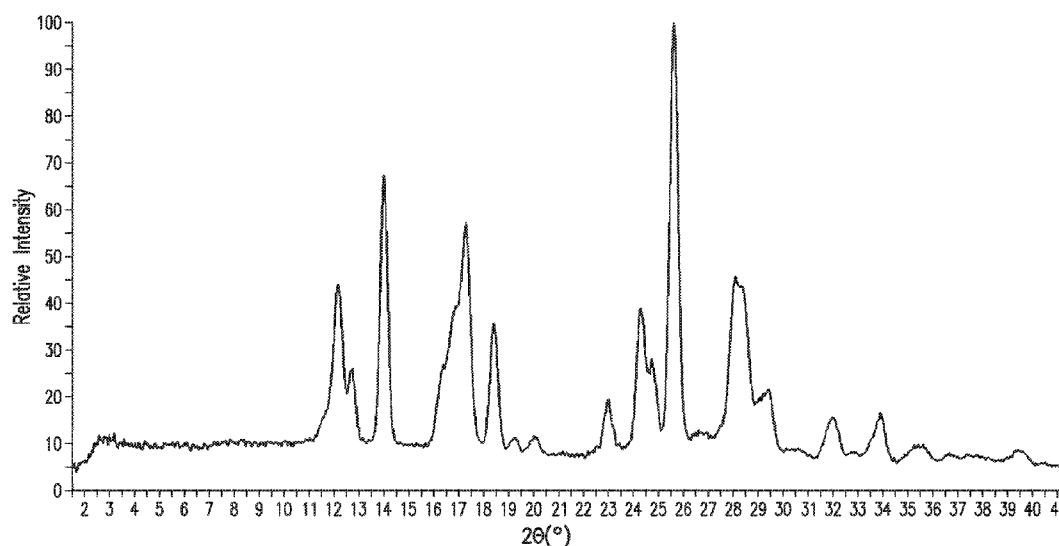


FIG. 1

(57) Abstract: Provided herein are solid dispersions comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and a polymer and solid forms comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione and a coformer. Pharmaceutical compositions comprising the solid dispersions and solid forms (e.g., cocrystals) and methods for treating, preventing and managing various disorders are also disclosed.

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SOLID DISPERSIONS AND SOLID FORMS COMPRISING
4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE, METHOD OF PREPARATION
AND USE THEREOF

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/361,926, filed July 13, 2016.

FIELD

[0002] Provided herein are solid dispersions and cocrystals comprising 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pharmaceutical compositions comprising such solid dispersions and cocrystals and methods of use for treating, preventing, and managing various disorders are also provided herein.

BACKGROUND

[0003] The identification and selection of a solid form of a pharmaceutical compound are complex, given that a change in solid form may affect a variety of physical and chemical properties, which may provide benefits or drawbacks in processing, formulation, stability, bioavailability, storage, handling (*e.g.*, shipping), among other important pharmaceutical characteristics. Useful pharmaceutical solids include crystalline solids and amorphous solids, depending on the product and its mode of administration. Amorphous solids are characterized by a lack of long-range structural order, whereas crystalline solids are characterized by structural periodicity. The desired class of pharmaceutical solid depends upon the specific application; amorphous solids are sometimes selected on the basis of, *e.g.*, an enhanced dissolution profile, while crystalline solids may be desirable for properties such as, *e.g.*, physical or chemical stability (*see, e.g.*, S. R. Vippagunta *et al.*, *Adv. Drug. Deliv. Rev.*, (2001) 48:3-26; L. Yu, *Adv. Drug. Deliv. Rev.*, (2001) 48:27-42).

[0004] Whether crystalline or amorphous, solid forms of a pharmaceutical compound include single-component and multiple-component solids. Single-component solids consist essentially of the pharmaceutical compound or active ingredient in the absence of other compounds. Variety among single-component crystalline materials may potentially arise from the phenomenon of polymorphism, wherein multiple three-dimensional arrangements exist for a particular pharmaceutical compound (*see, e.g.*, S. R. Byrn *et al.*, *Solid State Chemistry of Drugs*, (1999) SSCI, West Lafayette).

[0005] Additional diversity among the potential solid forms of a pharmaceutical compound may arise from the possibility of multiple-component solids. Crystalline solids comprising two or more ionic species may be termed salts (*see, e.g.*, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*,

P. H. Stahl and C. G. Wermuth, Eds., (2002), Wiley, Weinheim). Additional types of multiple-component solids that may potentially offer other property improvements for a pharmaceutical compound or salt thereof include, *e.g.*, hydrates, solvates, co-crystals and clathrates, among others (*see, e.g.*, S. R. Byrn *et al.*, *Solid State Chemistry of Drugs*, (1999) SSCI, West Lafayette). Moreover, multiple-component crystal forms may potentially be susceptible to polymorphism, wherein a given multiple-component composition may exist in more than one three-dimensional crystalline arrangement.

[0006] Solid dispersion is a dispersion of active ingredients in an inert carrier or matrix at solid state, normally prepared by the melting (fusion), solvent, or melting-solvent methods. (*see, e.g.*, Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, 60, 1281-1302 (1971)). Although it has been reported that solid dispersions can result in improved solubility of an active pharmaceutical ingredient (API), challenges in developing formulations with desirable properties remain. One such challenge is the physical instability of the API. During processing or storage, the amorphous API compounds tend to convert to their crystalline forms. When used as solid dispersion carriers, water soluble polymers may kinetically and/or thermodynamically stabilize amorphous compounds and inhibit the recrystallization of the compound in the GI tract. However, a water soluble polymer that can provide satisfactory stability and dissolution performance might not be found, especially for some compounds with very strong crystallization tendency.

[0007] Cocrystals are crystalline molecular complexes of two or more non-volatile compounds bound together in a crystal lattice by non-ionic interactions. Pharmaceutical cocrystals are cocrystals of a therapeutic compound, *e.g.*, an API, and one or more non-volatile compound(s) (referred to herein as coformer). A coformer in a pharmaceutical cocrystal is typically a non-toxic pharmaceutically acceptable molecule, such as, for example, food additives, preservatives, pharmaceutical excipients, or other APIs. In recent years, pharmaceutical cocrystals have emerged as a possible alternative approach to enhance physicochemical properties of drug products.

[0008] The variety of possible solid forms creates potential diversity in physical and chemical properties for a given pharmaceutical compound. The discovery and selection of solid forms are of great importance in the development of an effective, stable and marketable pharmaceutical product.

[0009] Pomalidomide has a chemical name of 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione. Pomalidomide is a compound that inhibits, for example, LPS induced monocyte TNF α , IL-1 β , IL-12, IL-6, MIP-1, MCP-1, GM-CSF, G-CSF, and COX-2 production, and may be used in treating various disorders. *See, e.g.*, U.S. Patent Nos. 5,635,517, 6,316,471, 6,476,052, 7,393,863, 7,629,360, and 7,863,297, the entireties of which are incorporated herein by reference. Pomalidomide has direct anti-myeloma tumoricidal and immunomodulatory activities, and inhibits stromal cell support for multiple

myeloma tumor cell growth. Pomalidomide inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergizes with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell-mediated immunity, and inhibits production of pro-inflammatory cytokines (*e.g.*, TNF- α and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells. A molecular target of Pomalidomide is cereblon, a protein that forms a ubiquitin E3 ligase complex with DNA damage-binding protein (DDBA), culin 4 (CUL4) and protein Roc1. Pomalidomide binding to cereblon induces the polyubiquitination of two substrate proteins Ikaros (IKF1) and Aiolos (IKZF3). Pomalidomide is known to have CNS penetration. Due to its diversified pharmacological properties, pomalidomide is useful in treating, preventing, and/or managing various diseases or disorders.

[0010] Pomalidomide and methods of synthesizing the compound are described, *e.g.*, in U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327, the entireties of which are incorporated herein by reference. Solid forms of pomalidomide have been described in WO 2013/126326.

[0011] Pomalidomide in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated a disease progression on or within 60 days of completion of the last therapy.

[0012] Central nervous system tumors (including brain and spinal cord) are the most common solid tumors among children and make up to 25% of all childhood cancer cases. In the United States, approximately 2,500 children are diagnosed annually with brain tumors. The most common brain tumors fall under the category of glioma and account for 53% of tumors in children ages 0-14 years and 37% in adolescents ages 15-19 years. Other common pediatric CNS tumors include meduloblastomas and ependymomas.

[0013] Gliomas are primary brain tumors of glial origin with different cell lineages. Some of the more common tumors of this class found in children include fibrillary astrocytomas, juvenile pilocytic astrocytoma (JPA), oligodendrogliomas, ependymomas, glioblastoma multiforme, and pleomorphic xanthoastrocytomas. Gliomas represent most of the brain tumors found in the cerebral hemispheres in children. Astrocytomas (of all types) represent approximately half of the gliomas in this location. Gliomas are classified by the World Health Organization (WHO) into four grades. Most (80%) of these tumors in children are low grade (grade I and II) including the most frequently occurring pilocytic

astrocytoma (WHO grade I) and diffuse astrocytoma (WHO grade II) and about 20% are WHO grade III or IV (high-grade gliomas). High grade gliomas account for 3% to 7% of primary brain tumors in children and include anaplastic astrocytomas (WHO grade III) and glioblastomas (WHO grade IV) with glioblastoma multiforme (GBM) being the most aggressive type.

[0014] Diffuse intrinsic brain stem gliomas (DIPG) which are mainly grade III or IV astrocytomas have the worst prognosis with overall survival of approximately 9 months, and most patients die from the disease within 2 years. They account for 60% to 75% of brainstem tumors and are the major cause of mortality in children with brain tumors. They usually occur between the ages of 5 to 10 years with short time of onset of symptoms. High-grade gliomas are particularly difficult to treat due to their infiltrative nature and resistance to radiotherapy and current chemotherapy regimens. Patients with these types of tumors generally succumb to their disease and the 5-year survival rate remains < 10%.

[0015] Medulloblastomas, one of the embryonal brain tumor types, are primary brain tumors that occur in the cerebellum of children and young adults. Medulloblastomas are the most common malignant brain tumor in pediatrics and the second most common pediatric brain tumor overall, representing approximately 20% of all pediatric CNS tumors. This tumor has the propensity to disseminate along the cerebrospinal fluid (CSF) pathway, and approximately 30% of patients have metastatic disease at diagnosis. Medulloblastomas can be stratified into four distinct histological subtypes that together with age at diagnosis and the metastatic status of the disease, categorize patients into risk groups, which could be used to predict the survival outcome. These groups include classical medulloblastoma, large cell/anaplastic medulloblastoma, nodular desmoplastic medulloblastoma, and medulloblastoma with extensive nodularity. Large-cell/anaplastic medulloblastomas are associated with poor prognosis especially in patients less than 3 years of age, while the nodular desmoplastic and medulloblastoma with extensive nodularity, are associated with a better prognosis. The 5-year survival ranges from >80% (standardrisk) to 60% (high-risk).

[0016] Ependymomas are the third most common pediatric brain tumor and represent approximately 8% to 10% of all central nervous system tumors seen in children. Ependymomas are classified into myxopapillary ependymoma (WHO grade I), grade II ependymoma (cellular, papillary, clear cell, tanycytic) and anaplastic ependymoma (WHO grade III), although there does not appear to be a correlation between grade and clinical outcome.

[0017] Other less commonly seen histologies include central nervous system germ cell tumors, craniopharyngiomas, choroid plexus tumors, meningiomas, and atypical teratoid rhabdoid tumors.

[0018] Pomalidomide has a low aqueous solubility (approximately 10 µg/mL) which presents a challenge for the development of a pediatric (liquid) formulation of the drug. There remains a unmet need to explore different multiple-component solid forms (*e.g.*, solid dispersion and cocrystal) of pomalidomide that are stable and/or have improved solubilities.

SUMMARY

[0019] Provided herein are multi-component solid forms comprising pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a second compound.

[0020] In certain embodiments, the second compound is a polymer. In certain embodiments, provided herein are solid dispersions comprising pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a polymer.

[0021] In certain embodiments, the second compound is a coformer. In certain embodiments, provided herein are solid forms comprising pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a coformer. In one embodiment, the coformer is nicotinamide, L-arginine, or orotic acid.

[0022] Also provided herein are methods of preparing, isolating, and characterizing the solid dispersions and solid forms provided herein.

[0023] Also provided herein are pharmaceutical compositions comprising one or more solid dispersions and solid forms provided herein.

[0024] Also provided herein are methods of treating and managing various diseases or disorders. The methods comprise administering to a patient in need of such treatment or management a therapeutically effective amount of a solid dispersion or solid form provided herein.

[0025] Also provided herein are methods of preventing various diseases and disorders, which comprise administering to a patient in need of such prevention a prophylactically effective amount of a solid dispersion or solid form provided herein.

[0026] The various diseases and disorders include, but are not limited to: cancer, including hematologic cancer or solid tumor, for example, multiple myeloma, leukemia, lymphoma, sarcoma; amyloidosis; an immunodeficiency disorder; a CNS disorder; a CNS injury; sickle cell anemia; an inflammatory disease; an autoimmune disease; a viral disease; a genetic disease; Central Nervous System Tumors including glioma, nervous system neoplasms, neuroepithelioma, neurofibroma, neurofibromatosis, optic nerve glioma, medulloblastoma, ependymoma, diffuse intrinsic pontine

glioma, cranial nerve disease, cranial nerve neoplasms, ocular diseases, neuroepithelial neoplasms, nerve sheath neoplasms, neurocutaneous syndromes, optic nerve neoplasms, peripheral nervous system diseases, central nervous system germ cell tumors, craniopharyngiomas, choroid plexus tumors, meningiomas and atypical teratoid rhabdoid tumors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIG. 1 provides a representative X-ray Powder Diffraction (XRPD) pattern of Form A of pomalidomide.

[0028] FIG. 2 provides a representative FTIR spectrum of Form A of pomalidomide.

[0029] FIG. 3 provides representative XRPD patterns of pomalidomide dispersions with ethyl cellulose, hydroxypropyl methylcellulose phthalate 50, Eudragit RS 100, and hydroxypropyl methyl cellulose.

[0030] FIG. 4 provides representative XRPD patterns of pomalidomide dispersions with ethyl cellulose, hydroxypropyl methylcellulose phthalate 50, Eudragit RS 100, and hydroxypropyl methyl cellulose (after additional drying).

[0031] FIG. 5 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of HPMC-P, and 5% pomalidomide dispersion in HPMC-P (before AAC, after AAC, and after additional drying).

[0032] FIG. 6 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of Eudragit RS 100, and 10% pomalidomide dispersion in Eudragit RS 100 (before AAC, after AAC, and after additional drying).

[0033] FIG. 7 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of HPMC, and 10% pomalidomide dispersion in HPMC (before AAC, after AAC, and after additional drying).

[0034] FIG. 8 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of PEG 6000, and 5% pomalidomide dispersion in PEG 6000 (before AAC and after AAC).

[0035] FIG. 9A shows the solubility of pomalidomide released from HPMC-P dispersion (5% drug load) at room temperature in water and in 2% HPMC solution.

[0036] FIG. 9B shows the solubility of pomalidomide released from HPMC-P dispersion (5% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0037] FIG. 10 shows pH dependent solubility of pomalidomide released from HPMC-P dispersion (5% drug load).

[0038] FIG. 11 shows results of the gastric precipitation test for a pomalidomide dispersion in HPMC-P (5% drug load).

[0039] FIG. 12A shows the solubility of pomalidomide released from Eudragit RS 100 dispersion (5% drug load) at room temperature in water and in 2% HPMC solution.

[0040] FIG. 12B shows the solubility of pomalidomide released from Eudragit RS 100 dispersion (5% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0041] FIG. 13 shows pH dependent solubility of pomalidomide released from Eudragit RS 100 dispersion (5% drug load).

[0042] FIG. 14 shows results of the gastric precipitation test for a pomalidomide dispersion in Eudragit RS 100 (5% drug load).

[0043] FIG. 15A shows the solubility of pomalidomide released from Eudragit RS 100 dispersion (10% drug load) at room temperature in water and in 2% HPMC solution.

[0044] FIG. 15B shows the solubility of pomalidomide released from Eudragit RS 100 dispersion (10% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0045] FIG. 16 shows pH dependent solubility of pomalidomide released from Eudragit RS 100 dispersion (10% drug load).

[0046] FIG. 17 shows results of the gastric precipitation test for a pomalidomide dispersion in Eudragit RS 100 (10% drug load).

[0047] FIG. 18 shows the solubility of pomalidomide released from HPMC dispersion (5% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0048] FIG. 19 shows the solubility of pomalidomide released from HPMC dispersion (10% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0049] FIG. 20 shows the solubility of pomalidomide released from PEG 6000 dispersion (5% drug load) at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC solution in water, and in 5% Glycerin solution in water.

[0050] FIG. 21 shows pH dependent solubility of pomalidomide released from HPMC-AS LG dispersion (5% drug load).

[0051] FIG. 22 shows the solubility of pomalidomide released from HPMC-AS LG dispersion (5% drug load) at room temperature in water and in 2% HPMC solution.

[0052] FIG. 23 shows results of the gastric precipitation test for a pomalidomide dispersion in HPMC-AS LG (5% drug load).

[0053] FIG. 24 shows pH dependent solubility of pomalidomide released from HPMC-AS MG dispersion (5% drug load).

[0054] FIG. 25 shows the solubility of pomalidomide released from HPMC-AS MG dispersion (5% drug load) at room temperature in water and in 2% HPMC solution.

[0055] FIG. 26 shows results of the gastric precipitation test for a pomalidomide dispersion in HPMC-AS MG (5% drug load).

[0056] FIG. 27 shows pH dependent solubility of pomalidomide released from HPMC-AS HG dispersion (5% drug load).

[0057] FIG. 28 shows the solubility of pomalidomide released from HPMC-AS HG dispersion (5% drug load) at room temperature in water and in 2% HPMC solution.

[0058] FIG. 29 shows results of the gastric precipitation test for a pomalidomide dispersion in HPMC-AS HG (5% drug load).

[0059] FIG. 30 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of HPMC-P, and a 5% pomalidomide dispersion in HPMC-P.

[0060] FIG. 31 provides a representative DSC thermogram of a 5% pomalidomide dispersion in HPMC-P.

[0061] FIG. 32 provides a representative TGA thermogram of a 5% pomalidomide dispersion in HPMC-P.

[0062] FIG. 33 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of HPMC-AS HG, and 5% pomalidomide dispersion in HPMC-AS HG.

[0063] FIG. 34 provides a representative DSC thermogram of a 5% pomalidomide dispersion in HPMC-AS HG.

[0064] FIG. 35 provides a representative TGA thermogram of a 5% pomalidomide dispersion in HPMC-AS HG.

[0065] FIG. 36 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of nicotinamide, a solid form comprising pomalidomide and nicotinamide before exposure to AAC, and cocrystal Form NIA obtained after exposure to AAC.

[0066] FIG. 37A provides a representative overlay of FTIR spectrum between 4000 to 1800 cm^{-1} of Form A of pomalidomide, reference of nicotinamide, and cocrystal Form NIA.

[0067] FIG. 37B provides a representative overlay of FTIR spectrum between 1800 to 400 cm^{-1} of Form A of pomalidomide, reference of nicotinamide, and cocrystal Form NIA.

[0068] FIG. 38 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of L-arginine, Form A and cocrystal Form ARG before exposure to AAC, and Form A and L-arginine obtained after exposure to AAC.

[0069] FIG. 39A provides a representative overlay of FTIR spectrum between 4000 to 1800 cm^{-1} of Form A of pomalidomide, reference of L-arginine, and cocrystal Form ARG.

[0070] FIG. 39B provides a representative overlay of FTIR spectrum between 1800 to 400 cm^{-1} of Form A of pomalidomide, reference of L-arginine, and cocrystal Form ARG.

[0071] FIG. 40 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of orotic acid, Form A and cocrystal Form ORO1 before exposure to AAC, and Form A and orotic acid obtained after exposure to AAC.

[0072] FIG. 41A provides a representative overlay of FTIR spectrum between 4000 to 1800 cm^{-1} of Form A of pomalidomide, reference of orotic acid, and cocrystal Form ORO1.

[0073] FIG. 41B provides a representative overlay of FTIR spectrum between 1800 to 400 cm^{-1} of Form A of pomalidomide, reference of orotic acid, and cocrystal Form ORO1.

[0074] FIG. 42 provides a representative overlay of XRPD patterns of Form A of pomalidomide, reference of orotic acid, cocrystal Form ORO2 before exposure to AAC, and Form A and orotic acid obtained after exposure to AAC.

[0075] FIG. 43A provides a representative overlay of FTIR spectrum between 4000 to 1800 cm^{-1} of Form A of pomalidomide, reference of orotic acid, and cocrystal Form ORO2.

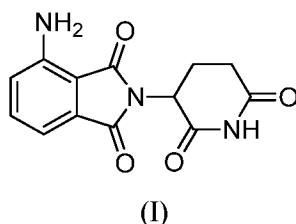
[0076] FIG. 43B provides a representative overlay of FTIR spectrum between 1800 to 400 cm^{-1} of Form A of pomalidomide, reference of orotic acid, and cocrystal Form ORO2.

DETAILED DESCRIPTION

DEFINITIONS

[0077] As used herein, and in the specification and the accompanying claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as single referents, unless the context clearly indicates otherwise.

[0078] As used herein, and unless otherwise specified, the compound referred to herein by the name pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, corresponds to a compound of Formula (I), depicted below. In certain embodiments, the term pomalidomide or 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindoline-1,3-dione, may be used herein to refer to either a free base form or an ionized form of a compound of formula (I) (*e.g.*, the molecule is protonated at one or more basic centers).



[0079] Unless otherwise specified, the terms “solid form,” “solid forms,” and related terms, when used herein to refer to pomalidomide, refer to a physical form comprising pomalidomide, which is not predominantly in a liquid or a gaseous state. As used herein, the terms “solid form” and “solid forms” encompass semi-solids. Solid forms may be crystalline, amorphous, partially crystalline, partially amorphous, or mixtures of forms. A “single-component” solid form comprising pomalidomide consists essentially of pomalidomide. A “multiple-component” solid form comprising pomalidomide comprises a significant quantity of one or more additional species, such as ions and/or molecules, within the solid form. For example, in particular embodiments, a crystalline multiple-component solid form comprising pomalidomide further comprises one or more species non-covalently bonded at regular positions in the crystal lattice. For another example, in particular embodiments, an amorphous multiple-component solid form comprising pomalidomide further comprises one or more polymer(s), and pomalidomide is dispersed in a solid matrix that comprises the polymer(s).

[0080] Unless otherwise specified, the term “crystalline” and related terms used herein, when used to describe a substance, component, product, or form, mean that the substance, component, product, or form is substantially crystalline, for example, as determined by X-ray diffraction. (*see, e.g., Remington’s Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA, 173 (1990); *The United States Pharmacopeia*, 23rd ed., 1843-1844 (1995)).

[0081] Unless otherwise specified, the term “crystal form,” “crystal forms,” and related terms herein refer to crystalline modifications comprising a given substance, including single-component crystal forms and multiple-component crystal forms, and including, but not limited to, polymorphs, solvates, hydrates, co-crystals, other molecular complexes, salts, solvates of salts, hydrates of salts, co-crystals of salts, and other molecular complexes of salts, and polymorphs thereof. In some embodiments, a crystal form of a substance may be substantially free of amorphous forms and/or other crystal forms. In other embodiments, a crystal form of a substance may contain less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of one or more amorphous form(s) and/or other crystal form(s) on a weight basis. Crystal forms of a substance may be obtained by a number of methods. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, recrystallization in confined spaces such as, *e.g.*, in nanopores or capillaries, recrystallization on surfaces or templates such as, *e.g.*, on polymers, recrystallization in the presence of additives, such as, *e.g.*, co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, grinding, and solvent-drop grinding.

[0082] Unless otherwise specified, the terms “polymorph,” “polymorphic form,” “polymorphs,” “polymorphic forms,” and related terms herein refer to two or more crystal forms that consist essentially of the same molecule, molecules or ions. Different polymorphs may have different physical properties, such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates, and/or vibrational spectra as a result of a different arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may affect pharmaceutical parameters, such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rate (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolours more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically a more stable polymorph) or both (*e.g.*, tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition,

the physical properties of the crystal may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (*e.g.*, particle shape and size distribution might be different between polymorphs).

[0083] Unless otherwise specified, the term “cocrystal” or “co-crystal,” as used herein, refers to a crystalline material comprised of two or more non-volatile compounds bond together in a crystal lattice by non-covalent interactions.

[0084] Unless otherwise specified, the term “pharmaceutical cocrystal” or “cocrystal” of an active pharmaceutical ingredient (API), as used herein, refers to a crystalline material comprised of an API and one or more non-volatile compound(s) (referred herein as a coformer). The API and the coformer interact through non-covalent forces in a crystal lattice.

[0085] Unless otherwise specified, the term “amorphous,” “amorphous form,” and related terms used herein mean that the substance, component, or product referred to is not substantially crystalline as determined by X-ray diffraction. In certain embodiments, an amorphous form of a substance may be substantially free of crystal forms. In other embodiments, an amorphous form of a substance may contain less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% of one or more crystal forms on a weight basis. In other embodiments, an amorphous form of a substance may comprise additional components or ingredients (for example, an additive, a polymer, or an excipient that may serve to further stabilize the amorphous form). In some embodiments, amorphous form may be a solid solution. Amorphous forms of a substance can be obtained by a number of methods. Such methods include, but are not limited to, heating, melt cooling, rapid melt cooling, solvent evaporation, rapid solvent evaporation, desolvation, sublimation, grinding, ball-milling, cryo-grinding, spray drying, and freeze drying.

[0086] Unless otherwise specified, the term “solid dispersion”, as used herein, refers to a solid state which comprises at least two constituents, wherein one constituent is homogeneously dispersed significantly evenly throughout the other constituent or constituents. It includes solid or glassy solutions, *i.e.*, the dispersion of the constituents is in such a way that the composition is chemically and physically homogeneous in nature. In one embodiment, the first constituent is an active pharmaceutical ingredient (API), and the second constituent is a matrix that comprises a polymer, wherein the API is dispersed significantly uniformly within the matrix (the polymer). The API may be present in an amorphous state or in fine crystalline dispersed form. Also, the API may be available as a mixture of amorphous and crystalline forms. A solid dispersion can comprise more than two constituents. For example, two or more API can be dispersed into the matrix, and the matrix can comprise two or more polymers. Without limitation, solid dispersions may be physically classified as a eutectic mixture, a solid solution, a glass

solution or suspension, an amorphous precipitate in a glassy or crystalline carrier, a complex, a complexed formation or a combination of the different systems. In addition, solid dispersions may be prepared using various techniques known to those skilled in the art, such as by co-dissolving the API and polymer in a solvent then spray-drying, spray-congealing, evaporation, curing or microwaving, blending and direct compression, mechanical admixture at an elevated but non-melting temperature, wet granulation, extrusion-spheronization, melt fusion, hot melt extrusion and the like. A “solid matrix” refers to a matrix that is solid.

[0087] Unless otherwise specified, the term “polymer”, as used herein, refers to a compound comprising repeating structural units (monomers) connected by covalent chemical bonds. Polymers may be further derivatized, crosslinked, grafted or end-capped. Non-limiting examples of polymers include copolymers, terpolymers, quaternary polymers, and homologues. The term “copolymer” refers to a polymer consisting essentially of two or more different types of repeating structural units (monomers).

[0088] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percents of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by one of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. In certain embodiments, the terms “about” and “approximately,” when used in this context, contemplate a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

[0089] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, *e.g.*, a specific temperature or temperature range, such as, for example, that describes a melting, dehydration, desolvation, or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position, such as, for example, in analysis by, for example, IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the solid form. Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, *e.g.*, infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies, and dissolution studies. In certain

embodiments, the terms “about” and “approximately,” when used in this context, indicate that the numeric value or range of values may vary within 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. For example, in some embodiments, the value of an XRPD peak position may vary by up to ± 0.2 degrees 2θ while still describing the particular XRPD peak.

[0090] As used herein, and unless otherwise specified, a crystalline or amorphous form that is “pure,” *i.e.*, substantially free of other crystalline or amorphous forms, contains less than about 10% by weight of one or more other crystalline or amorphous forms, less than about 5% by weight of one or more other crystalline or amorphous forms, less than about 3% by weight of one or more other crystalline or amorphous forms, or less than about 1% by weight of one or more other crystalline or amorphous forms.

[0091] As used herein, and unless otherwise specified, a solid form that is “substantially physically pure” is substantially free from other solid forms. In certain embodiments, a crystal form that is substantially physically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other solid forms on a weight basis. The detection of other solid forms can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, diffraction analysis, thermal analysis, elemental combustion analysis and/or spectroscopic analysis.

[0092] As used herein, and unless otherwise specified, a solid form that is “substantially chemically pure” is substantially free from other chemical compounds (*i.e.*, chemical impurities). In certain embodiments, a solid form that is substantially chemically pure contains less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% of one or more other chemical compounds on a weight basis. The detection of other chemical compounds can be accomplished by any method apparent to a person of ordinary skill in the art, including, but not limited to, methods of chemical analysis, such as, *e.g.*, mass spectrometry analysis, spectroscopic analysis, thermal analysis, elemental combustion analysis and/or chromatographic analysis.

[0093] As used herein, and unless otherwise indicated, a chemical compound, solid form, or composition that is “substantially free” of another chemical compound, solid form, or composition means that the compound, solid form, or composition contains, in certain embodiments, less than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.05%, or 0.01% by weight of the other compound, solid form, or composition.

[0094] As used herein, and unless otherwise specified, the term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable, relatively non-toxic acids, including inorganic acids and organic acids. In some embodiments, suitable acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, carbonic, citric, dihydrogenphosphoric, ethenesulfonic, fumaric, galactunoric, gluconic, glucuronic, glutamic, hydrobromic, hydrochloric, hydriodic, isobutyric, isethionic, lactic, maleic, malic, malonic, mandelic, methanesulfonic, monohydrogencarbonic, monohydrogen-phosphoric, monohydrogensulfuric, mucic, nitric, pamoic, pantothenic, phosphoric, phthalic, propionic, suberic, succinic, sulfuric, tartaric, toluenesulfonic acid (including *p*-toluenesulfonic, *m*-toluenesulfonic, and *o*-toluenesulfonic acids), and the like (see, e.g., S. M. Berge *et al.*, *J. Pharm. Sci.*, 66:1-19 (1977); and *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, Eds., (2002), Wiley, Weinheim). In some embodiments, suitable acids are strong acids (e.g., with pKa less than about 1), including, but not limited to, hydrochloric, hydrobromic, sulfuric, nitric, methanesulfonic, benzene sulfonic, toluene sulfonic, naphthalene sulfonic, naphthalene disulfonic, pyridine-sulfonic, or other substituted sulfonic acids. Also included are salts of other relatively non-toxic compounds that possess acidic character, including amino acids, such as aspartic acid and the like, and other compounds, such as aspirin, ibuprofen, saccharin, and the like. Acid addition salts can be obtained by contacting the neutral form of a compound with a sufficient amount of the desired acid, either neat or in a suitable solvent. As solids, salts can exist in crystalline or amorphous forms, or mixtures thereof. Salts can also exist in polymorphic forms.

[0095] Unless otherwise specified, the terms “solvate” and “solvated,” as used herein, refer to a solid form of a substance which contains solvent. The terms “hydrate” and “hydrated” refer to a solvate wherein the solvent is water. “Polymorphs of solvates” refer to the existence of more than one solid form for a particular solvate composition. Similarly, “polymorphs of hydrates” refer to the existence of more than one solid form for a particular hydrate composition. The term “desolvated solvate,” as used herein, refers to a solid form of a substance which can be made by removing the solvent from a solvate. The terms “solvate” and “solvated,” as used herein, can also refer to a solvate of a salt, co-crystal, or molecular complex. The terms “hydrate” and “hydrated,” as used herein, can also refer to a hydrate of a salt, co-crystal, or molecular complex.

[0096] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to

the administration of a compound provided herein, with or without other additional active agent, after the onset of symptoms of a particular disease.

[0097] As used herein, and unless otherwise specified, the terms “prevent,” “preventing” and “prevention” refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. In certain embodiments, the terms refer to the treatment with or administration of a compound provided herein, with or without other additional active compound, prior to the onset of symptoms, particularly to patients at risk of a disease or disorder provided herein. The terms encompass the inhibition or reduction of a symptom of a particular disease. Patients with familial history of a disease in particular are candidates for preventive regimens in certain embodiments. In addition, patients who have a history of recurring symptoms are also potential candidates for the prevention. In this regard, the term “prevention” may be interchangeably used with the term “prophylactic treatment.”

[0098] As used herein, and unless otherwise specified, the terms “manage,” “managing” and “management” refer to preventing or slowing the progression, spread, or worsening of a disease or disorder, or of one or more symptoms thereof. Often, the beneficial effects that a subject derives from a prophylactic and/or therapeutic agent do not result in a cure of the disease or disorder. In this regard, the term “managing” encompasses treating a patient who had suffered from the particular disease in an attempt to prevent or minimize the recurrence of the disease or one or more symptoms thereof.

[0099] As used herein, and unless otherwise specified, a “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or disorder, or to delay or minimize one or more symptoms associated with the disease or disorder. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of the disease or disorder. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or disorder, or enhances the therapeutic efficacy of another therapeutic agent.

[00100] As used herein, and unless otherwise specified, a “prophylactically effective amount” of a compound is an amount sufficient to prevent a disease or disorder, or one or more symptoms thereof, or prevent the recurrence of the disease or disorder, or one or more symptoms thereof. A prophylactically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other agents, that provides a prophylactic benefit in the prevention of the disease or disorder. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

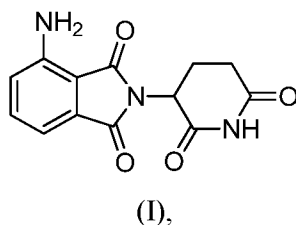
[00101] Unless otherwise specified, the term “composition” as used herein is intended to encompass a product comprising the specified ingredient(s) (and in the specified amount(s), if indicated), as well as any product which results, directly or indirectly, from combination of the specified ingredient(s) in the specified amount(s). By “pharmaceutically acceptable,” it is meant a diluent, excipient, or carrier in a formulation must be compatible with the other ingredient(s) of the formulation and not deleterious to the recipient thereof.

[00102] Unless otherwise specified, the term “subject” is defined herein to include animals, such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, and the like. In specific embodiments, the subject is a human.

[00103] Unless otherwise specified, to the extent that there is a discrepancy between a depicted chemical structure of a compound provided herein and a chemical name of a compound provided herein, the chemical structure shall control.

SOLID DISPERSIONS COMPRISING POMALIDOMIDE AND A POLYMER

[00104] In some embodiments, provided herein is a solid dispersion comprising a compound of Formula (I):



or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a polymer.

[00105] In one embodiment, the compound (*i.e.*, the compound of Formula (I), *i.e.*, pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof) is dispersed in a solid matrix that comprises the polymer.

[00106] In one embodiment, the polymer is a hydrophilic polymer. In one embodiment, the polymer is a water soluble polymer.

[00107] Non-limiting examples of polymers useful herein include cellulose esters and cellulose ethers, polyalkylene oxides, polyacrylates and polymethacrylates, homopolymers and copolymers of N-vinyl lactams, polyacrylamides, vinyl acetate polymers, graft copolymers of polyethylene glycol,

polyvinyl caprolactam and polyvinyl acetate, oligo- and polysaccharides, and mixtures of two or more thereof.

[00108] In one embodiment, the polymer is a cellulose ether polymer. In one embodiment, the polymer is methyl cellulose, ethyl cellulose, (hydroxyalkyl)cellulose (*e.g.*, hydroxyethyl cellulose (HEC) or hydroxypropyl cellulose (HPC)), or (hydroxyalkyl)alkyl-cellulose (*e.g.*, hydroxypropyl methyl cellulose (HPMC or hypromellose)). In one embodiment, the polymer is methyl cellulose. In another embodiment, the polymer is ethyl cellulose. In another embodiment, the polymer is HEC. In another embodiment, the polymer is HPC. In another embodiment, the polymer is HPMC.

[00109] In one embodiment, the polymer is a cellulose ester polymer. In one embodiment, the polymer is cellulose phthalate (*e.g.*, cellulose acetate phthalate or hydroxypropyl methyl cellulose phthalate (HPMC-P)) or cellulose succinate (*e.g.*, hydroxypropyl methyl cellulose succinate (HPMC-S) or hydroxypropyl methyl cellulose acetate succinate (HPMC-AS)). In one embodiment, the polymer is HPMC-P. In another embodiment, the polymer is HPMC-AS.

[00110] The cellulose ether and ester polymers can have various viscosity grades. In one embodiment, the HPMC is HPMC E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, or HPMC A15. In one embodiment, the HPMC-AS is HPMC-AS LF, HPMC-AS MF, HPMC-AS HF, HPMC-AS LG, HPMC-AS MG, or HPMC-AS HG. In one embodiment, the HPMC-P is HPMC-P 50 or HPMC-P 55. In one embodiment, the polymer is HPMC-P. In one embodiment, the polymer is HPMC-P 50. In one embodiment, the polymer is HPMC-AS LG. In one embodiment, the polymer is HPMC-AS MG. In one embodiment, the polymer is HPMC-AS HG.

[00111] In one embodiment, the polymer is a polyalkylene oxide. In one embodiment, the polymer is a high molecular weight polyalkylene oxide. In one embodiment, the polymer is polyethylene oxide (PEG or PEO) or copolymers of ethylene oxide and propylene oxide (poloxamers). Suitable PEGs include, without limitation, PEG 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and mixtures thereof. Suitable poloxamers include, without limitation, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, poloxamer 407 and mixtures thereof. In one embodiment, the polymer is poly(ethylene glycol) methyl. In one embodiment, the polymer is polyethylene glycol 6000 (PEG 6000).

[00112] In one embodiment, the polymer is a polyacrylate or polymethacrylate. In one embodiment, the polymer is methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylates), or poly(hydroxyalkyl methacrylates). Suitable polyacrylate or polymethacrylate include,

without limitation, those sold under the Eudragit™ trademark of Rohm GmbH as Eudragit RS 100, Eudragit L 100, Eudragit L 100-55, and Eudragit S 100, products of other manufacturers equivalent thereto, and mixtures thereof. In one embodiment, the polymer is Eudragit RS 100. In another embodiment, the polymer is Eudragit S 100.

[00113] In one embodiment, the polymer is a homopolymer or copolymer of N-vinyl lactams. In one embodiment, the polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. In one embodiment, the polymer is a homopolymer of polyvinylpyrrolidone (PVP or povidone) or a copolymer (*e.g.*, those comprising monomers of N-vinyl pyrrolidone and vinyl acetate (copovidone) or N-vinyl pyrrolidone and vinyl propionate). Suitable povidones include, without limitation, those having a K- value (a measure of viscosity of an aqueous solution of the povidone) of about 12, about 15, about 17, about 25, about 30 or about 90, and mixtures thereof. In one embodiment, the polymer is polyvinylpyrrolidone K30. In another embodiment, the polymer is poly(1-vinylpyrrolidone-co-vinyl acetate).

[00114] In one embodiment, the polymer is a polyacrylamide.

[00115] In one embodiment, the polymer is a vinyl acetate polymer (*e.g.*, copolymers of vinyl acetate and crotonic acid, polyvinyl acetate, polyvinyl alcohol, or partially hydrolyzed polyvinyl acetate).

[00116] In one embodiment, the polymer is a graft copolymer of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate (*e.g.*, Soluplus™ of BASF or equivalent product).

[00117] In one embodiment, the polymer is an oligo- or polysaccharide (*e.g.*, carrageenans, galactomannans, or xanthan gum).

[00118] In one embodiment, the polymer is methyl cellulose, ethyl cellulose, Eudragit RS 100, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose, Eudragit S 100, hydroxypropyl methylcellulose phthalate 50 (HPMC-P), poly(ethylene glycol) methyl, PEG 6000, polyvinylpyrrolidone K30, poly(1-vinylpyrrolidone-co-vinyl acetate), Sureteric, Pluronic F-68, Tween 80, or hydroxypropyl methylcellulose acetate-succinate (HPMC-AS).

[00119] In one embodiment, the polymer is ethyl cellulose, Eudragit RS 100, HPMC, hydroxypropyl cellulose, HPMC-P, poly(1-vinylpyrrolidone-co-vinyl acetate), or HPMC-AS.

[00120] In one embodiment, the compound (*i.e.*, the compound of Formula (I), *i.e.*, pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof) is present in an amount of from about 1% to about 50%, from about 1% to about 45%, from about 1% to about 40%, from about 1% to about 35%, from about 1% to about 30%, from about 1% to about 25%, from

about 1% to about 20%, from about 1% to about 15%, from about 1% to about 10%, or from about 1% to about 5% by weight of the solid dispersion.

[00121] In one embodiment, the compound is present in an amount of about 1%, about 2%, about 3%, about 4%, about 5%, about 7.5%, about 10%, about 12.5%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, or about 50% by weight of the solid dispersion.

[00122] In one embodiment, the compound is present in an amount of from about 1% to about 50% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of from about 2.5% to about 25% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of from about 2.5% to about 15% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of from about 5% to about 10% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of from about 2.5% to about 7.5% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of about 5% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of about 10% by weight of the solid dispersion. In one embodiment, the compound is present in an amount of about 20% by weight of the solid dispersion.

[00123] In one embodiment, the compound is substantially non-crystalline. In one embodiment, no more than about 20%, no more than about 15%, no more than about 10%, no more than about 5%, no more than about 4%, no more than about 3%, no more than about 2%, or no more than about 1% of the compound is crystalline as observed by X-ray powder diffraction.

[00124] In one embodiment, no more than about 5% of the compound is crystalline as observed by X-ray powder diffraction. In one embodiment, no more than about 2% of the compound is crystalline as observed by X-ray powder diffraction. In one embodiment, no more than about 1% of the compound is crystalline as observed by X-ray powder diffraction.

[00125] In one embodiment, no more than about 5% of the compound is crystalline. In one embodiment, no more than about 2% of the compound is crystalline. In one embodiment, no more than about 1% of the compound is crystalline.

[00126] In one embodiment, the crystalline form of the compound is Form A of the compound. A representative XRPD pattern of Form A of pomalidomide is provided in FIG. 1. In certain embodiments, the XRPD pattern comprises peaks at approximately 12.1, 17.4, 24.4, and 25.6 degrees 2 θ , plus or minus 0.2 degrees 2 θ . Polymorphs of pomalidomide have been described in WO 2013/126326, the entirety of which is incorporated herein by reference.

[00127] In one embodiment, the compound is amorphous.

[00128] In one embodiment, provided herein is a process for preparing a solid dispersion provided herein, comprising (a) providing a solution of the compound (*i.e.*, the compound of Formula (I), *i.e.*, pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof) and the polymer in a solvent system; and (b) removing the solvent to provide the solid dispersion.

[00129] In one embodiment, the solvent system is 1,4-dioxane, tetrahydrofuran, acetone, ethanol, water, or a mixture thereof. In one embodiment, the solvent system is tetrahydrofuran, acetone, water, or a mixture thereof. In one embodiment, the solvent system is acetone, a mixture of tetrahydrofuran and water, or a mixture of acetone and water.

[00130] In one embodiment, the solvent is acetone. In another embodiment, the solvent is ethanol.

[00131] In one embodiment, the solvent is a mixture of tetrahydrofuran and water. In one embodiment, the mixture has from about 75% to about 99% by volume of tetrahydrofuran and from about 1% to about 25% by volume of water. In one embodiment, the mixture has from about 85% by volume to about 97.5% of tetrahydrofuran and from about 2.5% to about 15% by volume of water. In one embodiment, the mixture has from about 90% to about 95% by volume of tetrahydrofuran and from about 5% to about 10% by volume of water. In one embodiment, the solvent is a 95/5 (v/v) mixture of tetrahydrofuran and water. In one embodiment, the solvent is a 90/10 (v/v) mixture of tetrahydrofuran and water.

[00132] In one embodiment, the solvent is a mixture of acetone and water. In one embodiment, the mixture has from about 75% to about 99% by volume of acetone and from about 1% to about 25% by volume of water. In one embodiment, the mixture has from about 85% to about 97.5% by volume of acetone and from about 2.5% to about 15% by volume of water. In one embodiment, the mixture has from about 90% to about 95% by volume of acetone and from about 5% to about 10% by volume of water. In one embodiment, the solvent is a 95/5 (v/v) mixture of acetone and water. In one embodiment, the solvent is a 90/10 (v/v) mixture of acetone and water.

[00133] In one embodiment, the solvent is removed by freeze evaporation.

[00134] In one embodiment, provided herein is a process for preparing a solid dispersion provided herein, comprising melting a mixture of the compound and the polymer.

[00135] In one embodiment, provided herein is a solid dispersion comprising from about 2.5% to about 25% by weight of the solid dispersion of substantially non-crystalline pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a cellulose ether or cellulose ester polymer. In one embodiment, the amount of pomalidomide is from

about 2.5% to about 15% by weight of the solid dispersion. In one embodiment, the amount of pomalidomide is from about 5% to about 10% by weight of the solid dispersion.

[00136] In one embodiment, the solid dispersion comprises about 20% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-P. In one embodiment, the solid dispersion comprise about 10% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-P. In one embodiment, the solid dispersion comprise about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-P. In one embodiment, the solid dispersion is obtained by freeze drying a solution of pomalidomide and HPMC-P in a mixture solvent of acetone and water. In one embodiment, the ratio of acetone to water is about 90/10 v/v.

[00137] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-P. In one embodiment, the solid dispersion is a powder. In one embodiment, the solid dispersion is a film. In one embodiment, the solid dispersion exhibits a mass loss of about 1.8%, as determined by TGA, upon heating from about 25 °C to about 100 °C. In one embodiment, the solid dispersion exhibits a mass loss of about 2.3%, as determined by TGA, upon heating from about 25 °C to about 150 °C. In one embodiment, the solid dispersion exhibits a mass loss of about 3.1%, as determined by TGA, upon heating from about 25 °C to about 170 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of acetone. In one embodiment, the solid dispersion exhibits no clear glass transition (T_g) temperature between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 3 months. In one embodiment, the solid dispersion exhibits about 10% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 6% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 9A, FIG. 9B, FIG. 10, and/or FIG. 11.

[00138] In one embodiment, the solid dispersion comprises about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC. In one embodiment, the solid dispersion comprises about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC. In one embodiment, the solid dispersion comprises about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC. In one embodiment, the

solid dispersion is obtained by freeze drying a solution of pomalidomide and HPMC in a mixture solvent of acetone and water. In one embodiment, the ratio of acetone to water is about 90/10 v/v.

[00139] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC. In one embodiment, the solid dispersion is a powder. In one embodiment, the solid dispersion exhibits a mass loss of about 2.5%, as determined by TGA, upon heating from about 25 °C to about 100 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of acetone. In one embodiment, the solid dispersion exhibits no clear glass transition (T_g) temperature between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 3 months. In one embodiment, the solid dispersion exhibits about 23% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 15% of water absorption at about 80% RH. In one embodiment, the solid dispersion is hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 18.

[00140] In one embodiment, provided herein is a solid dispersion comprising about 10% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC. In one embodiment, the solid dispersion is a powder. In one embodiment, the solid dispersion exhibits a mass loss of about 1.9%, as determined by TGA, upon heating from about 25 °C to about 100 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of acetone. In one embodiment, the solid dispersion exhibits no clear glass transition (T_g) temperature between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH for about 3 months. In one embodiment, the solid dispersion exhibits trace amount of crystallinity upon exposure to about 40 °C/75% RH for about 2 weeks. In one embodiment, the solid dispersion exhibits about 24% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 13% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 19.

[00141] In one embodiment, the solid dispersion comprises about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS LG. In one embodiment, the solid dispersion comprises about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS LG. In one embodiment, the solid dispersion comprises about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS LG. In one embodiment, the solid dispersion is obtained by freeze drying a solution of pomalidomide and HPMC-AS LG in a mixture solvent of tetrahydrofuran and water. In one embodiment, the ratio of tetrahydrofuran to water is about 95/5 v/v.

[00142] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS LG. In one embodiment, the solid dispersion exhibits a mass loss of from 2.25%, as determined by TGA, upon heating from about 25 °C to about 170 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of THF. In one embodiment, the solid dispersion exhibits no melting event between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 2 months. In one embodiment, the solid dispersion exhibits about 11.2% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 8% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 21, FIG. 22, and/or FIG. 23.

[00143] In one embodiment, the solid dispersion comprises about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS MG. In one embodiment, the solid dispersion comprises about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS MG. In one embodiment, the solid dispersion comprises about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS MG. In one embodiment, the solid dispersion is obtained by freeze drying a solution of pomalidomide and HPMC-AS MG in a mixture solvent of tetrahydrofuran and water. In one embodiment, the ratio of tetrahydrofuran to water is about 95/5 v/v.

[00144] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS MG. In one

embodiment, the solid dispersion exhibits a mass loss of about 1.86%, as determined by TGA, upon heating from about 25 °C to about 170 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of THF. In one embodiment, the solid dispersion exhibits a glass transition with midpoint at about 111 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 1 month. In one embodiment, the solid dispersion exhibits about 10.2% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 8% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 24, FIG. 25, and/or FIG. 26.

[00145] In one embodiment, the solid dispersion comprises about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS HG. In one embodiment, the solid dispersion comprises about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS HG. In one embodiment, the solid dispersion comprises about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS HG. In one embodiment, the solid dispersion is obtained by freeze drying a solution of pomalidomide and HPMC-AS HG in a mixture solvent of tetrahydrofuran and water. In one embodiment, the ratio of tetrahydrofuran to water is about 95/5 v/v.

[00146] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises HPMC-AS HG. In one embodiment, the solid dispersion exhibits a mass loss of about 1.45%, as determined by TGA, upon heating from about 25 °C to about 170 °C. In one embodiment, the solid dispersion exhibits a mass loss of about 1.73%, as determined by TGA, upon heating from about 25 °C to about 170 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of THF. In one embodiment, the solid dispersion exhibits a glass transition with midpoint at about 108 °C, as determined by DSC. In one embodiment, the solid dispersion exhibits a glass transition with midpoint at about 116 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 1 month. In one embodiment, the solid dispersion exhibits about 13.2% water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 9% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased

solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 27, FIG. 28, and/or FIG. 29.

[00147] In one embodiment, provided herein is a solid dispersion comprising from about 2.5% to about 25% by weight of substantially non-crystalline pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a polyacrylate or polymethacrylate polymer. In one embodiment, the amount of pomalidomide is from about 2.5% to about 15% by weight. In one embodiment, the amount of pomalidomide is from about 5% to about 10% by weight.

[00148] In one embodiment, the solid dispersion comprises about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises Eudragit RS 100. In one embodiment, the solid dispersion comprises about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises Eudragit RS 100. In one embodiment, the solid dispersion comprises about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises Eudragit RS 100. In one embodiment, the solid dispersion is obtained by freeze drying a solution of pomalidomide and Eudragit RS100 in a mixture solvent of tetrahydrofuran and water. In one embodiment, the ratio of tetrahydrofuran to water is about 95/5 v/v.

[00149] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises Eudragit RS 100. In one embodiment, the solid dispersion is a powder. In one embodiment, the solid dispersion exhibits a mass loss of about 0.7%, as determined by TGA, upon heating from about 25 °C to about 130 °C. In one embodiment, the solid dispersion exhibits a mass loss of about 0.5%, as determined by TGA, upon heating from about 25 °C to about 160 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of THF. In one embodiment, the solid dispersion exhibits no clear glass transition (T_g) temperature between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 3 months. In one embodiment, the solid dispersion exhibits about 5.2% of water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 3.5% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in

water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 12A, FIG. 12B, FIG. 13, and/or FIG. 14.

[00150] In one embodiment, provided herein is a solid dispersion comprising about 10% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises Eudragit RS 100. In one embodiment, the solid dispersion is a powder. In one embodiment, the solid dispersion exhibits a mass loss of about 0.6%, as determined by TGA, upon heating from about 25 °C to about 130 °C. In one embodiment, the solid dispersion exhibits a mass loss of about 0.6%, as determined by TGA, upon heating from about 25 °C to about 160 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residue solvent of THF. In one embodiment, the solid dispersion exhibits no clear glass transition (T_g) temperature between about 25 °C and about 350 °C, as determined by DSC. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH for about 3 months. In one embodiment, the solid dispersion crystallizes upon exposure to about 40 °C/75% RH for about 2 weeks. In one embodiment, the solid dispersion exhibits about 5.2% of water absorption at about 95% RH. In one embodiment, the solid dispersion exhibits about 3% of water absorption at about 80% RH. In one embodiment, the solid dispersion is moderately hygroscopic. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 15A, FIG. 15B, FIG. 16, and/or FIG. 17.

[00151] In one embodiment, provided herein is a solid dispersion comprising from about 2.5% to about 25% by weight of substantially non-crystalline pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, and a polyalkylene oxide polymer. In one embodiment, the amount of pomalidomide is from about 2.5% to about 15% by weight of the solid dispersion. In one embodiment, the amount of pomalidomide is from about 5% to about 10% by weight of the solid dispersion.

[00152] In one embodiment, the solid dispersion comprise about 20% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises PEG 6000. In one embodiment, the solid dispersion comprise about 10% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises PEG 6000. In one embodiment, the solid dispersion comprise about 5% by weight of an amorphous pomalidomide, dispersed in a solid matrix that comprises PEG 6000. In one embodiment, the solid dispersion is obtained by melting a mixture of pomalidomide and PEG 6000.

[00153] In one embodiment, provided herein is a solid dispersion comprising about 5% by weight of amorphous pomalidomide, dispersed in a solid matrix that comprises PEG 6000. In one embodiment, the solid dispersion exhibits a mass loss of about 0.2%, as determined by TGA, upon heating from about 25 °C to about 240 °C. Without being limited by a particular theory, the mass loss corresponds to loss of moisture. In one embodiment, the solid dispersion exhibits an endothermic event at about 61.8 °C, as determined by DSC. Without being limited by a particular theory, the endothermic event corresponds to the melting of PEG 6000. In one embodiment, the solid dispersion remains amorphous upon exposure to about 25 °C/58% RH or about 40 °C/75% RH for about 3 months. In one embodiment, the solid dispersion exhibits an increased solubility of pomalidomide in an aqueous media as compared to neat pomalidomide. In one embodiment, the aqueous media is water, 2% HPMC solution in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), or 5% Glycerin solution in water. In one embodiment, the increased solubility is demonstrated in (and can be calculated from) FIG. 20.

[00154] While not intending to be bound by any particular theory, certain solid dispersions provided herein exhibit physical properties, *e.g.*, stability, solubility and/or dissolution rate, appropriate for use in clinical and therapeutic dosage forms. In one embodiment, certain solid dispersions provided herein are appropriate for use in a pediatric (liquid) formulation. In some embodiments, such properties can be determined using techniques such as X-ray diffraction, microscopy, IR spectroscopy and thermal analysis, as described herein and known in the art.

SOLID FORMS COMPRISING POMALIDOMIDE AND A COFORMER

[00155] In one embodiment, provided herein are solid forms (*e.g.*, crystal forms, amorphous forms, or mixtures thereof) comprising (a) pomalidomide, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. In one embodiment, provided herein are solid forms (*e.g.*, crystal forms, amorphous forms, or mixtures thereof) comprising (a) a free base of pomalidomide, or a solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. Pomalidomide can be synthesized or obtained according to a method known in the literature or based upon the teachings herein.

[00156] In one embodiment, pomalidomide can be prepared according to methods described in, for example, U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327; and U.S. Patent Application Publication Nos. 2006/0178402 and 2011/0224440; the entireties of which are incorporated herein by reference.

[00157] The coformer can be any pharmaceutically acceptable coformer known in the art. In one embodiment, the coformer is saccharin, nicotinamide, 4-hydroxybenzamide, orotic acid, succinic acid, L(-)-malic acid, L(+)-arginine, fumaric acid, lactamide, or valerolactam.

[00158] In one embodiment, the coformer is nicotinamide, L-arginine, or orotic acid.

[00159] In one embodiment, solid forms provided herein may be a crystal form or an amorphous form or mixtures thereof (*e.g.*, mixtures of crystal forms, or mixtures of crystal and amorphous forms), which comprises (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. In one embodiment, provided herein is a crystal form comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. In one embodiment, provided herein is a cocrystal comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. In one embodiment, provided herein is an amorphous form comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. In one embodiment, provided herein is a mixture comprising (i) a cocrystal comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer; and (ii) a second form of pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. In one embodiment, the second solid form is a crystalline form of pomalidomide. In one embodiment, the crystalline form is Form A of pomalidomide. In one embodiment, the second solid form is an amorphous form of pomalidomide. In one embodiment, provided herein is a mixture comprising (i) a cocrystal comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer; and (ii) a second solid form of the coformer.

[00160] In one embodiment, provided herein is an unsolvated solid form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an anhydrous solid form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an unsolvated crystal form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an anhydrous crystal form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an unsolvated amorphous form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an anhydrous amorphous form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a solvated solid form comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a hydrated solid form comprising (a) pomalidomide and (b) a coformer (*e.g.*, a hydrate having a stoichiometric or non-stoichiometric amount

of water). In one embodiment, provided herein is a hydrated form of (a) pomalidomide and (b) a coformer, including, but not limited to, a hemihydrate, a monohydrate, a dihydrate, a trihydrate, and the like. In one embodiment, the hydrated form is substantially crystalline. In one embodiment, the hydrated form is substantially amorphous. In one embodiment, the anhydrous form is substantially crystalline. In one embodiment, the anhydrous form is substantially amorphous. In one embodiment, provided herein is an unsolvated cocrystal comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is an anhydrous cocrystal comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a hydrated cocrystal comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a solvated cocrystal comprising (a) pomalidomide and (b) a coformer.

[00161] Certain embodiments herein provide solid forms comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a solid form comprising (a) pomalidomide and (b) a coformer that is substantially crystalline. In one embodiment, provided herein is a cocrystal comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a solid form comprising a cocrystal comprising (a) pomalidomide and (b) a coformer. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising (a) pomalidomide and (b) a coformer and (ii) an amorphous form of pomalidomide. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising (a) pomalidomide and (b) a coformer and (ii) one or more additional crystal forms of pomalidomide.

[00162] Solid forms provided herein can be prepared by the methods described herein, or by techniques, including, but not limited to, heating, cooling, freeze drying, spray drying, lyophilization, quench cooling the melt, rapid solvent evaporation, slow solvent evaporation, solvent recrystallization, antisolvent addition, slurry recrystallization, crystallization from the melt, desolvation, recrystallization in confined spaces, such as, *e.g.*, in nanopores or capillaries, recrystallization on surfaces or templates, such as, *e.g.*, on polymers, recrystallization in the presence of additives, such as, *e.g.*, co-crystal counter-molecules, desolvation, dehydration, rapid cooling, slow cooling, exposure to solvent and/or water, drying, including, *e.g.*, vacuum drying, vapor diffusion, sublimation, grinding (including, *e.g.*, cryo-grinding and solvent-drop grinding), microwave-induced precipitation, sonication-induced precipitation, laser-induced precipitation, and precipitation from a supercritical fluid. The particle size of the resulting solid forms, which can vary (*e.g.*, from nanometer dimensions to millimeter dimensions), can be controlled, *e.g.*, by varying crystallization conditions, such as, *e.g.*, the rate of crystallization and/or the crystallization solvent system, or by particle-size reduction techniques, *e.g.*, grinding, milling, micronizing, or sonication.

[00163] In some embodiments, the cocrystal comprising (a) pomalidomide and (b) a coformer can be obtained by crystallization from certain solvent systems, for example, solvent systems comprising one or more of the following solvents: acetone, N,N-dimethylformamide (DMF), tetrahydrofuran (THF), methanol, 1,4-dioxane, N,N-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), water, acetonitrile, and isopropyl alcohol. Other examples of solvent systems are provided herein elsewhere. In certain embodiments, a solid form provided herein (*e.g.*, a cocrystal comprising (a) pomalidomide and (b) a coformer) can be obtained by slurry crystallization, evaporation crystallization, cooling crystallization, precipitation crystallization, saturated (API) solution co-crystallization, slurry conversion, and wet co-grinding.

[00164] In certain embodiments, cocrystals can be prepared using solid-state methods such as solid-state grinding and solvent-drop grinding. In certain embodiments, cocrystals can be prepared using high-throughput screening. In certain embodiments cocrystals can be prepared using solution-based crystallization.

[00165] In certain embodiments, slurry crystallization is effected by adding solvent or solvent mixtures to a solid substrate, and the slurry is stirred, and optionally heated to various temperatures. In certain embodiments, the slurry is heated at about 25 °C, about 50 °C, about 80 °C, or about 100 °C. In certain embodiments, upon heating and cooling, the residual solvents of the slurry can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[00166] In certain embodiments, evaporation crystallization is effected by adding a solvent or solvent mixture to a solid substrate, and allowing the solvent or solvent mixture to evaporate under ambient conditions. In certain embodiments, the residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[00167] In certain embodiments, precipitation crystallization is effected by adding a solvent or solvent mixture to a solid substrate, and subsequently adding an anti-solvent. In certain embodiments, the resultant mixture stands for a period of time, *e.g.*, overnight, and under certain conditions, for example at room temperature. In certain embodiments, the residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[00168] In certain embodiments, cooling crystallization is effected by adding a solvent or solvent mixture to a solid substrate at elevated temperature, and allowing the resultant mixture to stand for a

period of time at a reduced temperature. In certain embodiments, the elevated temperature is, for example, about 30 °C, about 40 °C, about 50 °C, about 60 °C, about 70 °C, or about 80 °C. In certain embodiments, the reduced temperature is, for example, about 15 °C, about 10 °C, about 5 °C, about 0 °C, about -5 °C, about -10 °C, about -15 °C, or about -20 °C. The residual solvent can be removed by wicking, or other suitable methods, such as filtration, centrifugation, or decantation, and the crystals can be dried in air or under vacuum.

[00169] In certain embodiments, saturated API solution co-crystallization is effected by adding the coformer to a saturated solution of the API, stirring the mixture for a period of time at ambient temperature.

[00170] In certain embodiments, the wet co-grinding is effected by grinding a mixture of the API and coformer in a small amount of solvent.

[00171] In certain embodiments, the non-covalent forces are one or more hydrogen bonds (H-bonds). The coformer may be H-bonded directly to the API or may be H-bonded to an additional molecule which is bound to the API. The additional molecule may be H-bonded to the API or bound ionically or covalently to the API. The additional molecule could also be a different API. In certain embodiments, the co-crystals may include one or more solvate molecules in the crystalline lattice, *i.e.*, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature. In certain embodiments, the co-crystals may be a co-crystal between a coformer and a salt of an API. In certain embodiments, the non-covalent forces are pi-stacking, guest-host complexation and/or van der Waals interactions. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads.

[00172] In certain embodiments, the co-crystals include an acid addition salt or base addition salt of an API. Acid addition salts include, but are not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric

acid, gluconic acid, glutaric acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid. Base addition salts include, but are not limited to, inorganic bases such as sodium, potassium, lithium, ammonium, calcium and magnesium salts, and organic bases such as primary, secondary and tertiary amines (*e.g.*, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, and N-ethylpiperidine).

[00173] The ratio of API to coformer may be stoichiometric or non-stoichiometric. In one embodiment, the ratio of API to coformer is about 5:1, 4:1, 3:1, 2.5:1, 2:1, 1.5:1, 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:4, or 1:5. In one embodiment, the ratio of API to coformer is about 1:1. In one embodiment, the co-crystal comprises more than one coformers. In one embodiment, the co-crystal comprises two coformers.

[00174] The compounds provide herein may also contain an unnatural proportion of an atomic isotope at one or more of the atoms that constitute such a compound. For example, the compound may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) sulfur-35 (^{35}S), or carbon-14 (^{14}C). Radiolabeled compounds are useful as therapeutic agents, *e.g.*, cancer therapeutic agents, research reagents, *e.g.*, binding assay reagents, and diagnostic agents, *e.g.*, *in vivo* imaging agents. All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed herein. In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes, including, but not limited to, hydrogen (^1H), deuterium (^2H), tritium (^3H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes in a stable form, that is, non-radioactive, including, but not limited to, hydrogen (^1H), deuterium (^2H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, a compound provided herein contains unnatural proportion(s) of one or more isotopes in an unstable form, that is, radioactive, including, but not limited to, tritium (^3H),

carbon-11 (^{11}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Cl), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, in a compound as provided herein, any hydrogen can be ^2H , for example, or any carbon can be ^{13}C , for example, or any nitrogen can be ^{15}N , for example, or any oxygen can be ^{18}O , for example, where feasible according to the judgment of one of skill. In certain embodiments, a compound provided herein contains unnatural proportions of deuterium (D). In exemplary embodiments, provided herein are isotopologues of pomalidomide, as disclosed in WO 2012/177678, which is incorporated by reference herein in its entirety. In one embodiment, provided herein are solid forms (*e.g.*, crystal forms, amorphous forms, or mixtures thereof) of isotopologues of pomalidomide provided herein.

[00175] In another embodiment, provided herein are compositions comprising one or more solid form(s) comprising (a) pomalidomide or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and (b) a coformer. Also provided herein are compositions comprising: (i) one or more solid form(s) provided herein (*e.g.*, one or more crystal forms, one or more amorphous forms, and mixtures thereof), and (ii) other active ingredient(s).

[00176] While not intending to be bound by any particular theory, certain solid forms provided herein exhibit physical properties, *e.g.*, solubility, dissolution rate, bioavailability, physical stability, chemical stability, flowability, fractability, or compressibility, appropriate for use in clinical and therapeutic dosage forms. In certain embodiments, a given API may form different cocrystals with many different counter-molecules, and some of these cocrystals may exhibit enhanced solubility or stability. In certain embodiments, pharmaceutical cocrystals increase the bioavailability or stability profile of a compound without the need for chemical (covalent) modification of the API.

Cocrystal Comprising Pomalidomide and Nicotinamide

[00177] Certain embodiments herein provide solid forms comprising pomalidomide and nicotinamide. In one embodiment, provided herein is a solid form comprising pomalidomide and nicotinamide that is substantially crystalline. In one embodiment, provided herein is a cocrystal comprising pomalidomide and nicotinamide. In one embodiment, provided herein is a solid form comprising a cocrystal comprising pomalidomide and nicotinamide. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and nicotinamide and (ii) a second solid form of pomalidomide. In one embodiment, the second solid form of pomalidomide is Form A of pomalidomide. In another embodiment, the second solid form of pomalidomide is amorphous pomalidomide. In one embodiment,

provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and nicotinamide and (ii) a second solid form of nicotinamide.

[00178] In some embodiments, the cocrystal comprising pomalidomide and nicotinamide provided herein is Form NIA.

[00179] In some embodiments, Form NIA is obtained by exposing a solid from comprising pomalidomide and nicotinamide to an aging condition. In one embodiment, Form NIA is obtained by exposing a solid from comprising pomalidomide and nicotinamide to an aging condition of about 40 °C and 75% RH for about 2 days. In one embodiment, the solid from comprising pomalidomide and nicotinamide is obtained by adding nicotinamide to a solvent system saturated with pomalidomide, stirring the mixture (*e.g.*, at ambient temperature for about 4 hours), removing any undissolved solid, and then slowly evaporating the mother liquid. In one embodiment, the solvent system saturated with pomalidomide is a mixture of DMA and acetone. In one embodiment, the solvent system is a 50:50 (v/v) mixture of DMA and acetone. In another embodiment, the solvent system saturated with pomalidomide is a mixture of DMF and acetone. In one embodiment, the solvent system is a 40:60 (v/v) mixture of DMF and acetone.

[00180] In some embodiments, Form NIA has a molar ratio of pomalidomide to nicotinamide of from about 5:1 to about 1:5. In one embodiment, the molar ratio of pomalidomide to nicotinamide is from about 2:1 to about 1:2. In some embodiments, the molar ratio of pomalidomide to nicotinamide is about 1:1.

[00181] A representative overlay of XRPD patterns of Form A of pomalidomide, reference of nicotinamide, a solid form comprising pomalidomide and nicotinamide before exposure to AAC, and cocrystal Form NIA obtained after exposure to AAC is provided in FIG. 36. In some embodiments, Form NIA is characterized by one or more XRPD peaks (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more peaks) selected from peaks located at the following or approximately the following positions: 6.3, 14.0, 15.4, 17.8, 20.3, 20.8, 21.9, 23.2, 24.2, 25.2, 27.0, 27.7, 28.6, and 36.1 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In some embodiments, Form NIA is characterized by 3 of the peaks. In some embodiments, Form NIA is characterized by 5 of the peaks. In some embodiments, Form NIA is characterized by 7 of the peaks. In some embodiments, Form NIA is characterized by 10 of the peaks. In some embodiments, Form NIA is characterized by 13 of the peaks. In some embodiments, Form NIA is characterized by all of the peaks.

[00182] In some embodiments, Form NIA is characterized by an XRPD pattern comprising peaks at approximately 17.8, 21.9, and 27.0 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the

XRPD pattern further comprises peaks at approximately 15.4 and 27.7 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 20.3 and 28.6 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In one embodiment, Form NIA is characterized by an XRPD pattern comprising peaks at approximately 6.3, 14.0, 15.4, 17.8, 20.3, 20.8, 21.9, 23.2, 24.2, 25.2, 27.0, 27.7, 28.6, and 36.1 degrees 2 θ , plus or minus 0.2 degrees 2 θ .

[00183] In some embodiments, the XRPD peaks above (degrees 2 θ peaks) are when analyzed using copper K α radiation. In some embodiments, Form NIA is characterized by an XRPD pattern comprising is characterized by an XRPD diffraction pattern which matches the Form NIA XRPD pattern presented in FIG. 36.

[00184] In some embodiments, Form NIA exhibits substantially no mass loss, as determined by TGA, upon heating from about 25 °C to about 170 °C.

[00185] In some embodiments, Form NIA exhibits an endothermic event, as determined by DSC, at about 138 °C. Without being limited by a particular theory, the event corresponds to melting.

[00186] In one embodiment, Form NIA is anhydrous.

[00187] In some embodiments, Form NIA is characterized by an FTIR spectrum which matches the FTIR spectrum presented in FIG. 37A and/or FIG. 37B.

Cocrystal Comprising Pomalidomide and L-Arginine

[00188] Certain embodiments herein provide solid forms comprising pomalidomide and L-arginine. In one embodiment, provided herein is a solid form comprising pomalidomide and L-arginine that is substantially crystalline. In one embodiment, provided herein is a cocrystal comprising pomalidomide and L-arginine. In one embodiment, provided herein is a solid form comprising a cocrystal comprising pomalidomide and L-arginine. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and L-arginine and (ii) a second solid form of pomalidomide. In one embodiment, the second solid form of pomalidomide is Form A of pomalidomide. In another embodiment, the second solid form of pomalidomide is amorphous pomalidomide. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and L-arginine and (ii) a second solid form of L-arginine.

[00189] In some embodiments, the cocrystal comprising pomalidomide and L-arginine provided herein is Form ARG.

[00190] In some embodiments, Form ARG is obtained by removing solvent from a solution containing pomalidomide and L-arginine. In one embodiment, Form ARG is obtained by slowly evaporating solvent from a solution saturated or nearly saturated with pomalidomide and L-arginine. In one embodiment, the solvent is a mixture of DMF and acetone. In one embodiment, the solvent is a 40:60 (v/v) mixture of DMF and acetone. In one embodiment, the solution containing pomalidomide and L-arginine is obtained by dissolving a mixture of pomalidomide and L-arginine in the solvent followed by removing any undissolved solid. In one embodiment, the molar ratio of pomalidomide to L-arginine in the mixture is from about 1:1 to about 1:5. In one embodiment, the ratio is from about 1:1.1 to about 1:4. In one embodiment, the ratio is about 1:1.1. In another embodiment, the ratio is about 1:4.

[00191] In some embodiments, Form ARG has a molar ratio of pomalidomide to L-arginine of from about 5:1 to about 1:5. In one embodiment, the molar ratio of pomalidomide to L-arginine is from about 2:1 to about 1:2. In some embodiments, the molar ratio of pomalidomide to L-arginine is about 1:1.

[00192] A representative overlay of XRPD patterns of Form A of pomalidomide, reference of L-arginine, Form A and cocrystal Form ARG before exposure to AAC, and Form A and L-arginine obtained after exposure to AAC is provided in FIG. 38. In some embodiments, Form ARG is characterized by one or more XRPD peaks (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more peaks) selected from peaks located at the following or approximately the following positions: 11.6, 12.3, 14.1, 16.0, 18.8, 19.8, 20.8, 23.4, 25.5, 26.9, and 28.1 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In some embodiments, Form ARG is characterized by 3 of the peaks. In some embodiments, Form ARG is characterized by 5 of the peaks. In some embodiments, Form ARG is characterized by 7 of the peaks. In some embodiments, Form ARG is characterized by 10 of the peaks. In some embodiments, Form ARG is characterized by all of the peaks.

[00193] In some embodiments, Form ARG is characterized by an XRPD pattern comprising peaks at approximately 16.0, 19.8, and 23.4 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 25.5 and 26.9 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 12.3 and 18.8 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In one embodiment, Form ARG is characterized by an XRPD pattern comprising peaks at approximately 11.6, 12.3, 14.1, 16.0, 18.8, 19.8, 20.8, 23.4, 25.5, 26.9, and 28.1 degrees 2 θ , plus or minus 0.2 degrees 2 θ .

[00194] In some embodiments, the XRPD peaks above (degrees 2 θ peaks) are when analyzed using copper K α radiation. In some embodiments, Form ARG is characterized by an XRPD pattern comprising is characterized by an XRPD diffraction pattern which matches the Form ARG XRPD pattern presented in FIG. 38.

[00195] In some embodiments, Form ARG exhibits a mass loss of about 2.2%, as determined by TGA, upon heating from about 25 °C to about 200 °C. Without being limited by a particular theory, the mass loss corresponds to loss of residual solvent of acetone and DMF.

[00196] In some embodiments, Form ARG exhibits an endothermic event, as determined by DSC, at about 224 °C. Without being limited by a particular theory, the event corresponds to melting and/or thermal decomposition.

[00197] In one embodiment, Form ARG is anhydrous.

[00198] In some embodiments, Form ARG is characterized by an FTIR spectrum which matches the FTIR spectrum presented in FIG. 39A and/or FIG. 39B.

Cocrystal Comprising Pomalidomide and Orotic Acid

[00199] Certain embodiments herein provide solid forms comprising pomalidomide and orotic acid. In one embodiment, provided herein is a solid form comprising pomalidomide and orotic acid that is substantially crystalline. In one embodiment, provided herein is a cocrystal comprising pomalidomide and orotic acid. In one embodiment, provided herein is a solid form comprising a cocrystal comprising pomalidomide and orotic acid. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and orotic acid and (ii) a second solid form of pomalidomide. In one embodiment, the second solid form of pomalidomide is Form A of pomalidomide. In another embodiment, the second solid form of pomalidomide is amorphous pomalidomide. In one embodiment, provided herein is a solid form comprising (i) a cocrystal comprising pomalidomide and orotic acid and (ii) a second solid form of orotic acid.

[00200] In some embodiments, the cocrystal comprising pomalidomide and orotic acid provided herein is Form ORO1.

[00201] In some embodiments, Form ORO1 is obtained by adding orotic acid to a solution saturated with pomalidomide. In one embodiment, Form ORO1 is obtained by adding orotic acid to a solution saturated with pomalidomide, stirring the mixture (*e.g.*, at ambient temperature for about 4 hours), removing any undissolved solid, and then slowly evaporating the mother liquid. In one embodiment, the solvent is a mixture of DMF and acetone. In one embodiment, the solvent is a 40:60 (v/v) mixture of DMF and acetone.

[00202] In some embodiments, Form ORO1 is obtained by slurring a mixture of pomalidomide and orotic acid in a solvent. In one embodiment, the solvent is a mixture of 1,4-dioxane and water. In one

embodiment, the solvent is a 50:50 (v/v) mixture of 1,4-dioxane and water. In one embodiment, the molar ratio of pomalidomide to orotic acid in the mixture is from about 1:1 to about 1:5. In one embodiment, the ratio is from about 1:1.1 to about 1:4. In one embodiment, the ratio is about 1:1.1. In another embodiment, the ratio is about 1:4.

[00203] In some embodiments, Form ORO1 has a molar ratio of pomalidomide to orotic acid of from about 5:1 to about 1:5. In one embodiment, the molar ratio of pomalidomide to orotic acid is from about 2:1 to about 1:2. In some embodiments, the molar ratio of pomalidomide to orotic acid is about 1:1.

[00204] A representative overlay of XRPD patterns of Form A of pomalidomide, reference of orotic acid, Form A and cocrystal Form ORO1 before exposure to AAC, and Form A and orotic acid obtained after exposure to AAC is provided in FIG. 40. In some embodiments, Form ORO1 is characterized by one or more XRPD peaks (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more peaks) selected from peaks located at the following or approximately the following positions: 6.9, 12.3, 14.0, 16.2, 17.3, 18.4, 18.9, 20.8, 22.1, 22.7, 24.3, 24.8, 25.5, 28.2, 29.2, and 33.9 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In some embodiments, Form ORO1 is characterized by 3 of the peaks. In some embodiments, Form ORO1 is characterized by 5 of the peaks. In some embodiments, Form ORO1 is characterized by 7 of the peaks. In some embodiments, Form ORO1 is characterized by 10 of the peaks. In some embodiments, Form ORO1 is characterized by 13 of the peaks. In some embodiments, Form ORO1 is characterized by all of the peaks.

[00205] In some embodiments, Form ORO1 is characterized by an XRPD pattern comprising peaks at approximately 14.0, 25.5, and 28.2 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 12.3 and 17.3 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 22.7 and 24.3 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In one embodiment, Form ORO1 is characterized by an XRPD pattern comprising peaks at approximately 6.9, 12.3, 14.0, 16.2, 17.3, 18.4, 18.9, 20.8, 22.1, 22.7, 24.3, 24.8, 25.5, 28.2, 29.2, and 33.9 degrees 2 θ , plus or minus 0.2 degrees 2 θ .

[00206] In some embodiments, the XRPD peaks above (degrees 2 θ peaks) are when analyzed using copper K α radiation. In some embodiments, Form ORO1 is characterized by an XRPD pattern comprising is characterized by an XRPD diffraction pattern which matches the Form ORO1 XRPD pattern presented in FIG. 40.

[00207] In some embodiments, Form ORO1 exhibits a mass loss of about 8.8%, as determined by TGA, upon heating from about 25 °C to about 110 °C. Without being limited by a particular theory, the

mass loss corresponds to loss of solvent. In one embodiment, the mass loss corresponds to loss of about 0.3 equivalent of 1,4-dioxane.

[00208] In some embodiments, Form ORO1 exhibits an endothermic event, as determined by DSC, at about 168 °C. Without being limited by a particular theory, the event corresponds to melting and/or solvent loss.

[00209] In one embodiment, Form ORO1 is a solvate. In one embodiment, Form ORO1 is a 1,4-dioxane solvate. In another embodiment, Form ORO1 is a DMF solvate.

[00210] In some embodiments, Form ORO1 is characterized by an FTIR spectrum which matches the FTIR spectrum presented in FIG. 41A and/or FIG. 41B.

[00211] In some embodiments, the cocrystal comprising pomalidomide and orotic acid provided herein is Form ORO2.

[00212] In some embodiments, Form ORO2 is obtained by adding orotic acid to a solution saturated with pomalidomide. In one embodiment, Form ORO2 is obtained by adding orotic acid to a solution saturated with pomalidomide, stirring the mixture (*e.g.*, at ambient temperature for about 4 hours), removing any undissolved solid, and then slowly evaporating the mother liquid. In one embodiment, the solvent is a mixture of DMF and methanol. In one embodiment, the solvent is a 50:50 (v/v) mixture of DMF and methanol. In another embodiment, the solvent is a mixture of DMA and acetone. In one embodiment, the solvent is a 50:50 (v/v) mixture of DMA and acetone. In another embodiment, the solvent is a mixture of DMSO and water. In one embodiment, the solvent is a 80:20 (v/v) mixture of DMSO and water.

[00213] In some embodiments, Form ORO2 has a molar ratio of pomalidomide to orotic acid of from about 5:1 to about 1:5. In one embodiment, the molar ratio of pomalidomide to orotic acid is from about 2:1 to about 1:2. In some embodiments, the molar ratio of pomalidomide to orotic acid is about 1:1.

[00214] A representative overlay of XRPD patterns of Form A of pomalidomide, reference of orotic acid, cocrystal Form ORO2 before exposure to AAC, and Form A and orotic acid obtained after exposure to AAC is provided in FIG. 42. In some embodiments, Form ORO2 is characterized by one or more XRPD peaks (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or more peaks) selected from peaks located at the following or approximately the following positions: 9.9, 14.7, 17.9, 21.0, 23.3, 24.1, 25.0, 26.9, 30.0, 32.6, 37.6, and 38.2 degrees 2 θ , plus or minus 0.2 degrees 2 θ . In some embodiments, Form ORO2 is characterized by 3 of the peaks. In some embodiments, Form ORO2 is characterized by 5 of the peaks. In some embodiments, Form ORO2 is characterized by 7 of the peaks. In some embodiments, Form

ORO2 is characterized by 10 of the peaks. In some embodiments, Form ORO2 is characterized by all of the peaks.

[00215] In some embodiments, Form ORO2 is characterized by an XRPD pattern comprising peaks at approximately 9.9, 24.1, and 26.9 degrees 2θ , plus or minus 0.2 degrees 2θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 21.0 and 25.0 degrees 2θ , plus or minus 0.2 degrees 2θ . In certain embodiments, the XRPD pattern further comprises peaks at approximately 17.9 and 23.3 degrees 2θ , plus or minus 0.2 degrees 2θ . In one embodiment, Form ORO2 is characterized by an XRPD pattern comprising peaks at approximately 9.9, 14.7, 17.9, 21.0, 23.3, 24.1, 25.0, 26.9, 30.0, 32.6, 37.6, and 38.2 degrees 2θ , plus or minus 0.2 degrees 2θ .

[00216] In some embodiments, the XRPD peaks above (degrees 2θ peaks) are when analyzed using copper K α radiation. In some embodiments, Form ORO2 is characterized by an XRPD pattern comprising is characterized by an XRPD diffraction pattern which matches the Form ORO2 XRPD pattern presented in FIG. 42.

[00217] In some embodiments, Form ORO2 exhibits a mass loss of about 27.9%, as determined by TGA, upon heating from about 25 °C to about 110 °C. Without being limited by a particular theory, the mass loss corresponds to loss of solvent. In one embodiment, the mass loss corresponds to loss of about 1.4 equivalent of DMSO.

[00218] In some embodiments, Form ORO2 exhibits an endothermic event, as determined by DSC, at about 110 °C. Without being limited by a particular theory, the event corresponds to solvent loss.

[00219] In one embodiment, Form ORO2 is a solvate. In one embodiment, Form ORO2 is a DMSO solvate. In another embodiment, Form ORO2 is a DMA solvate. In another embodiment, Form ORO2 is a DMF solvate.

[00220] In some embodiments, Form ORO2 is characterized by an FTIR spectrum which matches the FTIR spectrum presented in FIG. 43A and/or FIG. 43B.

METHODS OF TREATMENT, PREVENTION AND MANAGEMENT

[00221] Provided herein are methods of treating, preventing, and/or managing various diseases or disorders using a solid dispersion or solid form provided herein. In certain embodiments, provided are methods of treating, managing, and preventing various diseases and disorders, which comprise administering to a patient in need of such treatment, prevention or management a therapeutically or

prophylactically effective amount of a solid dispersion or solid form provided herein. Examples of diseases and disorders are described herein.

[00222] Examples of diseases and disorders include, but are not limited to: cancer, including hematologic cancer or solid tumor, for example, multiple myeloma, leukemia, lymphoma, sarcoma; amyloidosis; an immunodeficiency disorder; a CNS disorder; a CNS injury; sickle cell anemia; an inflammatory disease; an autoimmune disease; a viral disease; a genetic disease; Central Nervous System Tumors including glioma, nervous system neoplasms, neuroepithelioma, neurofibroma, neurofibromatosis, optic nerve glioma, medulloblastoma, ependymoma, diffuse intrinsic pontine glioma, cranial nerve disease, cranial nerve neoplasms, ocular diseases, neuroepithelial neoplasms, nerve sheath neoplasms, neurocutaneous syndromes, optic nerve neoplasms, peripheral nervous system diseases, central nervous system germ cell tumors, craniopharyngiomas, choroid plexus tumors, meningiomas and atypical teratoid rhabdoid tumors.

[00223] In one embodiment, provided herein is a method of treating, preventing and/or managing a disease provided herein, comprising administering to a patient in need of such treatment, prevention and/or management a therapeutically or prophylactically effective amount of a solid dispersion or solid form comprising pomalidomide as described herein and a therapeutically or prophylactically effective amount of a second active agent.

[00224] Examples of second active agents include, but are not limited to, cytokines, corticosteroids, ribonucleotide reductase inhibitors, platelet inhibitors, all-trans retinoic acids, kinase inhibitors, topoisomerase inhibitors, farnesyl transferase inhibitors, antisense oligonucleotides, vaccines, anti-cancer agents, anti-fungal agents, anti-inflammatory agents, immunosuppressive or myelosuppressive agents, and conventional therapies for MPD (*e.g.*, prednisone). Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in multiple myeloma cells (such as, for example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense[®]), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron[®]), steroids, gemcitabine, cisplatin, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa[®], taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, paclitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil[®]), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt[®]), sulindac, etoposide, and a mixture thereof. In one embodiment, specific second active agent is dexamethasone.

[00225] In one embodiment, provided herein are pharmaceutical compositions, single unit dosage forms, and kits, comprising a solid dispersion or solid form comprising pomalidomide as described herein, a second active ingredient, and/or blood or cells for transplantation therapy. For example, a kit may comprise a solid dispersion or solid form comprising pomalidomide as described herein, stem cells for transplantation, an immunosuppressive agent, and an antibiotic or other drug.

[00226] In one embodiment, provided herein is a method of modulating the differentiation of CD34⁺ stem, precursor, or progenitor cells to a predominantly erythroid lineage, comprising administering to a patient an effective amount of a solid dispersion or solid form comprising pomalidomide as described herein.

[00227] In one embodiment, provided herein is a method of modulating differentiation of a CD34⁺ cell to an erythroid lineage comprising differentiating said cell under suitable conditions and in the presence of pomalidomide.

[00228] The CD34⁺ cell may be any stem, progenitor, or committed cell able to differentiate into an erythroid cell. Such cells may be totipotent or pluripotent, or may be committed to a hematopoietic lineage. The CD34⁺ cell may be derived from any source; in particular embodiments, “embryonic-like” stem cells derived from the placenta. For a description of such embryonic-like stem cells and methods of obtaining them, see U.S. application publication no. US 2003/0180269 A1, published September 25, 2003, which is incorporated by reference herein in its entirety. Other CD34⁺ cells useful for the methods provided herein include stem cells obtained from any tissue (such as, for example, hematopoietic stem cells or embryonic stem cells) and non-committed progenitor cells from any tissue. Such CD34⁺ cells may be heterologous or autologous with reference to the intended recipient, when such cells, the differentiation of which is modulated according to the methods provided herein, are used to treat anemia or a hemoglobinopathy.

[00229] Differentiation of the CD34⁺ cells may typically take place over the course of 3-6 days. In *in vitro* assays in which CD34⁺ cells are cultured in the presence of pomalidomide, changes in gene expression indicating differentiation along an erythroid pathway may be evident by the third day of culture. In one embodiment, erythroid-specific gene expression is significantly increased, and phenotypic characteristics of erythroid cells are present in the CD34⁺ cells by day 6 of culture.

[00230] In one embodiment, therefore, CD34⁺ cells may be cultured *in vitro* in the presence of pomalidomide, for a period of days sufficient for erythroid-specific gene expression, particularly fetal hemoglobin gene expression, and/or cell characteristics to appear. In various embodiments, the CD34⁺ cells may be cultured for 3, 6, 9, or 12 days, or more. A solid dispersion or solid form comprising

pomalidomide or a solution thereof may be introduced once at the start of culture, and culturing continued until differentiation is substantially complete, or for 3, 6, 9, 12 or more days. Alternatively, a solid dispersion or solid form comprising pomalidomide or a solution thereof may be administered to a culture of CD34⁺ cells a plurality of times during culture. The CD34⁺ cells may be cultured and differentiated in the presence pomalidomide.

[00231] In one embodiment, a solid dispersion or solid form comprising pomalidomide may be used as a solution at any concentration from 0.01 μ M to 10 mM. In certain embodiments, the concentration is between 0.01 μ M and 10 μ M.

[00232] In addition to differentiating CD34⁺ cells *in vitro*, such cells may be differentiated within an individual, *in vivo*. In one embodiment, such an individual is a mammal, for example a human. As with *in vitro* differentiation of CD34⁺ cells, CD34⁺ cells within an individual may be differentiated by administration of a solid dispersion or solid form comprising pomalidomide as described herein. Such administration may be in the form of a single dose. Alternatively, the individual may be administered a solid dispersion or solid form comprising pomalidomide as described herein a plurality of times. Such administration may be performed, for example, over a period of 3, 6, 9, 12, or more days.

[00233] Where differentiation of CD34⁺ cells is to be accomplished *in vivo*, differentiation may be accomplished using pomalidomide alone, or a combination with a second active agent. For example, for an individual having a hemoglobinopathy such as sickle cell anemia or a thalassemia, who has a higher than normal level of SCF and/or erythropoietin, *in vivo* differentiation may be accomplished by administration of a solid dispersion or solid form comprising pomalidomide as described herein. Conversely, where an individual suffers an anemia that is the result of, or is characterized by, a lower-than-normal level of erythropoietic cytokines (*e.g.*, SCF or erythropoietin), such cytokines may be administered along with, or prior to, administration of a solid dispersion or solid form comprising pomalidomide. For example, an individual suffering from chemotherapy-induced anemia may be administered one or more cytokines (*e.g.*, a combination of SCF, Flt-3L, and/or IL-3) for, *e.g.*, 3-6 days, followed by administration for, *e.g.*, 3-6 days, of the solid dispersion or solid form comprising pomalidomide, particularly with SCF and erythropoietin, in an amount sufficient to cause a detectable increase in fetal hemoglobin expression in CD34⁺ cells of said individual. Alternatively, CD34⁺ cells may be contacted with one or more cytokines *in vitro* (*e.g.*, SCF, Flt-3L, and/or IL-3) for, *e.g.*, 3-6 days, followed by administration of the cells to an individual, along with SCF and erythropoietin in an amount sufficient to cause a detectable increase in fetal hemoglobin expression in the CD34⁺ cells. Such administration may be performed a single time or multiple times, and any one or more of such

administrations may be accompanied by the administration of a solid dispersion or solid form comprising pomalidomide, a second active agent, or a combination thereof.

[00234] In one embodiment is provided a method of inducing one or more genes associated with or essential for erythropoiesis or hematopoiesis, comprising contacting an hematopoietic stem, progenitor or precursor cell with pomalidomide in the presence of erythropoietin and stem cell factor, wherein said pomalidomide is present in a sufficient amount to cause said hematopoietic stem, progenitor or precursor cell to express one or more genes encoding fetal hemoglobin. In a specific embodiment, said hematopoietic stem, progenitor or precursor cell is a CD34⁺ cell. In another specific embodiment, said one or more genes associated with or essential for erythropoiesis or hematopoiesis are genes encoding Kruppel-like factor 1 erythroid; rhesus blood group-associated glycoprotein; glycophorin B; integrin alpha 2b; erythroid-associated factor; glycophorin A; Kell blood group precursor; hemoglobin α 2; solute carrier 4, anion exchanger; carbonic anhydrase hemoglobin γ A; hemoglobin γ G; hemoglobin ϵ 1; or any combination of the foregoing.

[00235] In some embodiments, the CD34⁺ cells are additionally differentiated, either *in vivo* or *in vitro*, in the presence of one or more cytokines. Cytokines useful to direct CD34⁺ cells along an erythroid differentiation pathway include, but are not limited to, erythropoietin (Epo), TNF α , stem cell factor (SCF), Flt-3L, and granulocyte macrophage-colony stimulating factor (GM-CSF). Epo and SCF are known to be erythropoietic cytokines. Thus, in one embodiment, CD34⁺ cells are differentiated in the presence of Epo or SCF. In another embodiment, the CD34⁺ cells are differentiated in the presence of Epo and SCF. In another embodiment, the CD34⁺ cells are differentiated in the presence of a combination of TNF α , SCF, Flt-3L, and/or GM-CSF. In another embodiment, said cells that are differentiated are one or more cells in cell culture. In another embodiment, said cells that are differentiated are cells within an individual. In an embodiment of *in vitro* differentiation, one or more of Epo, TNF α , SCF, Flt-3L and GM-CSF is contacted with pomalidomide. In an embodiment of *in vivo* differentiation, one or more of Epo, TNF α , SCF, Flt-3L and GM-CSF is administered to an individual in the same treatment regimen as the solid dispersion or solid form comprising pomalidomide as provided herein.

[00236] The cytokines used in the methods provided herein may be naturally-occurring cytokines, or may be an artificial derivative or analog of the cytokines. For example, analogs or derivatives of erythropoietin that may be used in combination with a solid dispersion or solid form provided herein include, but are not limited to, Aranesp[™] and Darbopoietin[™].

[00237] Cytokines used may be purified from natural sources or recombinantly produced. Examples of recombinant cytokines that may be used in the methods provided herein include filgrastim, or

recombinant granulocyte-colony stimulating factor (G-CSF), which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, CA); sargramostim, or recombinant GM-CSF, which is sold in the United States under the trade name Leukine® (Immunex, Seattle, WA); recombinant Epo, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, CA); and methionyl stem cell factor (SCF), which is sold in the United States under the trade name Ancestim™. Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. patent nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. patent nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference.

[00238] Other cytokines may be used which encourage the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells *in vitro* or *in vivo*, or which stimulate the division and differentiation of committed erythroid progenitors in cells *in vitro* or *in vivo*. Such cytokines include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-II (“rIL2”) and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-I a, and interferon gamma-I b; and G-CSF.

[00239] When administered to a person having a hemoglobinopathy, a solid dispersion or solid form comprising pomalidomide as described herein, particularly in the presence of Epo, particularly in the presence of the combination of TNF α , SCF, Flt-3L and GM-CSF, or more particularly in the presence of Epo and SCF, induces the production of erythrocytes, and the production of fetal hemoglobin as well as the production of AHSP. As noted above, cytokines used may include purified or recombinant forms, or analogs or derivatives of specific cytokines.

[00240] A solid dispersion or solid form comprising pomalidomide as described herein may also be administered in conjunction with one or more second compounds known to have, or suspected of having, a beneficial effect on a hemoglobinopathy. In this context, “beneficial effect” means any reduction of any symptom of a hemoglobinopathy or anemia.

[00241] For example, with specific reference to the hemoglobinopathy sickle cell anemia, the second compound can be a compound, other than a pomalidomide or a derivative thereof, that is known or suspected to induce the production of fetal hemoglobin. Such compounds include hydroxyurea, and butyrates or butyrate derivatives. The second compound may also be a compound that relaxes blood vessels, such as nitrous oxide, *e.g.*, exogenously-applied or administered nitrous oxide. The second compound may also be a compound that binds directly to hemoglobin S, preventing it from assuming the sickle-inducing conformation. For example, the plant extract known as HEMOXIN™ (NIPRISAN™; *see* United States Patent No. 5,800,819), which is an extract of a mixture of about 12 to about 17 parts by

weight of *Piper guineense* seeds, from about 15 to about 19 parts by weight of *Pterocarpus osun* stem, from about 12 to about 18 parts by weight of *Eugenia caryophyllata* fruit, and from about 25 to about 32 parts by weight of *Sorghum bicolor* leaves, and optionally 15-22 parts by weight potash, wherein the mixture is extracted with cold water, has antisickling activity. The second compound may also be a Gardos channel antagonist. Examples of Gardos channel antagonists include clotrimazole and triaryl methane derivatives. The second compound may also be one that reduces red blood cell adhesion, thereby reducing the amount of clotting pervasive in sickle cell anemia.

[00242] Other hemoglobinopathies may be treated with a second compound known or suspected to be efficacious for the specific condition. For example, β thalassemia may additionally be treated with the second compound Deferoxamine, an iron chelator that helps prevent the buildup of iron in the blood, or folate (vitamin B9). Thalassemia or sickle cell anemia may also be treated with protein C as the second compound (U.S. Patent No. 6,372,213). There is some evidence that herbal remedies can ameliorate symptoms of hemoglobinopathies, *e.g.*, thalassemia; such remedies, and any of the specific active compounds contained therein, may also be used as a second compound in the method provided herein. *See, e.g.*, Wu Zhikui *et al.* "The Effect of Bushen Shengxue Fang on β -thalassemia at the Gene Level," *Journal of Traditional Chinese Medicine* 18(4): 300-303 (1998); U.S. Patent No. 6,538,023 "Therapeutic Uses of Green Tea Polyphenols for Sickle Cell Disease". Treatment of autoimmune hemolytic anemia can include corticosteroids as the second compound.

[00243] Second compounds that are proteins may also be derivatives or analogs of other proteins. Such derivatives may include, but are not limited to, proteins that lack carbohydrate moieties normally present in their naturally occurring forms (*e.g.*, nonglycosylated forms), pegylated derivatives, and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. *See, e.g.*, Penichet, M.L. and Morrison, S.L., *J. Immunol. Methods* 248:91-101 (2001).

[00244] Cytokines and/or other compounds potentially useful in the treatment of anemia or a hemoglobinopathy may be administered at the same time as pomalidomide or a derivative thereof. In this regard, the cytokines or other compounds may be administered as formulations separate from a solid dispersion or solid form comprising pomalidomide, or, where possible, may be compounded with a solid dispersion or solid form comprising pomalidomide for administration as a single pharmaceutical composition. Alternatively, the cytokines, the other compounds, or both, may be administered separately from a solid dispersion or solid form comprising pomalidomide used in the methods provided herein, and may follow the same or different dosing schedules. In one embodiment, a solid dispersion or solid form comprising pomalidomide, cytokines, and/or any other compound useful to treat anemia or a

hemoglobinopathy, are administered at the same time, but in separate pharmaceutical formulations for flexibility in administration.

[00245] In addition to the treatment combinations outlined herein, the treated individual may be given transfusions. Such transfusions may be of blood, for example matched blood, or of a blood substitute such as Hemospan™ or Hemospan™ PS (Sangart).

[00246] In any of the treatment combinations described herein, the treated individual is eukaryotic. In one embodiment, the treated individual is a mammal, for example a human.

[00247] The methods described herein may be used to treat any anemia, including anemia resulting from a hemoglobinopathy. Hemoglobinopathies and anemias treatable by the methods provided herein may be genetic in origin, such as sickle-cell anemia or thalassemias. The hemoglobinopathy may be due to a disease, such as cancer, including, but not limited to, cancers of the hematopoietic or lymphatic systems. Other conditions treatable using the methods provided herein include hypersplenism, splenectomy, bowel resection, and bone marrow infiltration. The methods described herein may also be used to treat anemia resulting from the deliberate or accidental introduction of a poison, toxin, or drug. For example, anemias resulting from cancer chemotherapies may be treated using the methods and solid dispersions or solid forms provided herein. As such, the methods described herein may be employed when anemia or a hemoglobinopathy is the primary condition to be treated, or is a secondary condition caused by an underlying disease or treatment regimen.

[00248] In one embodiment, provided herein is a method of treating or managing a pediatric cancer, comprising administering to a patient in need of such treatment or management a therapeutically or prophylactically effective amount of a solid dispersion or solid form comprising pomalidomide as described herein.

[00249] In one embodiment, the pediatric cancer is a CNS cancer (pediatric CNS cancer). In one embodiment, the CNS cancer includes, but are not limited to, primary central nervous system lymphoma ("PCNSL"), primary vitreoretinal lymphoma ("PVRL"), intra-ocular lymphoma, central nervous system blastoid mantle cell lymphoma, central nervous system tumors, central nervous system solid tumors, central nervous system cancerous conditions, neuroblastoma, mantle cell lymphoma ("MCL"), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma ("ILL"), diffuse poorly differentiated lymphocytic lymphoma ("PDL"), centrocytic lymphoma, diffuse small-cleaved cell lymphoma ("DSCCL"), follicular lymphoma, mantle zone lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mantle zone lymphoma).

[00250] In one embodiment, the CNS cancer is located at meninges, pituitary, pineal, nasal cavity, frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebrum, ventricle, cerebellum, brain stem, spinal cord, cauda equina, cranial nerves, other parts of brain, or other parts of the nervous system.

[00251] In one embodiment, the pediatric cancer is a pediatric solid tumor. In one embodiment, the pediatric cancer is a CNS tumor (pediatric CNS tumor). In one embodiment, the CNS tumor is a brain tumor. In one embodiment, the CNS tumor is a spinal cord tumor.

[00252] In one embodiment, the pediatric cancer is gliomas. In some embodiments, the gliomas is located at frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebrum, ventricle, cerebellum, brain stem, spinal cord, cauda equine, cranial nerves, other parts of brain, and other parts of the nervous system. In some embodiments, the gliomas is selected from the group consisting of glioblastoma, astrocytoma (*e.g.*, anaplastic astrocytoma, diffuse astrocytoma, pilocytic astrocytoma), oligoastrocytic tumors, oligodendroglioma, ependymal tumors, and glioma malignant NOS. In one embodiment, the gliomas is fibrillary astrocytomas, juvenile pilocytic astrocytoma (JPA), oligodendrogliomas, ependymomas, glioblastoma multiforme, or pleomorphic xanthoastrocytomas. In one embodiment, the glioma is diffuse intrinsic brain stem gliomas (DIPG).

[00253] In one embodiment, the glioma is a WHO grade I glioma. In one embodiment, the glioma is a WHO grade II glioma. In one embodiment, the glioma is a WHO grade III glioma. In one embodiment, the glioma is a WHO grade IV glioma.

[00254] In one embodiment, the pediatric cancer is medulloblastomas. In one embodiment, the medulloblastomas include, but are not limited to, classical medulloblastoma, large cell/anaplastic medulloblastoma, nodular desmoplastic medulloblastoma, and medulloblastoma with extensive nodularity.

[00255] In one embodiment, the pediatric cancer is ependymomas. In one embodiment, the ependymomas include, but are not limited to, myxopapillary ependymoma (WHO grade I), grade II ependymoma (cellular, papillary, clear cell, tanycytic) and anaplastic ependymoma (WHO grade III).

[00256] In one embodiment, the pediatric cancer is central nervous system germ cell tumors, craniopharyngiomas, choroid plexus tumors, meningiomas, or atypical teratoid rhabdoid tumors.

[00257] In one embodiment, the diseases or disorders are various forms of leukemias such as chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, and acute myeloblastic leukemia, including leukemias that are relapsed, refractory, or resistant, as disclosed in U.S. publication no. 2006/0030594, published February 9, 2006, which is incorporated in its entirety by reference.

[00258] The term “leukemia” refers malignant neoplasms of the blood-forming tissues. The leukemia includes, but is not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, and acute myeloblastic leukemia. The leukemia can be relapsed, refractory or resistant to conventional therapy. The term “relapsed” refers to a situation where patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. The term “refractory or resistant” refers to a circumstance where patients, even after intensive treatment, have residual leukemia cells in their marrow.

[00259] In another embodiment, the diseases or disorders are various types of lymphomas, including Non-Hodgkin’s lymphoma (NHL). The term “lymphoma” refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. “NHL” refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver, and gastrointestinal tract. Examples of NHL include, but are not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma, diffuse small-cleaved cell lymphoma (DSCCL), follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

[00260] Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, arthritis, endometriosis, Crohn’s disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, and 5q-deletion syndrome.

[00261] Other disease or disorders treated, prevented, or managed include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but are not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn’s disease, ulcerative

colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

[00262] In certain embodiments, a solid dispersion or solid form provided herein, or a composition comprising a solid dispersion or solid form provided herein, is administered orally, parenterally, topically, or mucosally.

[00263] In certain embodiments, a solid dispersion or solid form provided herein, or a composition comprising a solid dispersion or solid form provided herein, is administered at a dosing frequency of once, twice, thrice, or four times daily. In certain embodiments, solid dispersion or solid form provided herein, or a composition comprising a solid dispersion or solid form provided herein, comprises pomalidomide in an amount of from about 0.1 to about 100 mg, from about 0.5 to about 50 mg, from, about 0.5 to about 25 mg, from about 1 mg to about 10 mg, from about 0.5 to about 5 mg, or from about 1 mg to about 5 mg. In certain embodiments, provided herein is a single unit dosage form suitable for oral administration to a human comprising: an amount equal to or greater than about 1, 2, 3, 4, or 5 mg of the active ingredient of a solid dispersion or solid form comprising pomalidomide provided herein; and a pharmaceutically acceptable excipient. In one embodiment, the amount of the active ingredient is about 0.5 mg. In another embodiment, the amount of the active ingredient is about 1 mg. In another embodiment, the amount of the active ingredient is about 2 mg. In another embodiment, the amount of the active ingredient is about 4 mg.

[00264] In one embodiment, the second active agent is administered intravenously or subcutaneously and once or twice daily, once every other day, once every week, once every two weeks, or once every three weeks, in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. In one embodiment, the second active agent is administered orally and once or twice daily, once every other day, once every week, once every two weeks, or once every three weeks, in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, from about 10 to about 200 mg, from about 10 to about 100 mg, or from about 20 to about 50 mg. In specific embodiments, the second active agent is administered once every week in an amount of about 40 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of compounds provided herein and any optional additional active agents concurrently administered to the patient.

[00265] As discussed elsewhere herein, also encompassed is a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. A

solid dispersion or solid form comprising pomalidomide as provided herein and other active ingredients can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

[00266] In one embodiment of the methods provided herein, the subject is a child or young adult. In one embodiment, the subject is 3 to 21 years of age.

CYCLING THERAPY

[00267] In certain embodiments, the prophylactic or therapeutic agents provided herein are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest (*i.e.*, discontinuation of the administration) for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

[00268] Consequently, in one embodiment, a solid dispersion or solid form provided herein is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. Cycling therapy further allows the frequency, number, and length of dosing cycles to be increased. Thus, another embodiment encompasses the administration of a solid dispersion or solid form provided herein for more cycles than are typical when it is administered alone. In yet another embodiment, a solid dispersion or solid form provided herein is administered for a greater number of cycles than would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

[00269] In one embodiment, a solid dispersion or solid form provided herein is administered daily and continuously for three or four weeks at a dose of the active ingredient of from about 0.1 mg to about 5 mg per day, followed by a rest of one or two weeks. In other embodiments, the dose can be from about 1 mg to about 5 mg per day (*e.g.*, 1, 2, 3, or 4 mg/day), given on Days 1-21 of each 28-day cycle until disease progression, followed by a rest of 7 days on Days 22-28 of each 28-day cycle, for example, in patients with relapsed and refractory multiple myeloma who are refractory to their last myeloma therapy and have received at least 2 prior therapies that included lenalidomide and bortezomib.

[00270] In one embodiment, a solid dispersion or solid form provided herein and a second active ingredient are administered orally, with administration of the solid dispersion or solid form provided herein occurring 30 to 60 minutes prior to the second active ingredient, during a cycle of four to six

weeks. In another embodiment, the combination of a solid dispersion or solid form provided herein and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle.

[00271] In one embodiment, a solid dispersion or solid form provided herein is administered at a dose of about 4 mg per day given on Days 1-21, followed by a rest of 7 days on Days 22-28 of each 28-day cycle, alone or in combination with low dose dexamethasone (*e.g.*, 40 mg/day given on Days 1, 8, 15 and 22 of each 28-day cycle), for example, in patients with relapsed and refractory multiple myeloma who are refractory to their last myeloma therapy and have received at least 2 prior therapies that included lenalidomide and bortezomib.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[00272] Pharmaceutical compositions can be used in the preparation of single unit dosage forms comprising one or more solid dispersions or solid forms provided herein. In one embodiment, provided herein are pharmaceutical compositions and dosage forms comprising one or more solid dispersions or solid forms comprising a compound provided herein, or a pharmaceutically acceptable salt, solvate (*e.g.*, hydrate), stereoisomer, co-crystal, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms provided herein can further comprise one or more pharmaceutically acceptable excipients or carriers.

[00273] In some embodiments, pharmaceutical compositions and dosage forms provided herein can also comprise one or more additional active ingredients. Examples of optional second, or additional, active ingredients are disclosed herein elsewhere.

[00274] In one embodiment, single unit dosage forms provided herein are suitable for oral, parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules or hard gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient. In one embodiment, the single dosage forms provided herein are tablets,

caplets, or capsules comprising one or more solid dispersions or solid forms provided herein. In one embodiment, the single dosage forms provided herein are tablets or capsules comprising one or more solid dispersions or solid forms provided herein.

[00275] The composition, shape, and type of dosage forms will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms are used will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[00276] In one embodiment, pharmaceutical compositions and dosage forms comprise one or more excipients or carriers. Suitable excipients are known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, in one embodiment, provided are pharmaceutical compositions and dosage forms that contain little, if any, lactose or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions provided herein can comprise excipients which are known in the art and are listed in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002), which is incorporated herein in its entirety.

[00277] Also provided are anhydrous pharmaceutical compositions and dosage forms comprising active ingredient(s), since water may facilitate the degradation of some compounds. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, in one embodiment, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include,

but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

[00278] Also provided are pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as “stabilizers,” include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[00279] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. In one embodiment, dosage forms comprise the active ingredient in an amount of from about 0.10 to about 10 mg, or from about 0.10 to about 5 mg. In other embodiments, dosage forms comprise an active ingredient provided herein in an amount of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 2.5, 3, 4, or 5 mg.

[00280] In other embodiments, dosage forms comprise a second active ingredient in an amount from about 1 mg to about 1000 mg, from about 5 mg to about 500 mg, from about 10 mg to about 350 mg, from about 5 mg to about 250 mg, from about 5 mg to about 100 mg, from about 10 mg to about 100 mg, from about 10 mg to about 50 mg, or from about 50 mg to about 200 mg. In one embodiment, the specific amount of the second active agent will depend on the specific agent used, the diseases or disorders being treated or managed, and the amount(s) of a compound provided herein, and any optional additional active agents concurrently administered to the patient.

[00281] In particular embodiments, provided herein is a pharmaceutical composition comprising a solid dispersion or solid form comprising pomalidomide as provided herein and a pharmaceutically acceptable excipient or carrier. In particular embodiments, provided herein is a pharmaceutical composition comprising a cocrystal comprising pomalidomide and a coformer provided herein and a pharmaceutically acceptable excipient or carrier. In particular embodiments, provided herein is a pharmaceutical composition comprising an amorphous solid dispersion comprising pomalidomide provided herein and a pharmaceutically acceptable excipient or carrier. Exemplary embodiments of formulations of pomalidomide are described in, for example, U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, and 7,709,502; and U.S. Patent Application Publication No. 2011/0045064; the entireties of which are incorporated herein by reference.

Oral Dosage Forms

[00282] Pharmaceutical compositions that are suitable for oral administration can be provided as discrete dosage forms, such as, but not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In one embodiment, such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy known to those skilled in the art. *See generally, Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990). As used herein, oral administration also includes buccal, lingual, and sublingual administration.

[00283] In one embodiment, the oral dosage form provided herein is a tablet. In one embodiment, the oral dosage form provided herein is a capsule. In one embodiment, the oral dosage form provided herein is a caplet.

[00284] In one embodiment, oral dosage forms provided herein are prepared by combining the active ingredients in an intimate admixture with one or more pharmaceutically acceptable carrier or excipient, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide, according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[00285] In one embodiment, oral dosage forms are tablets or capsules, in which case solid excipients are employed. In specific embodiments, capsules comprising one or more solid dispersions or solid forms comprising pomalidomide as provided herein can be used for oral administration. In one embodiment, the total amount of pomalidomide in the capsule is about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg. In one embodiment, the total amount of pomalidomide in the capsule is about 1 mg, about 2 mg, or about 4 mg. In one embodiment, the total amount of pomalidomide in the capsule is about 1 mg or about 2 mg. Each capsule can contain pomalidomide as the active ingredient and one or more of the following inactive ingredients: mannitol, pregelatinized starch and sodium stearyl fumarate. In specific embodiments, the 1 mg capsule shell can contain gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink and black ink. In specific embodiments, the 2 mg capsule shell can contain gelatin,

titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3 and white ink. In another embodiment, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[00286] In certain embodiments, the dosage form is a tablet, wherein the tablet is manufactured using standard, art-recognized tablet processing procedures and equipment. In certain embodiments, the method for forming the tablets is direct compression of a powdered, crystalline and/or granular composition comprising a solid dispersion or solid form provided herein, alone or in combination with one or more excipients, such as, for example, carriers, additives, polymers, or the like. In certain embodiments, as an alternative to direct compression, the tablets may be prepared using wet granulation or dry granulation processes. In certain embodiments, the tablets are molded rather than compressed, starting with a moist or otherwise tractable material. In certain embodiments, compression and granulation techniques are used.

[00287] In certain embodiments, the dosage form is a capsule, wherein the capsules may be manufactured using standard, art-recognized capsule processing procedures and equipments. In certain embodiments, soft gelatin capsules may be prepared in which the capsules contain a mixture comprising a solid dispersion or solid form provided herein and vegetable oil or non-aqueous, water miscible materials, such as, for example, polyethylene glycol and the like. In certain embodiments, hard gelatin capsules may be prepared containing granules of solid dispersions or solid forms provided herein in combination with a solid pulverulent carrier, such as, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin. In certain embodiments, a hard gelatin capsule shell may be prepared from a capsule composition comprising gelatin and a small amount of plasticizer such as glycerol. In certain embodiments, as an alternative to gelatin, the capsule shell may be made of a carbohydrate material. In certain embodiments, the capsule composition may additionally include polymers, colorings, flavorings and opacifiers as required. In certain embodiments, the capsule comprises HPMC.

[00288] Examples of excipients or carriers that can be used in oral dosage forms provided herein include, but are not limited to, diluents (bulking agents), lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents, binding agents (binders), excipient supports, glidants, permeation enhancement excipients, plasticizers and the like, *e.g.*, as known in the art. It will be understood by those in the art that some substances serve more than one purpose in a pharmaceutical composition. For instance, some substances are binders that help hold a tablet together after compression,

yet are also disintegrants that help break the tablet apart once it reaches the target delivery site. Selection of excipients and amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works available in the art.

[00289] In certain embodiments, dosage forms provided herein comprise one or more binders. Binders may be used, *e.g.*, to impart cohesive qualities to a tablet or a capsule, and thus ensure that the formulation remains intact after compression. Suitable binders include, but are not limited to, starch (including potato starch, corn starch, and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, *e.g.*, acacia sodium alginate, polyvinylpyrrolidone (PVP), cellulosic polymers (including hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), methyl cellulose, ethyl cellulose, hydroxyethyl cellulose (HEC), carboxymethyl cellulose and the like), veegum, carbomer (*e.g.*, carbopol), sodium, dextrin, guar gum, hydrogenated vegetable oil, magnesium aluminum silicate, maltodextrin, polymethacrylates, povidone (*e.g.*, KOLLIDON, PLASDONE), microcrystalline cellulose, among others. Binding agents also include, *e.g.*, acacia, agar, alginic acid, cabomers, carrageenan, cellulose acetate phthalate, ceratonia, chitosan, confectioner's sugar, copovidone, dextrates, dextrin, dextrose, ethylcellulose, gelatin, glyceryl behenate, guar gum, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, hypromellose, inulin, lactose, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethylacrylates, povidone, sodium alginate, sodium carboxymethylcellulose, starch, pregelatinized starch, stearic acid, sucrose, and zein. In one embodiment, the binding agent can be, relative to the weight of the dosage form, in an amount of from about 50% to about 99% w/w. In certain embodiments, a suitable amount of a particular binder is determined by one of ordinary skill in the art.

[00290] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (FMC Corporation, Marcus Hook, PA), and mixtures thereof. In one embodiment, a specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103TM and Starch 1500 LM.

[00291] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms provided herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in a pharmaceutical composition is, in

one embodiment, present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[00292] In certain embodiments, dosage forms provided herein comprise one or more diluents. Diluents may be used, *e.g.*, to increase bulk so that a practical size tablet or capsule is ultimately provided. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, microcrystalline cellulose (*e.g.*, AVICEL), microfine cellulose, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (*e.g.*, EUDRAGIT), potassium chloride, sodium chloride, sorbitol and talc, among others. Diluents also include, *e.g.*, ammonium alginate, calcium carbonate, calcium phosphate, calcium sulfate, cellulose acetate, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, erythritol, ethylcellulose, fructose, fumaric acid, glyceryl palmitostearate, isomalt, kaolin, lactitol, lactose, mannitol, magnesium carbonate, magnesium oxide, maltodextrin, maltose, medium-chain triglycerides, microcrystalline cellulose, microcrystalline silicified cellulose, powered cellulose, polydextrose, polymethylacrylates, simethicone, sodium alginate, sodium chloride, sorbitol, starch, pregelatinized starch, sucrose, sulfobutylether- β -cyclodextrin, talc, tragacanth, trehalose, and xylitol. Diluents may be used in amounts calculated to obtain a desired volume for a tablet or capsule. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00293] Disintegrants may be used in the compositions to provide tablets or capsules that disintegrate when exposed to an aqueous environment. Dosage forms that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredient(s) may be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. In one embodiment, pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, or from about 1 to about 5 weight percent of disintegrant.

[00294] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligins; and mixtures thereof. The

amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[00295] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00296] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include,

but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[00297] In one embodiment, a solid oral dosage form comprises a compound provided herein, and one or more excipients selected from anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin. In one embodiment, capsules comprise one or more solid dispersions or solid forms comprising pomalidomide provided herein, and one or more of the following inactive ingredients: mannitol, pregelatinized starch, sodium stearyl fumarate, gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, black ink, FD&C red 3, and a combination thereof.

[00298] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00299] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00300] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-

parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00301] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, *e.g.*, acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00302] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00303] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00304] The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form.

Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00305] Coloring and flavoring agents can be used in all of the above dosage forms.

[00306] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

EXAMPLES

[00307] Certain embodiments provided herein are illustrated by the following non-limiting examples.

[00308] In one embodiment, pomalidomide may be synthesized using methods described in U.S. Patent Nos. 5,635,517, 6,335,349, 6,316,471, 6,476,052, 7,041,680, 7,709,502, and 7,994,327, all of which are incorporated herein in their entireties.

Characterization Methods

High-throughput X-ray powder diffraction

[00309] XRPD patterns were obtained using the Crystallics T2 high-throughput XRPD set-up. The plates were mounted on a Bruker GADDS diffractometer equipped with a Hi-Star area detector. The XRPD platform was calibrated using Silver Behenate for the long d-spacings and Corundum for the short d-spacings.

[00310] Data collection was carried out at room temperature using monochromatic CuK α radiation in the 2 θ region between 1.5° and 41.5°, which is the most distinctive part of the XRPD pattern. The diffraction pattern of each well was collected in two 2 θ ranges ($1.5^\circ \leq 2\theta \leq 21.5^\circ$ for the first frame, and $19.5^\circ \leq 2\theta \leq 41.5^\circ$ for the second) with an exposure time of 90s for each frame. No background subtraction or curve smoothing was applied to the XRPD patterns.

[00311] The carrier material used during XRPD analysis was transparent to X-rays and contributed only slightly to the background.

DSC

[00312] Melting properties were obtained from DSC thermograms, recorded with a heat flux DSC822e instrument (Mettler-Toledo GmbH, Switzerland). The DSC822e was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; δH_f = 28.45 J/g). Samples (approximately 2 mg) were sealed in standard 40 μ l aluminum pans, pin-holed and heated in the DSC

from 25°C to 350 °C, at a heating rate of 10 °C/min, unless described differently in the experiment. Dry N₂ gas, at a flow rate of 50 ml/min was used to purge the DSC equipment during measurement.

Modulated Temperature DSC

[00313] The MDSC experiment was measured in a standard 40 µL aluminum pan, pin-holed and heated in the DSC from 50 °C to 225 °C. The underlying heating rate was 2 °C/min, modulation period 48 sec and modulation amplitude 0.8 °C. Dry N₂ gas, at a flow rate of 50 mL/min was used to purge the DSC equipment during measurement. Weight of samples was approximately 3.5 mg.

TGMS

[00314] Mass loss due to solvent or water loss from the crystals was determined by TGA/SDTA. Monitoring the sample weight, during heating in a TGA/SDTA851e instrument (Mettler-Toledo GmbH, Switzerland), resulted in a weight vs. temperature curve. The TGA/SDTA851e was calibrated for temperature with indium and aluminum. Samples were weighed into 100 µl aluminum crucibles and sealed. The seals were pin-holed and the crucibles heated in the TGA from 25 to 300°C at a heating rate of 10°C min⁻¹. Dry N₂ gas was used for purging.

Dynamic Vapor Sorption

[00315] Moisture sorption isotherms were collected on a DVS-1 system from Surface Measurement Systems (London, UK). Typical sample size was between 7 to 11 mg of solid material. The relative humidity was cycled between 45% to 95% (sorption) to 0% (desorption) and back to 45% (sorption) in steps of 10% at a constant temperature of 25 °C. Weight equilibration per step was set with a holding time of 60 minutes. After the profile was finished, the sample was measured by HT-XRPD to verify if crystallization had occurred.

Digital imaging

[00316] Digital images were automatically collected for all the wells of each well-plate, employing a Wattec QN211 camera controlled by Crystallics Photoslider software.

Example 1 Pomalidomide Starting Material Characterization

[00317] Pomalidomide were provided as a yellowish powder for the solid dispersion and co-crystal screen studies. For reference purposes, XRPD, TGMS, HPLC and FT-IR were used to characterize the pomalidomide starting material. The XRPD analysis (FIG. 1) showed the pomalidomide starting material is crystalline, and the crystalline form is designated “Form A” of pomalidomide. The HPLC analysis showed a single peak indicating the compound is 100% pure (area %). The TGMS analysis showed no

significant mass loss prior to the thermal decomposition. An endothermic melt event is observed at 314 °C followed by thermal decomposition. The FTIR analysis (FIG. 2) confirmed the presence of a primary amine and a secondary amide moiety visible at 3500-3300 cm⁻¹ characteristic of the N-H stretching. On this basis, possible co-crystal formation may be visible by shifts of vibration in this region.

[00318] A shake flask solubility determination was performed on pomalidomide to aid in the selection of solvents for the solid dispersion and cocrystal screen. After 24 hours equilibration at room temperature under continuous stirring, the solids were separated from the mother liquors. Solids were analyzed by XRPD and the API concentration in the mother liquor was determined by HPLC analysis. The results of the solubility determination are summarized in the table below. All solids analyzed were the same crystalline form, Form A.

Solvent	Solubility (mg/mL)	Solid Form
Methanol/Water (25/75)	0	A
1,4-Dioxane	5.1	A
1,4-Dioxane/Water (50/50)	0.9	A
Chloroform	0.1	A
Acetonitrile/Chloroform (50/50)	0.3	A
Acetone/Isopropanol (50/50)	0.4	A
Anisole	0.1	A
2-Butanone	0.4	A
Ethyl acetate	0.1	A
Tetrahydrofuran/Water (25/75)	0.1	A

Example 2 Amorphous Solid Dispersion Screening by Fast Evaporation (No. 1)

[00319] The amorphous solid dispersion screening experiment was performed by fast evaporation with 15 polymer excipients at 2 API loadings (about 25% and about 50%). One solvent mixture of tetrahydrofuran/water (95/5, v/v) was used.

[00320] Approximately 5 mg of the API was weighed into 1.4 ml HPLC vials together with the excipient(s), followed by the addition of 1000 µl of in THF/water (95/5) to reach a concentration of approximately 5 mg/mL (corresponding to the solubility of pomalidomide in this solvent mixture). Each vial was capped and the mixtures were stirred at 90 °C for 60 min to ensure complete homogeneity or dissolution. After this time, the solvents were completely evaporated under vacuum (100 mbar, nitrogen flow) at 40 °C for 15 min. The resulting materials were further dried under vacuum (0 mbar) at room temperature overnight and analyzed by HT-XRPD. The materials were then subjected to 40 °C and 75% RH for three days and re-analyzed by HT-XRPD and digital imaging.

[00321] XRPD analysis of the 30 samples led to the identification of 6 amorphous materials from 6 excipients: ethyl cellulose, Eudragit RS100, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methylcellulose phthalate 50, and poly(1-vinylpyrrolidone-co-vinyl acetate). The rest of the samples were attributed to the crystalline Form A of pomalidomide. The amorphous dispersions were produced mainly with a low drug loading (25% of drug loading). In most of the cases, the amorphous dispersions were physically stable upon exposure to stress conditions for 3 days. The dispersions with hydroxypropyl cellulose and poly(1-vinylpyrrolidone-co-vinyl acetate) showed signs of crystallinity after the stress conditions. The results of the screen are shown in the table below.

Excipients	Drug load	XRPD result
Methyl cellulose	25%	Form A
	50%	Form A
Ethyl Cellulose	25%	Amorphous
	50%	Form A
Eudragit RS 100	25%	Amorphous
	50%	Form A
Hydroxyethyl-cellulose	25%	Form A
	50%	Form A
Hydroxypropyl methyl cellulose (HPMC)	25%	Amorphous
	50%	Form A
Hydroxypropyl cellulose (HPC)	25%	Amorphous
	50%	Form A
Eudragit S 100	25%	Form A
	50%	Form A
Hydroxypropyl methylcellulose phthalate 50 (HPMC-P)	25%	Amorphous
	50%	Form A
Poly(ethylene glycol) methyl	25%	Form A
	50%	Form A
Polyethylene Glycol 6000 (PEG 6000)	25%	Form A
	50%	Form A
Polyvinylpyrrolidone K30	25%	Form A
	50%	Form A
Poly(1-vinylpyrrolidone-co-vinyl acetate) (PVP-VA)	25%	Amorphous
	50%	Form A
Sureteric	25%	Form A
	50%	Form A
Pluronic F-68	25%	Form A
	50%	Form A
Tween 80	25%	Form A
	50%	Form A

[00322] The polymers that led to physically stable amorphous dispersions were reproduced at larger scale (ethyl cellulose, hydroxypropyl methylcellulose phthalate 50, Eudragit RS 100, and hydroxypropyl

methyl cellulose). In this case, approximately 15 mg of API were weighed together with the excipient into 1.4 ml HPLC vials, followed by the addition of 3000 μ l of in THF/water (95/5) to reach a concentration of approximately 5 mg/mL (corresponding to the solubility of pomalidomide in this solvent mixture). Each vial was capped and the mixtures were stirred at 90 °C for 60 min to ensure complete homogeneity or dissolution. After this time, the solvents were completely evaporated under vacuum (100 mbar, nitrogen flow) at 40 °C for 15 min. The resulting materials were further dried under vacuum (5 mbar) at room temperature overnight and analyzed by HT-XRPD. Additional drying was applied for 24 hours at full vacuum to try to remove the solvent content.

[00323] The XRPD patterns of the pomalidomide dispersions with the four excipients (ethyl cellulose, hydroxypropyl methylcellulose phthalate 50, Eudragit RS 100, and hydroxypropyl methyl cellulose) are shown in FIG. 3, which confirmed the amorphous nature of these dispersions.

[00324] The thermal analyses of the four physically stable dispersions indicated that all of them contained a significant amount of solvent. A mass loss of about 1.6% was observed for the amorphous solid dispersion prepared with ethyl cellulose prior to the thermal decomposition corresponding to tetrahydrofuran. A mass loss of about 8.9% was observed for the amorphous solid dispersion prepared with hydroxypropyl methylcellulose phthalate 50 prior to the thermal decomposition. A mass loss of about 6.8% was observed for the amorphous solid dispersion prepared with Eudragit RS 100 prior to the thermal decomposition corresponding to tetrahydrofuran. A mass loss of about 5.7% was observed for the amorphous solid dispersion prepared with hydroxypropyl methyl cellulose prior to the thermal decomposition corresponding to tetrahydrofuran.

[00325] In order to investigate if the dispersion can be obtained with less residual solvent, the samples were further dried under full vacuum (5 mbar) for 24 hours. Subsequently, the solids were re-harvested and analyzed by HT-XRPD (FIG. 4). Low crystallizations were observed for all four samples.

Example 3 Amorphous Solid Dispersion Screening by Fast Evaporation (No. 2)

[00326] The amorphous solid dispersion screening experiment was performed by fast evaporation with 6 polymer excipients at 3 API loadings (about 5%, 10%, and 20%). Three solvents were used: tetrahydrofuran/water (95/5, v/v), ethanol, and acetone.

[00327] Approximately 5 mg of pomalidomide was weighed into standard glass HPLC vials or 8 mL vials together with the excipient. Solvent was added, with a volume to reach a concentration of the API corresponding to the solubility of pomalidomide in this solvent (approximately 5 mg/mL in tetrahydrofuran/water (95/5, v/v), approximately 1.0 mg/mL in ethanol, and approximately 1.6 mg/mL in

acetone). Each vial was capped and the mixtures were stirred at 45 °C (THF/water, acetone) or 60 °C (ethanol) for 60 min to ensure complete dissolution. After this time, the solvents were completely evaporated under vacuum (100 mbar, nitrogen flow) at 40 °C for 15 min. The resulting materials were further dried under vacuum (0 mbar) at room temperature overnight and analyzed by HT-XRPD. The materials were then subjected to 40 °C and 75% RH for two weeks and re-analyzed by HT-XRPD and digital imaging. The results of the screen are shown in the table below.

Polymer	Solvent	5% drug load		10% drug load		20% drug load	
		Before AAC	After AAC	Before AAC	After AAC	Before AAC	After AAC
Ethyl Cellulose	THF / Water (95/5)	Am	A	Am	A	Am	A
Eudragit RS 100	THF / Water (95/5)	Am	Am	Am	Am	Am	A
HPMC	THF / Water (95/5)	A	A	A	A	A	A
HPC	THF / Water (95/5)	A	A	A	A	A	A
HPMC-P	THF / Water (95/5)	Am	Am	Am	Am	Am	Am
PVP-VA	THF / Water (95/5)	Am	Am*	Am	Am*	Am	A*
Ethyl Cellulose	Ethanol	A	A	A	A	A	A
Eudragit RS 100	Ethanol	Am	A	A	A	A	A
HPMC	Ethanol	A	A	A	A	A	A
HPC	Ethanol	A	A	A	A	A	A
HPMC-P	Ethanol	Am	Am	A	A	A	A
PVP-VA	Ethanol	A	A	A	A	A	A
Ethyl Cellulose	Acetone	A	A	A	A	A	A
Eudragit RS 100	Acetone	Am	Am	A	A	A	A
HPMC	Acetone	Am	Am	Am	Am	Am	Am
HPC	Acetone	A	A	A	A	A	A
HPMC-P	Acetone	Am	Am	Am	Am	A	A
PVP-VA	Acetone	Am	Am*	Am	Am*	Am	A

A: traces of the crystalline pomalidomide was observed.

Am: the sample appeared to be amorphous pomalidomide.

* = deliquescent

[00328] Amorphous materials were obtained with Eudragit RS 100, hydroxypropyl methyl cellulose (HPMC) and hydroxypropyl methyl cellulose phthalate 50 (HPMC-P). These dispersions remained amorphous after exposure for two weeks to the accelerated stability stress conditions. The initially amorphous material obtained with poly(1-vinylpyrrolidone-co-vinyl acetate) (PVP-VA) became deliquescent upon exposure to the stability stress conditions.

[00329] With HPMC amorphous material was obtained from acetone, while from THF/water 95/5 or from ethanol crystalline pomalidomide was observed.

[00330] Experiments with tetrahydrofuran/water 95/5 and acetone yielded mostly amorphous solids. The samples with acetone contained less residual solvent than the samples with tetrahydrofuran/water

95/5. Most samples obtained from ethanol were immediately crystalline, or crystallized after exposure to stability stress conditions or upon additional drying.

[00331] Per polymer, stable amorphous samples with the highest drug loading were chosen for further analysis by TGMS. The results are summarized in the table below. Dispersions from acetone had residual solvent of approximately 3–4%, while the samples from THF/water and ethanol contained approximately 7%.

Polymer	Solvent	Drug loading (w%)	TGA mass loss	Upon additional drying	DSC
HPMC-P	Ethanol	5%	6.9% ethanol	Crystallizes	-
HPMC-P	Acetone	5%	3.4% acetone	Am (1% residual)	No glass transition or melting event
Eudragit RS 100	THF / Water (95/5)	10%	4.7% tetrahydrofuran	Am (1.1% solvent)	No glass transition or melting event
HPMC	Acetone	10%	No TGA measured before drying.	Am (1.5% residual)	No glass transition or melting event
HPMC-P	Acetone	10%	4.0% acetone	Crystallizes	-
HPMC-P	THF / Water (95/5)	20%	7.4% tetrahydrofuran	Crystallizes	-
HPMC	Acetone	20%	3.0% acetone	Crystallizes	-

Am: the sample appeared to be amorphous pomalidomide.

[00332] The samples that had high residual solvent levels were further dried under vacuum at elevated temperature. Upon drying the samples with 5% drug loading in HPMC-P obtained from acetone (XRPD overlap shown in FIG. 5), 10% drug loading in Eudragit RS100 from THF/water 95/5 (XRPD overlap shown in FIG. 6), and 10% drug loading in HPMC from acetone (XRPD overlap shown in FIG. 7) remained amorphous. These samples were further characterized by DSC and HPLC. No glass transition was observed in the DSC thermograms. The chemical stability of the samples was confirmed by HPLC analyses and was 100% (area%) for all samples.

Example 4 Amorphous Solid Dispersion Screening by Melting

[00333] Melting experiments were performed with seven different polymers. A potential advantage of the melting experiments is that no solvent is introduced to the mixture.

[00334] Approximately 40 mg of pomalidomide was weighed into 8 mL vials together with the excipient and mixed with a spatula. The samples were heated slowly on a heating plate or in an oven to maximum the melting point of the polymer. The samples were cooled to room temperature and analyzed

by HT-XRPD. The materials were then subjected to 40 °C and 75% RH for two weeks and re-analyzed by HT-XRPD and digital imaging. The results of the screen are shown in the table below.

Polymer	Temp (°C)	Comment	5% drug load		10% drug load		20% drug load	
			Before AAC	After AAC	Before AAC	After AAC	Before AAC	After AAC
Ethyl Cellulose	180	Did not melt, turned brown	A	A	A	A	A	A
HPC	200	Did not melt, turned brown	A	A	A	A	A	A
HPMC-P	145	Did not melt, turned brown	A	A	A	A	A	A
PEG 6000	65	Melted but did not dissolve	Polymer + Am	Polymer + trace A + Am	Polymer + Am	Polymer + Am	A + Polymer	A + Polymer
Polyvinylpyrrolidone K30	220	Melted but did not dissolve	A	A	A	A	A	A
PVP-VA	220	Melted and dissolved	A	A	A	A	A	A
Pluronic F-68	55	Melted but did not dissolve	Polymer	Polymer*	Polymer	*	A + Polymer	A + Polymer

A: traces of the crystalline pomalidomide was observed.

Am: the sample appeared to be amorphous pomalidomide.

Polymer: PEG 6000 and pluronic F-68 are crystalline polymers.

* = deliquescent

[00335] A stable amorphous solid was obtained with PEG 6000 (XRPD overlap shown in FIG. 8).

The sample obtained from the melting experiment with PEG 6000 was further analyzed by DSC. The dispersion has a relatively low melting point of 62 °C, most likely due to the low melting point of the polymer.

Example 5 Scale-up, Solubility and Stability Studies of Amorphous Solid Dispersions

Materials

[00336] Polymers used for the dispersions: EUDRAGIT RS 100/500 G manufactured by Evonik Roehm Pharma Polymers (Lot No: E070408106) with following specifications: Residual solvent 1% of methanol, Ammonio methacrylate units 5.25%, ethyl acrylate < 0.2%, methyl methacrylate <0.2%, viscosity: 2 mm/s²; hydroxypropyl methylcellulose purchased from Acros, product No. 244021000 and Lot No. A0289450; hydroxypropyl methylcellulose acetate succinate LG, purchased from Syntapharm Ges. F. Pharmachemie GmbH. Product No 1825/3407 CAS No 71138-97-1, 8% Acetyl and 15% Succinyl groups, average grain size 1 mm³, viscosity 3mm/s²); hydroxypropyl methylcellulose acetate succinate

MG, AquaSolve™ HPMC-AS MG was obtained from Ashland Industries Europe GmbH, product No 825181, Lot No 60410001, 10.8% Acetyl and 11.8% Succinyl groups; hydroxypropyl methylcellulose acetate succinate HG, AquaSolve™ HPMC-AS HG was obtained from Ashland Industries Europe GmbH, product No 825185, Lot No 65G410001; hydroxypropyl methylcellulose phthalate 50 (HPMC-P) manufactured by Acros Organics (Lot-No: A020250161) with following specifications: phthalyl content: 23.4%, Water 1.3%, free phthalic Acid: 0.18%; PEG 6000. Manufactured by Fluka, product number 81260, Lot No 1315619, fine flakes.

[00337] Polymer for the 2 wt% HPMC solution in water: hydroxypropyl methyl cellulose manufactured by Sigma-Aldrich (Batch No: MKBL7839V) with following specifications: powder, viscosity: 6.4 cps (2% in H₂O at 20 °C).

[00338] The buffer solutions used for the solubility studies were prepared according to the US Pharmacopeia and were of the following compositions: pH 4: 50 mM potassium biphthalate solution, adjusted with HCl to pH 4; pH 5: 50 mM potassium biphthalate solution, adjusted with NaOH to pH 5; pH 6: 50 mM monobasic potassium phosphate solution, adjusted with NaOH to pH 6; pH 7: 50 mM monobasic potassium phosphate solution, adjusted with NaOH to pH 7. The FaSSIF solution was prepared with “FaSSIF, FeSSIF & FaSSGF Powder” obtained from biorelevant.com.

[00339] All other chemicals were obtained either from Sigma Aldrich, Fisher Scientific or VWR. Chemicals used were of research grade. Solvents used for HPLC analysis were of HPLC grade.

Scale-up of amorphous solid dispersions

[00340] Pomalidomide together with the excipient were weighed into 100 mL round bottom flasks. A volume of solvent was added to reach a concentration of the API corresponding to the solubility of pomalidomide in this solvent. The mixtures were sonicated and vortexed for approximately an hour to ensure complete dissolution. After this time, the solutions were freeze-dried and placed under vacuum (0.1 mbar). The resulting materials were further dried under vacuum (0 mbar) at 40 °C overnight and analyzed by HT-XRPD, DSC, TGMS and HPLC. The mixture with PEG 6000 was heated at 60 °C for one hour, to allow pomalidomide to dissolve in the molten polymer. The experimental conditions are listed in the table below.

Exp ID	Mass API (mg)	Excipient	Mass Excipient (mg)	Drug load (%)	Solvent	Vol. (mL)	Conc. API (mg/mL)
SUD1	29.0	HPMC-P	554.8	5	Acetone/water (90/10 v/v)	15	1.9
SUD2	25.1	Eudragit RS 100	478.9	5	THF/water (95/5 v/v)	5	5.0

SUD3	51.6	Eudragit RS 100	453.7	10	THF/water (95/5 v/v)	10	5.2
SUD4	29.1	HPMC	554.0	5	Acetone/water (90/10 v/v)	15	1.9
SUD5	56.1	HPMC	518.7	10	Acetone/water (90/10 v/v)	30	1.9
SUD6	25.0	PEG 6000	473.2	5	-	-	-
SUD7	34.6	HPMC-P	665.8	5	Acetone/water (90/10 v/v)	22	1.6
SUD8	36.4	Eudragit RS 100	675.0	5	THF/water (95/5 v/v)	10	3.6
SUD9	70.4	Eudragit RS 100	632.5	10	THF/water (95/5 v/v)	23	3.1
SUD10	36.2	HPMC-AS LG	667.1	5	Acetone/water (90/10 v/v)	20	1.8
SUD11	34.3	HPMC-AS LG	665.4	5	THF/water (95/5 v/v)	12	2.9
SUD14	37.1	HPMC-AS MG	701.1	5	THF/water (95/5 v/v)	12	3.1
SUD15	36.8	HPMC-AS HG	697.7	5	THF/water (95/5 v/v)	12	3.1

Solubility study at 37 °C

[00341] The solubility of the amorphous solid dispersions with HPMC-P, Eudragit RS100, HPMC and PEG 6000 were determined at 37 °C in bio-relevant media and viscous water solutions. Suspensions were prepared with approximately 10 mg of dispersion and 1 mL of media. The concentration of pomalidomide in solution was determined after 2, 3 and 4 hours. Small volumes of liquid were filtered and 50 µL was diluted in the same volume of acetonitrile to prevent precipitation before HPLC analysis. The experiments were performed in triplicate.

Solubility study at 25 °C

[00342] The solubility of pomalidomide was determined at room temperature with the HPMC-P, Eudragit RS100 and HPMC-AS dispersions. The media used were buffers with pH 4, 5, 6 and 7, water and 2 wt% HPMC in water solution. The buffers with pH 4 and pH 5 were phthalate buffers. The buffers with pH 6 and pH 7 were phosphate buffers.

[00343] Slurries were prepared of the dispersions with HPMC-P (5% drug load), Eudragit (5 and 10% drug loading) and HPMC-AS (5% drug load), approximately 10 mg of dispersion was used in 1 mL of media. The concentration of pomalidomide in solution was determined after 2, 4, 7 and 24 hours. Small volumes of the liquid were filtered and 50 µL of the filtered solution was diluted in acetonitrile to prevent precipitation before analysis by HPLC. The pH of the solution was recorded after 24 hours.

Precipitation studies in gastric fluids

[00344] The gastric precipitation studies were performed with the dispersions with HPMC-P, Eudragit RS100 and HPMC-AS. Suspensions or solutions with a concentration of 0.4 mg/mL pomalidomide in 12 mL of 2 wt% HPMC solution in water or pH buffer solution were prepared. From these suspensions/solutions the concentration of pomalidomide in solution was determined by HPLC analysis.

One mL of these suspensions/solutions was added to 15 mL or 25 mL of simulated gastric fluid (0.1 N HCl).

[00345] The suspensions in gastric fluids were incubated at 25 °C and 37 °C. At 1 hour interval samples were taken and the concentration of pomalidomide in solution was determined. The percentage of the maximum concentration was calculated. The pH of the solutions was recorded after 24 hours.

Results

Amorphous solid dispersion with HPMC-P, 5% drug load

[00346] *Scale-up*: two batches of amorphous solid dispersion with HPMC-P were prepared. The batches were prepared by freeze drying a solution of pomalidomide and HPMC-P (5% drug load) in acetone/water (90/10 v/v). The samples were dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. Although both dispersions were prepared in identical fashion, albeit with a slightly different solvent volume (15 mL versus 22 mL), the dispersions had a different physical appearance. SUD1 was a powder whereas SUD7 was a film.

[00347] The samples were analyzed by HT-XRPD (crystallinity), DSC (phase purity), TGA (residual solvent) and HPLC (chemical purity). The powder (SUD1) contained less residual solvent as the TGA gives a loss on drying of 1.8%, the film (SUD7) lost 3.1% weight on drying. Both samples were amorphous and the DSC trace showed no thermal events such as re-crystallizations. The DSC trace also did not show a clear glass transition (T_g) temperature between 25 °C and 350 °C.

[00348] *Physical stability study*: the HPMC-P dispersion (SUD1) was stored in open containers at 25 °C/58% RH and 40 °C/75% RH. At regular intervals samples were taken and analyzed by HT-XRPD. The results show that the dispersion remained amorphous up to 3 months of storage.

[00349] *Stress studies at 80 °C and 100 °C*: the physical and chemical stability were evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for 3 days and one month and for one month in open ampoules at 80 °C/75% RH. After the incubation period the solids were analyzed by HT-XRPD and HPLC. The dispersions remained amorphous under the applied conditions. However, the chemical purity of the samples stored under stress conditions was decreased by 20-30%. Exposure of pomalidomide or the HPMC-P to the stress conditions did not result in chemical degradation. The XRPD analysis of one of the samples showed a hint of crystallinity. The trace amount of crystallinity is likely pomalidomide, as the position relates to the most intensive peak of pomalidomide around 25.6 °2θ.

[00350] *Dynamic vapor sorption study*: the dispersion of 5% pomalidomide in HPMC-P (SUD7) was used for a hygroscopicity study by DVS analysis. The sample was subjected to one full cycle of sorption

and desorption from 45% - 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of about 10% at 95% RH. Upon drying, the sample lost water again gradually. The hysteresis between sorption and desorption was about 1%. With 6% water sorption at 80% RH, SUD7 can be considered moderately hygroscopic. XRPD analysis of the sample after DVS analysis indicated that the material had not crystallized during the sorption and desorption cycle.

[00351] *Solubility as function of the medium:* the solubility of pomalidomide released from the HPMC-P dispersion was initially determined at room temperature in water and in a 2% HPMC formulation solution in water (FIG. 9A). This experiment was followed by the solubility determination at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC in water, and 5% Glycerin solution in water (FIG. 9B).

[00352] For the solubility determination, suspensions of 12 mg SUD1 (5% pomalidomide in HPMC-P) were prepared in 1 mL aqueous medium. The suspensions were incubated at RT and 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis. In water after 24 hours the solution was not homogenous and particles were still visible. This in contrast to the dissolution in 2% HPMC solution which formed a homogenous milky suspension after 24 hours stirring.

[00353] The theoretical maximum solubility of pomalidomide in this experiment was approximately 0.6 mg/mL. The solubilities determined at room temperature show that pomalidomide is slightly more soluble from the dispersion. At 37 °C the solubility of pomalidomide was significantly increased from the dispersion compared to the neat API.

[00354] The solubility in simulated intestinal fluid (FaSSIF) reached approximately 65% of this maximum. The dissolution of pomalidomide from the dispersion in HPMC-P was fast as the maximum solubility for each medium was reached in about 2 hours. Only in water was the solubility increasing with time. The supersaturated state for pomalidomide in solution was maintained in each media for at least 4 hours.

[00355] *Solubility as function of the pH:* the solubility of pomalidomide released from the HPMC-P dispersion was determined as function of the pH. Suspensions of the 5% pomalidomide dispersion in HPMC-P (SUD7) were incubated at room temperature for 24 hours. At regular intervals, samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test the final pH of the solutions was measured. In water and in buffer pH 4 the formulation was poorly miscible with the medium. After 24 hours stirring the solution

was still clear with particles floating around. At higher pH values (pH 5, 6 and 7) a milky yellowish homogenous suspension was formed.

[00356] The best solubilities were found in the buffer solutions with pH 5 (phthalate buffer) and pH 6 (phosphate buffer). In buffers with pH 5, 6 and 7 the highest solubility is seen at the first sampling point at 2 hours. Later time points show a decline in solubility suggesting that the API is precipitating as the supersaturated state cannot be maintained (FIG. 10).

[00357] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from a HPMC-P dispersion was evaluated. This experiment simulates the ingestion of a liquid formulation with pomalidomide in HPMC-P containing 4 mg drug equivalent. All volumes and quantities were adjusted to 1/10th of the physiological volumes.

[00358] A suspension of 0.4 mg/mL (pomalidomide equivalents) of the HPMC-P dispersion (SUD7) was prepared in 2% HPMC (in water). After preparation, the suspension was stirred for 4 hours before a sample was taken for HPLC analysis. The concentration pomalidomide in solution was 0.047 mg/mL (solute). Of this suspension 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined.

[00359] In the formulation (2% HPMC solution) 12% of pomalidomide was in solution and the remaining part was present as a solid. After the gastric dump, the amount of pomalidomide in solution was determined as percentage of the amount of pomalidomide present (FIG. 11). This amount did not change significantly suggesting that the fraction of pomalidomide in solution did not change. The ratio between solute and solid in formulation remained the same after the gastric dump. The results indicates that pomalidomide did not precipitate but did not dissolve either. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C.

Amorphous solid dispersion with Eudragit RS 100, 5% drug load

[00360] *Scale-up:* two amorphous solid dispersions (SUD2 and SUD8) were prepared with Eudragit RS 100 with 5% pomalidomide by freeze drying a solution of API and Eudragit RS100 in tetrahydrofuran/water (95/5 v/v). The samples were dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. The samples were analyzed by HT-XRPD, DSC, TGA and HPLC.

[00361] Both samples were amorphous powders and had similar characteristics. The samples SUD2 and SUD8 had 0.7% and 0.5% of residual solvent, respectively, as determined by TGA analysis and the

chemical purity was 99.1% and 99.7% (area%), respectively. No glass transition was observed in the DSC analysis, also no re-crystallization or melting events were recorded up to 350 °C confirming the homogenous stable amorphous nature of the dispersions.

[00362] *Physical stability study:* the physical stability of the Eudragit RS 100 dispersion with 5% drug load was evaluated in open containers at 25 °C/58% RH and 40 °C/75% RH. The samples were analyzed by HT-XRPD at regular intervals to evaluate the physical stability. The dispersion remained amorphous up to 3 months under both conditions.

[00363] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability was evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for three days and one month and in an open ampoule at 80 °C/75% RH for one month. After the incubation period the solids were analyzed by HT-XRPD and HPLC. Over time, the sample remained amorphous demonstrating the physical stability of the dispersions. The chemical purity of pomalidomide in this dispersion was not affected indicating that pomalidomide is compatible with Eudragit RS 100.

[00364] *Dynamic vapor sorption study:* the Eudragit RS 100 dispersion with 5% drug load (SUD8) was used for a hygroscopicity study by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45% – 95% - 0% - 45% RH. The samples showed absorption of water of 5.2% at 95% RH. This water uptake was reversible as the water was lost upon drying with a hysteresis less than 0.5%. With 3.5% water sorption at 80% RH, SUD8 can be considered moderately hygroscopic. XRPD analysis of the samples after DVS analysis indicated that the amorphous dispersion remained stable after sorption and desorption of water.

[00365] *Solubility as function of the medium:* the solubility of pomalidomide released from the Eudragit dispersion was initially determined in water and in a 2% HPMC solution in water at room temperature (FIG. 12A). This experiment was followed by the solubility determination at 37 °C in water, SGF, FaSSIF, 2% HPMC in water and 5% Glycerin solution in water (FIG. 12B).

[00366] For the solubility determination suspensions of 11 mg SUD2 (5% pomalidomide in Eudragit RS 100) were prepared in 1 mL aqueous medium. The suspensions were incubated at RT and 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis.

[00367] The best solubility was obtained in 2% HPMC solution and was 0.25 mg/mL at 37 °C and 0.2 mg/mL at RT. After 4 hours the solubility started to decline, indicating precipitation of pomalidomide. Eudragit RS 100 is not miscible in water or aqueous solutions and in the 2% HPMC solution the polymer was better miscible the particles swelled and hence was able to improve the solubility most significantly.

[00368] The solubility in each medium at 37 °C showed a sudden increase after 4 hours, indicating a slow dissolution rate, likely due to the poor miscibility of Eudragit RS 100 in the aqueous media. In the 2% HPMC solution the dissolution was faster and was maintained over the 4 hour test period.

[00369] *Solubility as function of pH:* the solubility of pomalidomide released from the Eudragit dispersion (5% drug load) was determined as function of the pH. Suspensions of a 5% pomalidomide dispersion in Eudragit RS 100 (SUD8) were incubated at room temperature for 24 hours. At regular intervals, samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test, the final pH of the solutions was measured.

[00370] The results are presented in FIG. 13. The physical appearance and pH of the suspensions did not change over time. The solubility of Eudragit RS 100 is not dependent on the pH of the medium.

[00371] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from the Eudragit dispersion was evaluated. This experiment simulates the ingestion of a liquid formulation with pomalidomide in Eudragit RS 100 containing 4 mg drug equivalent. All volumes and quantities were adjusted to 1/10th of the physiological volumes.

[00372] A suspension of 0.4 mg/mL (pomalidomide equivalents) of the Eudragit RS 100 dispersion (5% drug load) was prepared in 2% HPMC in water solution. After preparation of the suspension the mixture was stirred for 4 hours before a sample was taken for HPLC analysis. The concentration pomalidomide in solution was 0.102 mg/mL (solute). Of this suspension, 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined.

[00373] In the formulation (2% HPMC solution) 26% of pomalidomide was in solution and the remaining part was present as a solid. After the gastric dump the amount of pomalidomide in solution was again determined from the concentration in the total volume. No precipitation occurred and especially at 37 °C the concentration of pomalidomide in solution had increased (FIG. 14). In 25 mL the maximum concentration in solution was almost reached and in 15 mL 64% of the maximum concentration was almost reached. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C.

Amorphous solid dispersion with Eudragit RS 100, 10% drug load

[00374] *Scale-up:* two amorphous solid dispersions were prepared with Eudragit RS 100 and 10% drug load by freeze drying a solution of pomalidomide and Eudragit RS 100 in tetrahydrofuran/water

(95/5 v/v). The samples were dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. The samples were analyzed by HT-XRPD, DSC, TGA and HPLC.

[00375] Both samples (SUD3 and SUD9) were amorphous powders with 0.6% residual solvent. The chemical purities of the samples were 98.0% and 99.6% (area%), respectively. No glass transition was recorded by DSC analysis, also no re-crystallization or melting events were recorded prior to decomposition around 200 °C confirming the amorphous nature of the dispersions.

[00376] *Physical stability study:* the Eudragit RS 100 dispersion (SUD3) with 10% drug load was stored in open containers at 25 °C/58% RH and 40 °C/75% RH. At regular intervals, samples were taken and analyzed by HT-XRPD. The sample remained amorphous up to three months at 25 °C/58% RH, but crystallized within two weeks at 40 °C/75% RH. These results suggest that the higher drug load may result in a non-homogenous amorphous dispersion.

[00377] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability was evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for three days and one month and in an open ampoule at 80 °C/75% RH for one month. After the incubation period the solids were analyzed by HT-XRPD and HPLC. The dispersions were chemically stable but pomalidomide crystallized under the stress conditions tested. These results indicate the non-homogenous nature of the dispersion prepared in Eudragit RS 100 with a 10% pomalidomide load.

[00378] *Dynamic vapor sorption study:* the Eudragit RS 100 dispersion with 10% drug load (SUD9) was used for a hygroscopicity study by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45 – 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of about 5.2% at 95% RH. Upon drying the water was lost and the hysteresis between sorption and desorption was less than 0.5%. The dispersion is hygroscopic with a water uptake of about 3% at 80% RH. The XRPD analysis of the sample afterwards confirmed that pomalidomide had not crystallized.

[00379] *Solubility as a function of the medium:* the solubility of pomalidomide released from the Eudragit dispersion with 10% drug load was determined at room temperature in water and in a 2% HPMC solution in water (FIG. 15A). This experiment was followed by the solubility determination at 37 °C in water, SGF, FaSSIF, 2% HPMC in water and 5% Glycerin solution in water (FIG. 15B).

[00380] For the solubility determination suspensions of 10 mg SUD3 (10% pomalidomide in Eudragit RS 100) were prepared in 1 mL aqueous medium. The suspensions were incubated at RT and 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis. The best solubility was obtained in 2%

HPMC solution and was 0.3 mg/mL at 37 °C and 0.1 mg/mL at RT. The concentration of pomalidomide in solution decreased over time indicating the precipitation of pomalidomide. Eudragit RS 100 is not miscible with water or aqueous solutions. However, in the 2% HPMC solution the polymer was more miscible and the particles swelled. The dispersion with 5% drug load had a higher solubility at room temperature in 2% HPMC than the dispersion with 10% drug load. It seems that the ratio of API/polymer and surfactant may affect the dissolution of pomalidomide from the Eudragit dispersions.

[00381] The solubility in each medium at 37 °C remained the same over 4 hours. Only in the 2% HPMC solution the solubility was initially much higher but started to decline after 2 hours suggesting pomalidomide is precipitating from this solution.

[00382] *Solubility as function of pH:* the solubility of pomalidomide released from the dispersion with 10% drug load in Eudragit was determined as function of the pH. Suspensions of a 10% pomalidomide dispersion in Eudragit RS 100 (SUD9) were incubated at room temperature for 24 hours. At regular intervals samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test, the final pH of the solutions was measured.

[00383] The results are presented in FIG. 16. The physical appearance and pH of the suspensions did not change over time. The solubility of Eudragit RS 100 is not dependent on the pH of the medium. There was no difference in solubility at room temperature between the dispersions with 10% drug load versus 5% drug load.

[00384] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from the Eudragit dispersion with 10% drug load was evaluated. This experiment simulates the ingestion of a liquid formulation with pomalidomide in Eudragit RS 100 containing 4 mg drug equivalent. All volumes and quantities were adjusted to 1/10th of the physiological volumes.

[00385] A suspension of 0.4 mg/mL (pomalidomide equivalents) of the Eudragit RS 100 dispersion (10% drug load) was prepared in 2% HPMC in water solution. After preparation the suspension was stirred for 2 hours before a sample was taken for HPLC analysis. The concentration of pomalidomide in solution was 0.080 mg/mL (solute). Of this suspension 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined. The results are presented in FIG. 17.

[00386] In the formulation (2% HPMC solution) 20% of pomalidomide was in solution and the remaining part was present as a solid. After the gastric dump the amount of pomalidomide in solution was again determined from the concentration in the total volume. No precipitation occurred at both temperatures. At 37 °C the concentration of pomalidomide in solution had increased. In 25 mL 80% of the maximum concentration was reached and in 15 mL 50% of the maximum concentration was reached. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C.

Amorphous solid dispersion with HPMC, 5% drug load

[00387] *Scale-up:* an amorphous solid dispersion was prepared with HPMC and 5% drug load by freeze-drying a solution of pomalidomide and HPMC in acetone/water (90/10 v/v). The sample was dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. The sample was analyzed by HT-XRPD, DSC, TGA and HPLC.

[00388] The HPMC dispersion with 5% drug load was an amorphous powder. The dispersion contained 2.5% residual solvent as determined by TGA analysis. The dispersion was chemically pure (100 area%). In the DSC curve was besides the broad endothermic event related to solvent loss a broad weak endothermic event observed around 250 °C. This weak event might be due to the start of decomposition.

[00389] *Physical stability study:* the HPMC dispersion with 5% pomalidomide was stored in open containers at 25 °C/58% RH and 40 °C/75% RH. At regular intervals, samples were taken and analyzed by HT-XRPD. The results show that the dispersion was physically stable up to 3 months under the applied conditions.

[00390] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability was evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for 3 days and one month and in open ampoules at 80 °C/75% RH for one month. After the incubation period the solids were analyzed by HT-XRPD and HPLC. The dispersion was physically and chemically stable at all tested conditions. The stability test results indicate that pomalidomide forms a stable homogenous dispersion with HPMC.

[00391] *DVS study:* the dispersion of 5% pomalidomide in HPMC was used for a hygroscopicity study by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45% - 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of approximately 23% at 95% RH. Upon drying the sample lost the water again gradually. The hysteresis between sorption and desorption was about 2.4% at 65% RH. With 15% water sorption at 80%

RH, SUD4 can be considered hygroscopic. XRPD analysis of the sample after DVS analysis indicated that the material had not crystallized.

[00392] *Solubility study at 37 °C:* the solubility of pomalidomide from the HPMC dispersion with 5% drug load was determined at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC in water, and 5% Glycerin solution in water (FIG. 18).

[00393] For the solubility determination suspensions of 14 mg of SUD4 (5% drug load in HPMC) were prepared in 1 mL of aqueous medium. The suspensions were incubated at 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis. The dispersions with HPMC have overall a solubility of 0.10 – 0.15 mg/mL in each media. The suspensions formed gels with the aqueous solutions and hence the solubility was less influenced by differences between the media.

Amorphous solid dispersion with HPMC, 10% drug load

[00394] *Scale-up:* an amorphous solid dispersion was prepared with HPMC and 10% drug load by freeze drying a solution of pomalidomide and HPMC in acetone/water (90/10 v/v). The sample was dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. The sample was analyzed by HT-XRPD, DSC, TGA and HPLC.

[00395] The HPMC dispersion with 10% drug load was an amorphous powder. The dispersion contained 1.9% residual solvent as determined by TGA analysis. The dispersion was chemically pure (100 area%). In the DSC curve, a broad endothermic event related to solvent loss was observed, but no glass transition, melt or re-crystallization events was recorded prior to decomposition.

[00396] *Physical stability study:* the HPMC dispersion with 10% pomalidomide was stored in open containers at 25 °C/58% RH and 40 °C/75% RH. At regular intervals, samples were taken and analyzed by HT-XRPD. The sample remained amorphous at 25 °C/58% RH up to 3 months. In the sample incubated at 40 °C/75% RH a hint of crystallinity was observed after 1 week. After 2 weeks the amount of crystalline material had increased. The observed diffraction peaks correspond to the more intense peaks from Form A of pomalidomide.

[00397] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability of the HPMC dispersion with 10% drug load was evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for 3 days and one month respectively and in open ampoules at 80 °C/75% RH for one month. After the incubation period the solids were analyzed by HT-

XRPD and HPLC. The dispersion was chemically stable but crystallized under the conditions tested. This result indicated that dispersions with 10% pomalidomide are not homogenous.

[00398] *DVS study*: the dispersion of 10% pomalidomide in HPMC was used for a hygroscopicity study by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45% - 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of about 24% at 95% RH. Upon drying the sample lost the water again gradually. With 13% water sorption at 80% RH, SUD5 is moderately hygroscopic. The XRPD pattern of the sample after the DVS study showed a trace of crystallinity of pomalidomide.

[00399] *Solubility study at 37 °C*: the solubility of pomalidomide from the HPMC dispersion was determined at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC in water, and 5% Glycerin solution in water (FIG. 19).

[00400] For the solubility determination suspensions of 11 mg of SUD5 (10% drug load in HPMC) were prepared in 1 mL of aqueous medium. The suspensions were incubated at 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis. The solubility of pomalidomide was between 0.10 – 0.15 mg/mL in each medium and had formed gels.

Amorphous solid dispersion with PEG 6000, 5% drug load

[00401] *Scale-up*: a scale-up with PEG 6000 was prepared by melting. Pomalidomide and PEG 6000 were weighed into a 40 mL glass vial and mixed with a spatula. The material was heated at 60 °C for an hour. The sample was analyzed by HT-XRPD, DSC, TGA and HPLC. The sample was amorphous with 0.2% of moisture and a chemical purity of 100% (area%). In DSC was an endothermic melting event observed at 61.8 °C, which corresponds to the melting of PEG 6000.

[00402] *Physical stability study*: the PEG 6000 dispersion with 5% drug load was stored in open containers at 25 °C/58% RH and at 40 °C/75% RH. At regular intervals, samples were taken and analyzed by XRPD. The sample remained amorphous up to three months under both tested conditions and only the diffractogram of PEG 6000 was observed. Due to the low melting point of PEG 6000 stability studies conducted at 80 °C and 100 °C were omitted.

[00403] *Solubility study at 37 °C*: the solubility of pomalidomide from the PEG 6000 dispersion was determined at 37 °C in water, simulated gastric fluid (SGF), simulated intestinal fluid (FaSSIF), 2% HPMC in water, and 5% Glycerin solution in water (FIG. 20).

[00404] For the solubility determination suspensions of 12 mg of SUD6 (5% drug load in PEG 6000) were prepared in 1 mL of aqueous medium. The suspensions were incubated at 37 °C under continuous stirring. Samples were taken after 2, 3 and 4 hours and the concentration of pomalidomide in solution was determined by HPLC analysis. The solubility was slightly increased compared to the crystalline pomalidomide (about 2 to 3 folds). PEG 6000 dissolved in aqueous solutions but pomalidomide precipitated after dissociation from the dispersion.

Amorphous solid dispersion with HPMC-AS LG, 5% drug load

[00405] *Scale-up:* an amorphous solid dispersion was prepared with HPMC-AS LG and 5 % drug load. While the dispersions with HPMC and HPMC-P yielded amorphous dispersions with acetone/water (90/10 v/v), with HPMC-AS LG in acetone/water (90/10 v/v) the pomalidomide remained crystalline.

[00406] A new batch was prepared by freeze drying a solution of pomalidomide and HPMC-AS LG in tetrahydrofuran/water (95/5 v/v) (SUD11). The sample was dried for 18 hours at room temperature under deep vacuum followed by 18 hours drying at 40 °C and deep vacuum. The sample was analyzed by HT-XRPD, DSC, TGA and HPLC. The sample was amorphous with 2.25% of residual solvent and a purity of 99.6% (area%). The mass loss occurred up to 150 °C and the weak events observed in the DSC curve are likely related to the solvent loss. The event at 170 °C is likely related to the start of decomposition. No melting event was recorded by DSC between 25 – 350°C, indicating that the dispersion was homogenous and fully amorphous.

[00407] *Physical stability study:* the HPMC-AS LG dispersion with 5% drug load was stored in a open container at 25 °C/58% RH and 40 °C/75% RH. The samples were analyzed by HT-XRPD at regular intervals. The dispersion remained amorphous for up to two months at 25 °C/58% RH and 40 °C/75% RH.

[00408] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability was evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for three days and one month and in an open ampoule at 80 °C/75% RH for one month. After the incubation time, the samples were analyzed by HT-XRPD and HPLC. The dispersion did not change and was physically and chemically stable under the tested conditions.

[00409] *DVS study:* a hygroscopicity study was performed with the HPMC-AS LG dispersion with 5% drug load by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45% - 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of 11.2% at 95% RH. Upon drying the sample lost the water and there was no hysteresis

between sorption and desorption. With 8% of water uptake at 80% RH, the sample can be considered moderately hygroscopic. The XRPD analysis of the sample after the DVS analysis indicated that the material had not crystallized.

[00410] *Solubility at room temperature:* the solubility of pomalidomide released from the HPMC-AS LG dispersion was determined as a function of the pH. Suspensions of 10 mg of SUD11 (5% pomalidomide dispersion in HPMC-AS LG) were prepared in 1 mL of buffer solution. The suspensions were incubated at room temperature for 24 hours. At regular intervals samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test the final pH of the solutions was measured. The results are presented in FIG. 21.

[00411] The solubility of pomalidomide released from the HPMC-AS LG dispersion was also determined in water and in a 2% HPMC solution in water at room temperature. The results are presented in FIG. 22.

[00412] The solubility of HPMC-AS is pH dependent and the L-grade is best soluble at pH lower than 5. This was also observed in the results as the highest solubility was reached in buffer solution pH 4 (0.23 mg/mL). After 7 hours the concentration of pomalidomide started to drop, indicating that the supersaturated state was maintained for up to 7 hours. The solubility was slightly lower at pH 5 and decreased further with increasing pH. The pH of the suspension in buffer solution pH 6 had dropped to pH 5.2 and the pH of buffer solution pH 7 had dropped to 6.5 after 24 hours.

[00413] The initial solubility seemed to be fast as the suspensions colored quickly yellow after addition of the buffer solutions with pH 4, 5 and 6 (due to the dissolution of pomalidomide which is yellow). The suspension with buffer solution pH 7 did not change much in color. The suspensions all turned into homogenous milky suspensions.

[00414] The solubility in the 2 wt% HPMC solution was initially higher than in water. The solubility was 0.2 mg/mL after 2 hours in the 2% HPMC solution, but declined over time. The suspension turned into a homogenous milky suspension, whereas the dispersion in water was not miscible and the particles remained floating through the solution. After 24 hours there was no difference in concentration pomalidomide in solution between water and 2% HPMC solution.

[00415] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from the HPMC-AS LG dispersion was evaluated. This experiment simulates the ingestion of a liquid formulation with pomalidomide in HPMC-AS LG containing 4 mg drug equivalent. All volumes and quantities were adjusted to 1/10th of the physiological volumes.

[00416] A suspension of 0.4 mg/mL (pomalidomide equivalents) of the HPMC-AS LG (5% drug load) was prepared in 2wt% HPMC solution. After preparation, the suspension was stirred for 2 hours before a sample was taken for HPLC analysis. The concentration of pomalidomide in solution was 0.160 mg/mL (solute). Of this suspension 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined. The results are presented in FIG. 23.

[00417] In the formulation (2% HPMC solution) 40% of pomalidomide was in solution and the remaining part was present as solid. After the gastric dump the amount of pomalidomide in solution was about 64% in the 15 mL volumes and 73 – 80% in the 25 mL volumes. The temperature had no significant effect on the solubility. Pomalidomide did not precipitate for four hours. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C. The final concentrations of pomalidomide after the gastric dump test are close to the solubility values of pomalidomide in these solutions.

Amorphous solid dispersion with HPMC-AS MG, 5% drug load

[00418] *Scale-up:* an amorphous solid dispersion was prepared with HPMC-AS MG and 5% pomalidomide by freeze drying a solution of pomalidomide and HPMC-AS MG in tetrahydrofuran/water (95/5 v/v). The sample was dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C under deep vacuum. The sample was characterized by XRPD, DSC, TGA and HPLC. The sample was amorphous with 1.86% of residual solvent and a purity of 100% (area%). A glass transition was recorded by DSC with midpoint at 111 °C (with heating rate of 10 °C/min).

[00419] *Physical stability study:* the HPMC-AS MG dispersion with 5% drug load was stored in open containers at 25 °C/58% RH and 40 °C/75% RH for a physical stability test. The samples were analyzed by HT-XRPD at regular intervals. The dispersion remained amorphous up to one month at 25 °C/58% RH and 40 °C/75% RH.

[00420] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability were evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for 3 days and one month and in an open ampoule at 80 °C/75% RH for one month. After the incubation period the solids were analyzed by HT-XRPD and HPLC. The dispersions remained amorphous and were chemically stable when the samples were heated in closed ampoules. When heated under high relative humidity the sample crystallized and started to form impurities.

[00421] *DVS study:* a hygroscopicity study was performed with the HPMC-AS MG dispersion with 5% drug load by DVS analysis. The sample was subjected to one full cycle of sorption and desorption

from 45% - 95% - 0% - 45% relative humidity. The sample showed an almost linear absorption of water with a maximum of 10.2% at 95% RH. Upon drying the sample lost the water and there was no hysteresis between sorption and desorption. The dispersion is moderately hygroscopic as the water uptake at 80% RH was 8%. The XRPD analysis of the sample after the DVS analysis indicated that the material had not crystallized.

[00422] *Solubility at room temperature:* the solubility of pomalidomide released from the HPMC-AS MG dispersion was determined as a function of the pH. Suspensions of 11 mg of SUD14 (5% pomalidomide dispersion in HPMC-AS MG) were prepared in 1 mL of buffer solution. The suspensions were incubated at room temperature for 24 hours. At regular intervals samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test the final pH of the solutions was measured. The results are presented in FIG. 24.

[00423] The solubility of pomalidomide released from the HPMC-AS MG dispersion was also determined in water and in a 2% HPMC solution in water at room temperature. The results are presented in FIG. 25.

[00424] The dispersion with HPMC-AS M-grade had the best solubility in buffer solution with pH 6 and was close to 0.3 mg/mL after 4 hours. After 7 hours the concentration of pomalidomide in solution started to decrease. In buffers with pH 4 and 5 the solubility was approximately 0.2 mg/mL, and remained at that level up to 4 or 7 hours. In the buffer with pH 7, the solubility was approximately 0.1 mg/mL. The pH value of the buffer solution at pH 6 had dropped to pH 5.5 and the pH 7 solution dropped to 6.4 indicating interactions of the buffer solution with the dispersion. Even though the solubility in buffer solution pH 7 was the lowest, the dispersion was best dissolved in this buffer as a suspension was formed with only very fine particles. In the other buffer solutions the dispersions formed milky suspensions with larger particles.

[00425] The initial solubility in the 2% HPMC solution was 0.2 mg/mL but declined over time to reach a similar concentration as in water after 24 hours.

[00426] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from the HPMC-AS MG dispersion was evaluated. This experiment simulates the ingestion of a liquid formulation with pomalidomide in HPMC-AS MG containing 4 mg drug equivalent. All volumes and quantities were adjusted to 1/10th of the physiological volumes.

[00427] A suspension of 0.4 mg/mL (pomalidomide equivalents) of the HPMC-AS MG (5% drug load) was prepared in pH 6 buffer solution. After preparation, the suspension was stirred for 2 hours

before a sample was taken for HPLC analysis. The concentration of pomalidomide in solution was 0.226 mg/mL (solute). Of this suspension, 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined. The results are presented in FIG. 26.

[00428] In the formulation (pH 6 buffer solution) 57% of pomalidomide was in solution and the remaining part was present as solid. After the gastric dump the maximum concentration of pomalidomide in solution was reached at 37 °C. At room temperature about 70 -73% of pomalidomide was in solution. Pomalidomide did not precipitate for four hours. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C. The final concentrations of pomalidomide after the gastric dump test are close to the solubility values of pomalidomide in these solutions.

Amorphous solid dispersion with HPMC-AS HG, 5% drug load

[00429] *Scale-up:* an amorphous solid dispersion was prepared with HPMC-AS HG and 5% pomalidomide by freeze drying a solution of pomalidomide and HPMC-AS HG in tetrahydrofuran/water (95/5 v/v). The sample was dried for 18 hours at RT under deep vacuum followed by 18 hours drying at 40 °C under deep vacuum. The sample was characterized by XRPD, DSC, TGA and HPLC. The sample was amorphous with 1.45% of residual solvent and a purity of 100% (area%). A glass transition was recorded by DSC with midpoint at 108 °C, with a heating rate of 10 °C/min.

[00430] *Physical stability study:* the HPMC-AS HG dispersion with 5% drug load was stored in open containers at 25 °C/58% RH and 40 °C/75% RH. The samples were analyzed by HT-XRPD at regular intervals. The dispersion remained amorphous up to one month at 25 °C/58% RH and 40 °C/75% RH.

[00431] *Stress studies at 80 °C and 100 °C:* the physical and chemical stability were evaluated under high temperature stress conditions. Samples were stored in closed ampoules at 100 °C and at 80 °C for 3 days and one month respectively and in an open ampoule at 80 °C/75% RH for one month. After the incubation period, the solids were analyzed by HT-XRPD and HPLC. The dispersion was physically and chemically stable when heated in closed ampoules. When heated under high relative humidity the sample crystallized and started to form impurities.

[00432] *DVS study:* a hygroscopicity study was performed with the HPMC-AS HG dispersion with 5% drug load by DVS analysis. The sample was subjected to one full cycle of sorption and desorption from 45% - 95% - 0% - 45% relative humidity. The sample showed a gradual absorption of water with a maximum of 13.2% at 95% RH. Upon drying the sample lost the water and there was no hysteresis between sorption and desorption. With 9% of water uptake at 80% RH, the dispersion is classified as

moderately hygroscopic. The XRPD analysis of the sample after the DVS analysis indicated that the material had not crystallized.

[00433] *Solubility at room temperature:* the solubility of pomalidomide released from the 5% drug load in HPMC-AS HG dispersion was determined as a function of the pH. Suspensions of 11 mg of SUD15 (5% pomalidomide dispersion in HPMC-AS HG) were prepared in 1 mL of buffer solution. The suspensions were incubated at room temperature for 24 hours. At regular intervals, samples were taken and analyzed by HPLC. The concentration of pomalidomide in solution was calculated against a calibration curve. Upon completion of the test the final pH of the solutions was measured. The results are presented in FIG. 27.

[00434] The solubility of pomalidomide released from the HPMC-AS HG dispersion was also determined in water and in a 2% HPMC solution in water at room temperature. The results are presented in FIG. 28.

[00435] The solubility of HPMC-AS HG gave best solubility results in the buffer solution with pH 7. The solubility of pomalidomide after 2 hours was determined at 0.5 mg/mL, which was close to 100% of the suspension. After 4 hours the concentration had dropped to 0.25 mg/mL. The initial solubility in buffer solutions with pH 4, 5 and 6 was similar with approximately 0.2 mg/mL up to 4 or 7 hours. After 24 hours the solubility of pomalidomide in buffer solution pH 6 and 7 was the same with 0.16 mg/mL. The solubility after 24 hours in buffer solutions with pH 4 and 5 had dropped below 0.1 mg/mL.

[00436] The pH of suspensions with buffer solutions pH 4, 5 and 6 did not change after 24 hours. The pH of the suspension with buffer solution pH 7 dropped slightly to pH 6.6. In the buffer solution with pH 7 the dispersion reached almost complete dissolution and no particles remained of the HPMC-AS polymer. The other dispersions formed milky suspensions with bigger particles.

[00437] The solubility of pomalidomide released from the HPMC-AS HG dispersion determined in water and in a 2% HPMC solution in water at room temperature gave similar results as with the HPMC-AS L and M-grades. These results indicate that the grade of HPMC-AS does not affect the solubility in the 2% HPMC solution.

[00438] *Precipitation studies in simulated gastric fluids:* the effect of a sudden pH shift on the solubility of pomalidomide from the HPMC-AS HG dispersion was evaluated. This experiment simulates what happens when a liquid based formulation is swallowed.

[00439] A solution of 0.4 mg/mL (pomalidomide equivalents) of the HPMC-AS HG dispersion (5% drug load) was prepared in pH 7 buffer solution. After preparation the mixture was stirred until the dispersion was completely dissolved (1 hour) before a sample was taken for HPLC analysis. The

concentration of pomalidomide in solution was 0.464 mg/mL (solute). Of this solution, 1 mL was added at once to 15 or 25 mL of 0.1 N HCl solution (25 °C and 37 °C). The mixtures were subsequently incubated at 25 °C and 37 °C and every hour a sample was taken and the amount of pomalidomide in solution determined. The results are presented in FIG. 29.

[00440] In the formulation (pH 7 buffer solution) all of the pomalidomide was dissolved (solute was 100%). After the gastric dump, pomalidomide remained in solution and did not precipitate. The pH had not changed after 4 hours and was 1.0 at room temperature and 0.9 at 37 °C. The final concentrations of pomalidomide after the gastric dump test are close to the solubility values of pomalidomide in these solutions.

[00441] A qualitative ranking of the dispersions based on physical chemical characterization of the dispersions is provided in the table below. Physical and chemical stability is given more weight in the ranking, followed closely by the enhancement of the solubility in bio-relevant media. Good solubility in either pH buffers or Glycerin and HPMC solutions makes it more likely that a liquid formulation with the appropriate dose may be prepared from the dispersion.

	HPMC-P	Eudragit RS-100 (5% DL)	Eudragit RS-100 (10% DL)	HPM C (5% DL)	HPM C (10% DL)	PEG 6000	HPMC -AS-LG	HPMC -AS-MG	HPMC -AS-HG
Physical stability	***	***	*	***	*	***	***	***	***
Chemical stability	*	***	***	***	***	N.A.	***	***	***
Solubility in bio-relevant media	***	**	**	**	**	*	N.A.	N.A.	N.A.
Solubility in 2% HPMC or glycerin	***	***	**	**	**	*	***	***	***
Solubility in pH buffers	**	*	*	N.A.	N.A.	*	**	***	***
Hygroscopicity	**	***	***	*	*	N.A.	**	**	**
Final ranking	*	***	*	**	*	*	**	***	***

Qualitative score: *** > ** > *

N.A. = not available (not tested)

Example 6 Scale-up of Amorphous Solid Dispersions with HPMC-P, 5% Drug Load

[00442] The amorphous solid dispersion with HPMC-P was prepared by dissolving 90.7 mg of pomalidomide and 1741 mg of HPMC-P in 60 mL of acetone/water (90/10 v/v). The solution was freeze dried and further dried under deep vacuum for 1 day at RT and 2 days at 40 °C. The material was analyzed by HT-XRPD, DSC, TGMS and HPLC. The HT-XRPD result in FIG. 30 shows the amorphous

nature of the dispersion. The DSC curve in FIG. 31 shows no glass transition but also no melting of pomalidomide indicating no crystalline pomalidomide is present in the batch. In the TGMS analysis in FIG. 32 a mass loss of 2.31% residual acetone was observed. The HPLC chromatogram confirmed that the chemical purity of the batch was 99.8% (area%).

Example 7 Scale-up of Amorphous Solid Dispersions with HPMC-AS HG, 5% Drug Load

[00443] The amorphous solid dispersion with HPMC-AS HG was prepared by dissolving 91.5 mg of pomalidomide and 1751 mg of HPMC-AS HG in 50 mL of tetrahydrofuran/water (95/5 v/v). The solution was freeze dried and further dried under vacuum for 1 day at RT and 2 days at 40 °C. The batch was analyzed by HT-XRPD, DSC, TGMS and HPLC. The HT-XRPD result in FIG. 33 shows the amorphous nature of the dispersion. The DSC curve in FIG. 34 shows a glass transition at 116 °C. Another event was observed at 170 °C, and the analysis by Modulated DSC showed that this event is non-reversible. In the TGMS analysis in FIG. 35 a mass loss of 1.73% residual tetrahydrofuran was observed. The chemical purity was verified by HPLC analysis and was 100% (area%).

Example 8 Pharmacokinetic Evaluation of Pomalidomide in Male Cynomolgus Monkeys

[00444] The objective of this study was to evaluate the pharmacokinetics of pomalidomide (crystalline form and amorphous solid dispersions) in cynomolgus monkeys after a single oral (PO) gavage administration. The study information is summarized in the following Table.

Species and strain	Monkey, Cynomolgus
Test article	Phase 1: pomalidomide (crystalline material) Phase 2: pomalidomide (Amorphous solid dispersion; HPMC-P, 5% drug load, 99.8% purity by HPLC, 2.3% acetone) Phase 3: pomalidomide (Amorphous solid dispersion; HPMC-AS HG, 5% drug load, 100% purity by HPLC, 1.7% tetrahydrofuran)
Route of administration	Oral gavage (PO)
Number of animals/group	3 males
Dose and Dose Vehicle	Oral dose: 1 mg/kg Oral dose vehicle for Phases 1, 2, and 3: 2.0% (w/v) hydroxypropyl methylcellulose (HPMC) (5.0 mPas) in deionized water
Dosing sessions	Phase 1: PO (fasted) pomalidomide (crystalline) Phase 2: PO (fasted) pomalidomide (HPMC-P dispersion) Phase 3: PO (fasted) pomalidomide (HPMC-AS HG dispersion)
Dosing frequency	Single dose for each phase
Sample collection duration	0 to 48 hrs for each phase

Dose volume (mL/kg)	10 mL/kg
Detection method and LLOQ	LC/MS/MS; LLOQ = 1 ng/mL
Analyte	pomalidomide

[00445] Pomalidomide material was administered to male cynomolgus monkeys via PO in a three-phase sequential design with a one week washout between each phase. Phase 1 was a single oral dose of crystalline pomalidomide under fasted state, Phase 2 was a single oral dose of amorphous solid dispersion with 5% drug load of pomalidomide in HPMC-P under fasted state, and Phase 3 was a single oral dose of amorphous solid dispersion with 5% drug load of pomalidomide in HPMC-AS HG under fasted state. Pharmacokinetic parameters were determined using a non-compartmental model and are presented in the following Table.

Phase	Test Article	Dose (mg/kg)	Sex	PK Parameters		
				t _{max} (h)	C _{max} (ng/mL)	AUC _t (ng•h/mL)
1	pomalidomide (crystalline)	1	Male	4 (2 – 4)	413 (86)	4140 (1310)
2	pomalidomide (HPMC-P dispersion)			0.5 (0.5 – 1)	924 (257)	4440 (1830)
3	pomalidomide (HPMC-AS HG dispersion)			1 (0.5 – 1)	881 (50)	4610 (1460)

AUC_t = Area under the concentration-time curve calculated from 0 to the last quantified time point post dosing; C_{max} = Maximum concentration; t_{max} = Time of C_{max}.

N = 3 animals / sex; Values are presented as mean and SD (in parentheses) except for t_{max} where median and range (in parentheses) are shown.

[00446] In monkeys, following a 1 mg/kg dose in Phase 1, the rate of absorption for pomalidomide (crystalline) was moderate, with a mean t_{max} of 4 hours, the mean exposure (AUC_t) was 4140 ng•h/mL and maximum concentration (C_{max}) was 413 ng/mL. In monkeys, following a 1 mg/kg dose in Phase 2, pomalidomide (HPMC-P dispersion) was rapidly absorbed, with a mean t_{max} of 0.5 hours, the mean exposure (AUC_t) was 4440 ng•h/mL and C_{max} was 924 ng/mL. Following a 1 mg/kg dose in Phase 3, pomalidomide (HPMC-AS HG dispersion) was rapidly absorbed, with a mean t_{max} of 1 hour, the mean exposure (AUC_t) was 4610 ng•h/mL and C_{max} was 881 ng/mL. The AUC_t was similar in each phase of the study, but the amorphous material (phases 2 and 3) had a shorter t_{max} and higher C_{max} than the crystalline material (phase 1), which indicates that the amorphous material may be more soluble.

Example 9 Preparation of Cocrystal Comprising Pomalidomide and a Coformer

[00447] The co-crystal screen on pomalidomide was carried out with 10 chemically diverse co-formers and six solvent systems. The screen included four different co-crystallization methods carried out as follows:

[00448] Method A (cooling-evaporative co-crystallization): 120 cooling-evaporative experiments were performed in 1.8 ml HPLC vials, with 10 co-formers, two API:CF ratios and 6 different solvents. The starting material (about 20 mg) and co-former (1:1.1 and 1:4 ratios) were dosed in 1.8 mL vials. A suitable volume of solvent was added to reach a close to saturated solution. Following, the vials were placed in Crystal16™ to undergo a temperature profile. At the end of the temperature profile, the solids were separated from the liquids and dried. The mother liquors, after separation of solids, were slowly evaporated. In all cases where no solids had precipitated, the solvents were slowly evaporated.

[00449] Method B (saturated API solution co-crystallization): 60 saturated API solution co-crystallization experiments were performed with 10 co-formers and 6 different solvents. Slurries of the API were prepared by weighing about 20 mg of pomalidomide. Subsequently, between 2-7 mL of solvent was added to each experiment to have a close to saturated solution, depending on the solubility of pomalidomide in the solvent or solvent mixture selected. The slurries were left stirring overnight (16 hours) at room temperature. After this time, the slurries were filtered so a saturated solution was obtained. The co-former was added to a saturated solution of the API. The mixtures were aged for 4 hours at ambient temperature while stirring. Subsequently, the solids were separated from the liquids and dried. The mother liquors, after separation of solids were slowly evaporated.

[00450] Method C (slurry conversion co-crystallization): 60 slurry conversion co-crystallization experiments were performed with 10 co-formers and 6 different solvents. The starting material (about 20 mg) and the co-former (1:1.1 ratio) were dosed in 1.8 mL vials. A suitable volume of solvent was added to obtain a slurry. The mixtures were placed in Crystal16™ to undergo a temperature profile. At the end of the temperature profile, the solids were separated from the liquids and dried. The mother liquors, after separation of solids were slowly evaporated.

[00451] Method D (wet grinding co-crystallization): 60 wet grinding co-crystallization experiments were performed with 10 co-formers and 6 different solvents. About 40 mg of the API was weighed into metal grinding vials, containing two stainless steel grinding balls. The co-formers (about 1.1 equivalent) and solvents were added and shaken for 1 hour with a frequency of 30 Hz.

[00452] The 10 co-formers selected for this study were saccharin, nicotinamide, 4-hydroxybenzamide, orotic acid, succinic acid, L(-)-malic acid, L(+)-arginine, fumaric acid, lactamide, and valerolactam.

[00453] The solvents used for each methods are listed in the following Table.

Cooling evaporation	Saturated solutions	Slurry	Co-Grinding
1,4-Dioxane	1,4-Dioxane	THF	2-Butanone
DMF/acetone (40/60)	DMF/methanol (50/50)	Acetone	1,4-Dioxane/water (50/50)
THF/water (95/5)	DMA/acetone (50/50)	Ethanol	Isopropyl acetate
Acetonitrile/chloroform (50/50)	THF/water (95/5)	Ethyl acetate	IPA
Methanol	DMSO/water (80/20)	Water	Chloroform
DMA/IPA (50/50)	DMF/acetone (40/60)	1,4-Dioxane/water (50/50)	2-Methyltetrahydrofuran

[00454] All solids obtained from the co-crystallization studies were analyzed by XRPD.

Subsequently, the solids were exposed to accelerated ageing conditions (40 °C and 75% RH) (AAC) for 2 days and re-analyzed by XRPD.

[00455] The XRPD analysis showed that most of the solids obtained from the co-crystallization studies were mixtures of the API with the co-formers, the API starting material alone, or the co-formers alone. 14 unique XRPD patterns were identified with saccharin, 4-hydroxybenzamide, fumaric acid, L-arginine, orotic acid, malic acid and nicotinamide as the co-formers. The secondary analyses (TGMS and FTIR) confirmed successful co-crystallization of four cocrysals of pomalidomide with L-arginine, orotic acid, or nicotinamide.

Nicotinamide

[00456] Form NIA is a potential co-crystal formed by pomalidomide and nicotinamide. This co-crystal was produced after accelerated aging conditions from two saturated API solution co-crystallization experiments, from DMA/acetone (50/50, v/v) and from DMF/acetone (40/60, v/v). The XRPD patterns of the experiment in DMF/acetone before and after AAC are presented in FIG. 36.

[00457] The TGMS analysis showed no mass loss prior to the thermal decomposition, indicating that Form NIA is an anhydrous form. One single endothermic melt was determined at 138 °C which might be attributed to the endothermic melt of NIA.

[00458] Compared to pomalidomide, the vibration shifts visible in the FTIR spectrum of NIA suggest the formation of a co-crystal of pomalidomide and nicotinamide especially in the region 3400-3000 cm⁻¹ (FIG. 37A) and 1800-1400 cm⁻¹ (FIG. 37B).

L-Arginine

[00459] Form ARG is a potential co-crystal formed by pomalidomide and L-arginine. This co-crystal was obtained from the cooling crystallization experiments in DMF/acetone (40/60, v/v) with two API:CF ratios (1:1.1 and 1:4). In both cases, Form ARG was produced as a mixture containing some non-reacted API. The XRPD analysis showed that this mixture dissociated and converted to a physical mixture of API and L-arginine after exposure to accelerated aging conditions (FIG. 38).

[00460] A mass loss of 2.2 % was determined in the thermal analysis of the co-crystal form. This mass loss might be attributed to some residual acetone and DMF. After the solvent loss, an endothermic event was identified at 224 °C corresponding to melting and thermal decomposition. The endothermic melt observed after the solvent loss might suggest the formation of an anhydrous pomalidomide and L-arginine co-crystal.

[00461] The overlay of FTIR spectra between 4000 to 1800 cm^{-1} (FIG. 39A) and between 1800 to 400 cm^{-1} (FIG. 39B) of starting material pomalidomide, reference of L-arginine, and Form ARG obtained in this study (a mixture with Form A) showed a few shift of vibrations between 1600-1400 cm^{-1} which might be attributed to the co-crystal formation. A strong influence of non-reacted pomalidomide is visible in this spectrum.

Orotic acid

[00462] Form ORO1 and Form ORO2 are two potential co-crystals formed by pomalidomide and orotic acid.

[00463] Form ORO1 was obtained from saturated API solution and slurry co-crystallization experiments in DMF/acetone (40/60, v/v) and 1,4-dioxane/water (50/50, v/v), respectively. In both cases, Form ORO1 was obtained in combination with the starting material Form A. After exposure to accelerated aging conditions, conversion to the starting material form or to a mixture of neat co-former and API was observed. The XRPD analysis was performed on the solid material obtained from the 1,4-dioxane/water (50/50, v/v) experiment (FIG. 40).

[00464] The thermal analysis confirmed the solvated nature of Form ORO1. A mass loss of 8.8% corresponding to 0.3 molecules of 1,4-dioxane was observed. One single endothermic event was identified at 168 °C attributed to the melting and solvent loss.

[00465] ORO1 was also produced from a DMF/acetone solvent mixture. Based on the solvated nature observed in the TGMS, ORO1 can form two isostructural solvates with similar crystal packing and unit cell parameters but with different solvents in the crystal structure (1,4-dioxane or DMF).

[00466] The overlay of FTIR spectra between 4000 to 1800 cm^{-1} (FIG. 41A) and between 1800 to 400 cm^{-1} (FIG. 41B) of starting material pomalidomide, reference of orotic acid, and Form ORO1 obtained in this study (a mixture with Form A) indicated that pomalidomide is able to make co-crystals with orotic acid. Mainly the starting material Form A of pomalidomide was visible in the Form ORO1 spectrum. However, changes were observed in the region 1800-1200 cm^{-1} which might be attributed to interactions between co-former molecules and pomalidomide.

[00467] Form ORO2 was identified from the saturated API solution co-crystallization experiment in: DMF/methanol (50/50, v/v), DMA/acetone (50/50, v/v) and DMSO/water (80/20, v/v). In most cases, Form ORO2 was obtained after evaporation of the mother liquor and in a physical mixture with the API. From DMSO/water (80/20, v/v), Form ORO2 was obtained as a pure solid form. The XRPD analysis of Form ORO2 before and after exposure to 40 °C and 75% RH for 2 days is presented in FIG. 42. Form ORO2 dissociates in its components after exposure to accelerated aging conditions for 2 days.

[00468] The thermal analysis of Form ORO2 indicated the presence of 27.9% of DMSO. This mass loss corresponds to 1.4 molecule of DMSO per molecule of API. This result confirmed the solvated nature of Form ORO2. A broad endotherm was observed with an onset of 110 °C corresponding to the solvent loss.

[00469] Form ORO2 was produced from other high boiling point solvents such as DMA and DMF. Therefore, it is likely that Form ORO2 is an isostructural solvated co-crystal that can be obtained with different solvents giving the same crystal structure.

[00470] The overlay of FTIR spectra between 4000 to 1800 cm^{-1} (FIG. 43A) and between 1800 to 400 cm^{-1} (FIG. 43B) of starting material pomalidomide, reference of orotic acid, and Form ORO2 obtained in this study showed significant shifts of vibration in the region 1800-1500 cm^{-1} . These changes suggest the formation of a pomalidomide and orotic acid co-crystal.

Example 10 Assays

TNFA Inhibition Assay in PBMC

[00471] Peripheral blood mononuclear cells (PBMC) from normal donors are obtained by Ficoll Hypaque (Pharmacia, Piscataway, NJ, USA) density centrifugation. Cells are cultured in RPMI 1640 (Life Technologies, Grand Island, NY, USA) supplemented with 10% AB+human serum (Gemini Bio-products, Woodland, CA, USA), 2 mM L-glutamine, 100 U/ml penicillin, and 100 $\mu\text{g}/\text{ml}$ streptomycin (Life Technologies).

[00472] PBMC (2×10^5 cells) are plated in 96-well flat-bottom Costar tissue culture plates (Corning, NY, USA) in triplicate. Cells are stimulated with LPS (from *Salmonella abortus equi*, Sigma cat. no. L-1887, St. Louis, MO, USA) at 1 ng/mL final in the absence or presence of compounds. Compounds provided herein are dissolved in DMSO (Sigma) and further dilutions are done in culture medium immediately before use. The final DMSO concentration in all assays can be about 0.25%. Compounds are added to cells 1 hour before LPS stimulation. Cells are then incubated for 18-20 hours at 37 °C in 5 % CO₂, and supernatants are then collected, diluted with culture medium and assayed for TNF α levels by ELISA (Endogen, Boston, MA, USA). IC₅₀s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100% and bottom to 0%, allowing variable slope (GraphPad Prism v3.02).

IL-2 and MIP-3 α Production by T Cells

[00473] PBMC are depleted of adherent monocytes by placing 1×10^8 PBMC in 10 ml complete medium (RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μ g/ml streptomycin) per 10 cm tissue culture dish, in 37°C, 5 % CO₂ incubator for 30-60 minutes. The dish is rinsed with medium to remove all non-adherent PBMC. T cells are purified by negative selection using the following antibody (Pharmingen) and Dynabead (Dyna) mixture for every 1×10^8 non-adherent PBMC: 0.3 ml Sheep anti-mouse IgG beads, 15 μ l anti-CD16, 15 μ l anti-CD33, 15 μ l anti-CD56, 0.23 ml anti-CD19 beads, 0.23 ml anti-HLA class II beads, and 56 μ l anti-CD14 beads. The cells and bead/antibody mixture is rotated end-over-end for 30-60 minutes at 4°C. Purified T cells are removed from beads using a Dynal magnet. Typical yield is about 50% T cells, 87-95% CD3⁺ by flow cytometry.

[00474] Tissue culture 96-well flat-bottom plates are coated with anti-CD3 antibody OKT3 at 5 μ g/ml in PBS, 100 μ l per well, incubated at 37°C for 3-6 hours, then washed four times with complete medium 100 μ l/well just before T cells are added. Compounds are diluted to 20 times of final in a round bottom tissue culture 96-well plate. Final concentrations are about 10 μ M to about 0.00064 μ M. A 10 mM stock of compounds provided herein is diluted 1:50 in complete for the first 20x dilution of 200 μ M in 2 % DMSO and serially diluted 1:5 into 2 % DMSO. Compound is added at 10 μ l per 200 μ l culture, to give a final DMSO concentration of 0.1 %. Cultures are incubated at 37°C, 5 % CO₂ for 2-3 days, and supernatants analyzed for IL-2 and MIP-3 α by ELISA (R&D Systems). IL-2 and MIP-3 α levels are normalized to the amount produced in the presence of an amount of a compound provided herein, and EC₅₀s calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope (GraphPad Prism v3.02).

Cell Proliferation Assay

[00475] Cell lines Namalwa, MUTZ-5, and UT-7 are obtained from the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (Braunschweig, Germany). The cell line KG-1 is obtained from the American Type Culture Collection (Manassas, VA, USA). Cell proliferation as indicated by ³H-thymidine incorporation is measured in all cell lines as follows.

[00476] Cells are plated in 96-well plates at 6000 cells per well in media. The cells are pre-treated with compounds at about 100, 10, 1, 0.1, 0.01, 0.001, 0.0001 and 0 μ M in a final concentration of about 0.25 % DMSO in triplicate at 37°C in a humidified incubator at 5 % CO₂ for 72 hours. One microcurie of ³H-thymidine (Amersham) is then added to each well, and cells are incubated again at 37°C in a humidified incubator at 5 % CO₂ for 6 hours. The cells are harvested onto UniFilter GF/C filter plates (Perkin Elmer) using a cell harvester (Tomtec), and the plates are allowed to dry overnight. Microscint 20 (Packard) (25 μ l/well) is added, and plates are analyzed in TopCount NXT (Packard). Each well is counted for one minute. Percent inhibition of cell proliferation is calculated by averaging all triplicates and normalizing to the DMSO control (0 % inhibition). Each compound is tested in each cell line in three separate experiments. Final IC₅₀s are calculated using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope. (GraphPad Prism v3.02).

Immunoprecipitation and Immunoblot

[00477] Namalwa cells are treated with DMSO or an amount of a compound provided herein for 1 hour, then stimulated with 10 U/ml of Epo (R&D Systems) for 30 minutes. Cell lysates are prepared and either immunoprecipitated with Epo receptor Ab or separated immediately by SDS-PAGE. Immunoblots are probed with Akt, phospo-Akt (Ser473 or Thr308), phosho-Gab1 (Y627), Gab1, IRS2, actin and IRF-1 Abs and analyzed on a Storm 860 Imager using ImageQuant software (Molecular Dynamics).

Cell Cycle Analysis

[00478] Cells are treated with DMSO or an amount of a compound provided herein overnight. Propidium iodide staining for cell cycle is performed using CycleTEST PLUS (Becton Dickinson) according to manufacturer's protocol. Following staining, cells are analyzed by a FACSCalibur flow cytometer using ModFit LT software (Becton Dickinson).

Apoptosis Analysis

[00479] Cells are treated with DMSO or an amount of a compound provided herein at various time points, then washed with annexin-V wash buffer (BD Biosciences). Cells are incubated with annexin-V binding protein and propidium iodide (BD Biosciences) for 10 minutes. Samples are analyzed using flow cytometry.

Luciferase Assay

[00480] Namalwa cells are transfected with 4 µg of AP1-luciferase (Stratagene) per 1×10^6 cells and 3 µl Lipofectamine 2000 (Invitrogen) reagent according to manufacturer's instructions. Six hours post-transfection, cells are treated with DMSO or an amount of a compound provided herein. Luciferase activity is assayed using luciferase lysis buffer and substrate (Promega) and measured using a luminometer (Turner Designs).

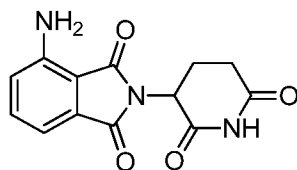
[00481] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

[00482] All of the patents, patent applications and publications referred to herein are incorporated herein in their entireties. Citation or identification of any reference in this application is not an admission that such reference is available as prior art. The full scope of the disclosure is better understood with reference to the appended claims.

CLAIMS

What is claimed is:

1. A solid dispersion comprising a compound of Formula (I):



(I),

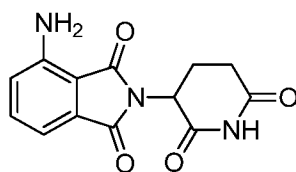
or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof, wherein the compound of Formula (I) is dispersed in a solid matrix that comprises at least one polymer.

2. The solid dispersion of claim 1, wherein the polymer is a hydrophilic polymer.
3. The solid dispersion of claim 1, wherein the polymer is selected from the group consisting of cellulose esters and cellulose ethers, polyalkylene oxides, polyacrylates and polymethacrylates, homopolymers and copolymers of N-vinyl lactams, polyacrylamides, vinyl acetate polymers, graft copolymers of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, oligo- and polysaccharides, and mixtures of two or more thereof.
4. The solid dispersion of claim 3, wherein the polymer is a cellulose ester or cellulose ether.
5. The solid dispersion of claim 3, wherein the polymer is a polyalkylene oxide.
6. The solid dispersion of claim 3, wherein the polymer is a polyacrylate or polymethacrylate.
7. The solid dispersion of claim 1, wherein the polymer is methyl cellulose, ethyl cellulose, Eudragit RS 100, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose, Eudragit S 100, hydroxypropyl methylcellulose phthalate 50 (HPMC-P), poly(ethylene glycol) methyl, polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone K30, poly(1-vinylpyrrolidone-co-vinyl acetate), Sureteric, Pluronic F-68, Tween 80, or hydroxypropyl methylcellulose acetate-succinate (HPMC-AS).
8. The solid dispersion of claim 7, wherein the polymer is ethyl cellulose, Eudragit RS 100, HPMC, hydroxypropyl cellulose, HPMC-P, poly(1-vinylpyrrolidone-co-vinyl acetate), or HPMC-AS.
9. The solid dispersion of claim 8, wherein the polymer is HPMC-P.

10. The solid dispersion of claim 8, wherein the polymer is HPMC-AS LG, HPMC-AS MG, or HPMC-AS HG.
11. The solid dispersion of claim 8, wherein the polymer is HPMC-AS HG.
12. The solid dispersion of any one of claims 1 to 11, wherein the compound of Formula (I) is present in an amount of from about 1% to about 50% by weight of the solid dispersion.
13. The solid dispersion of claim 12, wherein the compound of Formula (I) is present in an amount of from about 2.5% to about 25% by weight of the solid dispersion.
14. The solid dispersion of claim 13, wherein the compound of Formula (I) is present in an amount of from about 5% to about 10% by weight of the solid dispersion.
15. The solid dispersion of claim 13, wherein the compound of Formula (I) is present in an amount of about 5% by weight of the solid dispersion.
16. The solid dispersion of claim 13, wherein the compound of Formula (I) is present in an amount of about 10% by weight of the solid dispersion.
17. The solid dispersion of any one of claims 1 to 16, wherein the compound of Formula (I) is substantially non-crystalline.
18. The solid dispersion of any one of claims 1 to 16, wherein no more than 5% of the compound of Formula (I) is crystalline.
19. The solid dispersion of claim 18, wherein no more than 2% of the compound of Formula (I) is crystalline.
20. The solid dispersion of claim 19, wherein no more than 1% of the compound of Formula (I) is crystalline.
21. The solid dispersion of any one of claims 18 to 20, wherein the crystalline form of the compound of Formula (I) is Form A of the compound of Formula (I).
22. The solid dispersion of any one of claims 1 to 16, wherein the compound of Formula (I) is amorphous.

23. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC-P.
24. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises Eudragit RS 100.
25. The solid dispersion of claim 1, comprising about 10% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises Eudragit RS 100.
26. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC.
27. The solid dispersion of claim 1, comprising about 10% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC.
28. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises PEG 6000.
29. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC-AS LG.
30. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC-AS MG.
31. The solid dispersion of claim 1, comprising about 5% by weight of the solid dispersion of an amorphous compound of Formula (I), dispersed in a solid matrix that comprises HPMC-AS HG.
32. A pharmaceutical composition comprising the solid dispersion of any one of claims 1 to 31, and a pharmaceutically acceptable excipient.
33. A method of treating a disease or disorder, comprising administering to a subject having the disease or disorder a therapeutically effective amount of the solid dispersion of any one of claims 1 to 31 or the pharmaceutical composition of claim 32.
34. The method of claim 33, wherein the disease or disorder is cancer.
35. The method of claim 34, wherein the cancer is a pediatric CNS cancer.
36. The method of claim 34, wherein the cancer is glioma.

37. The method of any one of claims 33 to 36, wherein the disease or disorder is relapsed or refractory.
38. The method of any one of claims 33 to 37, further comprising administering a second active agent.
39. The method of any one of claims 33 to 38, wherein the subject is a child or young adult.
40. A process for preparing a solid dispersion of any one of claims 1-31, comprising (a) providing a solution of the compound of Formula (I) and the polymer in a solvent system; and (b) removing the solvent to provide the solid dispersion.
41. The process of claim 40, wherein the solvent system is tetrahydrofuran, acetone, water, or a mixture thereof.
42. The process of claim 41, wherein the solvent system is acetone, a mixture of tetrahydrofuran and water, or a mixture of acetone and water.
43. The process of any one of claims 40 to 42, wherein the solvent is removed by freeze evaporation.
44. A process for preparing a solid dispersion of claim 1, comprising melting a mixture of the compound of Formula (I) and the polymer.
45. A solid form comprising a compound of Formula (I):,



(I),

or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof; and a coformer, wherein the coformer is nicotinamide, L-arginine, or orotic acid.

46. The solid form of claim 45, wherein the coformer is nicotinamide.
47. The solid form of claim 46, having an X-ray powder diffraction pattern comprising peaks at approximately 17.8, 21.9, and 27.0 degrees 2θ , plus or minus 0.2 degrees 2θ .

48. The solid form of claim 47, having an X-ray powder diffraction pattern further comprising peaks at approximately 15.4 and 27.7 degrees 2θ , plus or minus 0.2 degrees 2θ .
49. The solid form of claim 46, having an X-ray powder diffraction pattern which matches the XRPD pattern presented in FIG. 36.
50. The solid form of claim 45, wherein the coformer is L-arginine.
51. The solid form of claim 50, having an X-ray powder diffraction pattern comprising peaks at approximately 16.0, 19.8, and 23.4 degrees 2θ , plus or minus 0.2 degrees 2θ .
52. The solid form of claim 51, having an X-ray powder diffraction pattern further comprising peaks at approximately 25.5 and 26.9 degrees 2θ , plus or minus 0.2 degrees 2θ .
53. The solid form of claim 50, having an X-ray powder diffraction pattern which matches the XRPD pattern presented in FIG. 38.
54. The solid form of claim 45, wherein the coformer is orotic acid.
55. The solid form of claim 54, having an X-ray powder diffraction pattern comprising peaks at approximately 14.0, 25.5, and 28.2 degrees 2θ , plus or minus 0.2 degrees 2θ .
56. The solid form of claim 55, having an X-ray powder diffraction pattern further comprising peaks at approximately 12.3 and 17.3 degrees 2θ , plus or minus 0.2 degrees 2θ .
57. The solid form of claim 55, having an X-ray powder diffraction pattern which matches the XRPD pattern presented in FIG. 40.
58. The solid form of claim 54, having an X-ray powder diffraction pattern comprising peaks at approximately 9.9, 24.1, and 26.9 degrees 2θ , plus or minus 0.2 degrees 2θ .
59. The solid form of claim 58, having an X-ray powder diffraction pattern further comprising peaks at approximately 21.0 and 25.0 degrees 2θ , plus or minus 0.2 degrees 2θ .
60. The solid form of claim 59, having an X-ray powder diffraction pattern which matches the XRPD pattern presented in FIG. 42.
61. The solid form of any one of claims 45 to 60, wherein the molar ratio of the compound of Formula (I) to the coformer is about 1:1.

62. The solid form of any one of claims 45 to 61, which is substantially crystalline.
63. The solid form of claim 62, which is substantially a cocrystal.
64. The solid form of claim 62, which is greater than 80%, greater than 90%, greater than 95%, greater than 97%, or greater than 99% a cocrystal.
65. The solid form of any one of claims 45 to 64, which is substantially pure.
66. The solid form of any one of claims 45 to 64, further comprising a second solid form of the compound of Formula (I).
67. The solid form of claim 66, wherein the second solid form of the compound of Formula (I) is Form A of the compound of Formula (I).
68. The solid form of claim 66, wherein the second solid form of the compound of Formula (I) is an amorphous form of the compound of Formula (I).
69. The solid form of any one of claims 45 to 64, further comprising a second solid form of the coformer.
70. A pharmaceutical composition comprising the solid form of any one of claims 45 to 69, and a pharmaceutically acceptable excipient.
71. A method of treating a disease or disorder, comprising administering to a subject having the disease or disorder a therapeutically effective amount of the solid form of any one of claims 45 to 69 or the pharmaceutical composition of claim 70.
72. The method of claim 71, wherein the disease or disorder is cancer.
73. The method of claim 72, wherein the cancer is a pediatric CNS cancer.
74. The method of claim 72, wherein the cancer is glioma.
75. The method of any one of claims 71 to 74, wherein the disease or disorder is relapsed or refractory.
76. The method of any one of claims 71 to 74, further comprising administering a second active agent.

77. The method of any one of claims 71 to 74, wherein the subject is a child or young adult.
78. The solid dispersion of any one of claims 1 to 31, or the pharmaceutical composition of claim 32 as a medicament.
79. The solid dispersion of any one of claims 1 to 31, or the pharmaceutical composition of claim 32 for use in a method of treating a disease or disorder.
80. The solid dispersion or the pharmaceutical composition for use of claim 79, wherein the disease or disorder is cancer.
81. The solid dispersion or the pharmaceutical composition for use of claim 80, wherein the cancer is a pediatric CNS cancer or a glioma.
82. The solid dispersion or the pharmaceutical composition for use of any one of claims 79 to 81, wherein the disease or disorder is relapsed or refractory.
83. The solid dispersion or the pharmaceutical composition for use of any one of claims 79 to 82, wherein the method further comprises administering a second active agent.
84. The solid dispersion or the pharmaceutical composition for use of any one of claims 79 to 83, wherein the subject is a child or young adult.
85. The solid form of any one of claims 45 to 69 or the pharmaceutical composition of claim 70 as a medicament.
86. The solid form of any one of claims 45 to 69 or the pharmaceutical composition of claim 70 for use in a method of treating a disease or disorder.
87. The solid form or the pharmaceutical composition for use of claim 86, wherein the disease or disorder is cancer.
88. The solid form or the pharmaceutical composition for use of claim 87, wherein the cancer is a pediatric CNS cancer or a glioma.
89. The solid form or the pharmaceutical composition for use of any one of claims 86 to 88, wherein the disease or disorder is relapsed or refractory.

90. The solid form or the pharmaceutical composition for use of any one of claims 86 to 89, wherein the method further comprises administering a second active agent.

91. The solid form or the pharmaceutical composition for use of any one of claims 86 to 90, wherein the subject is a child or young adult.

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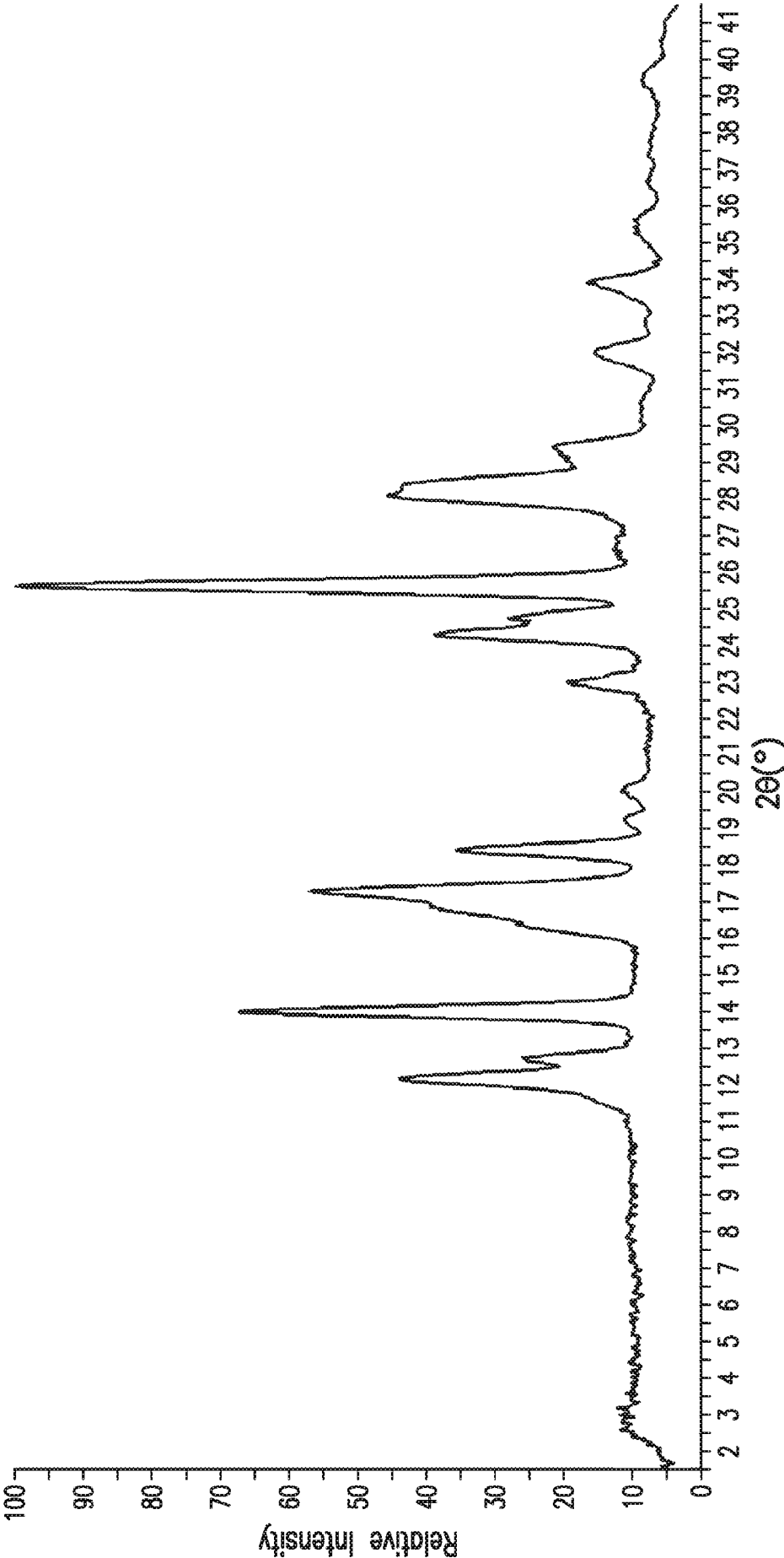


FIG. 1

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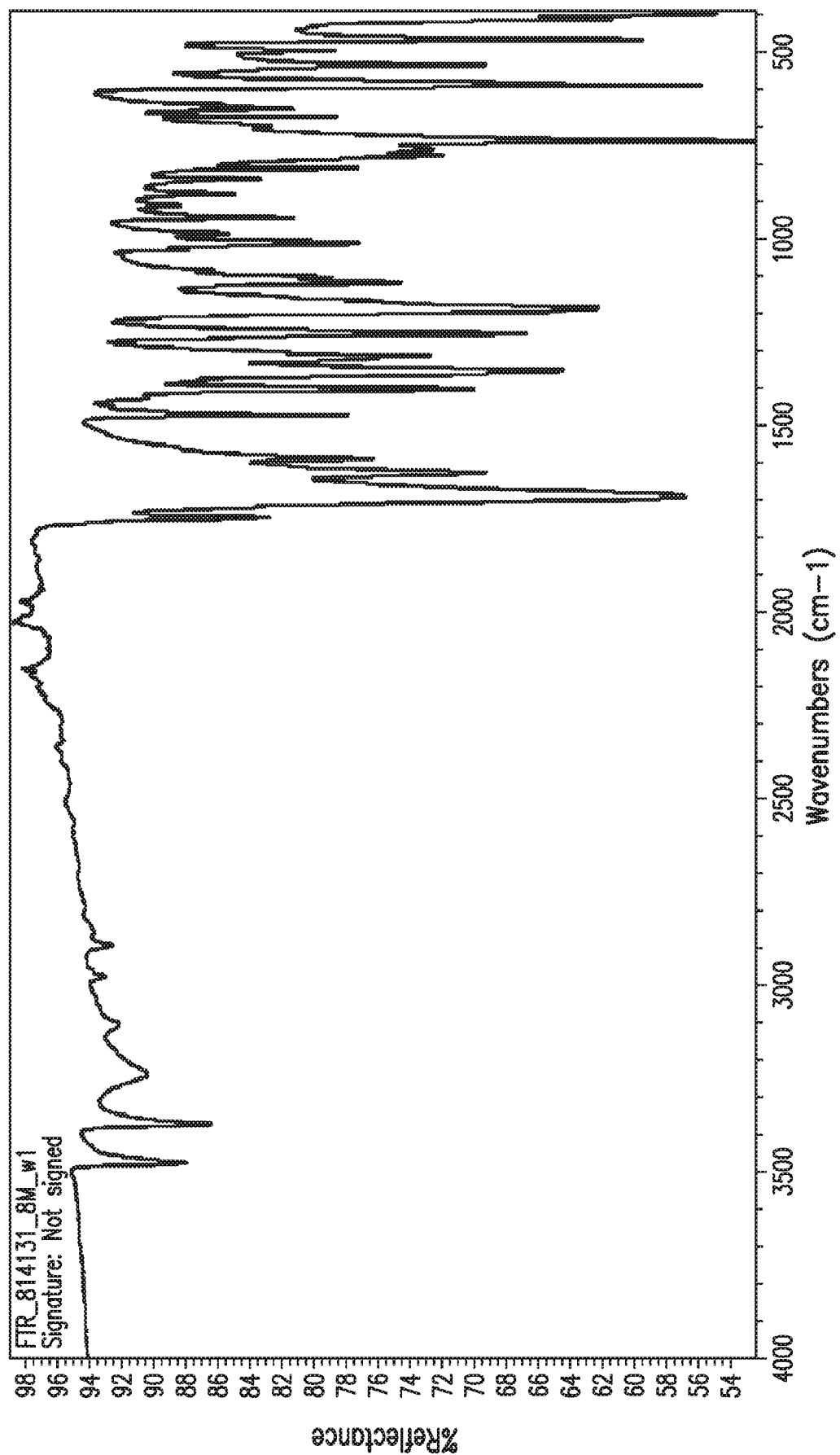


FIG. 2

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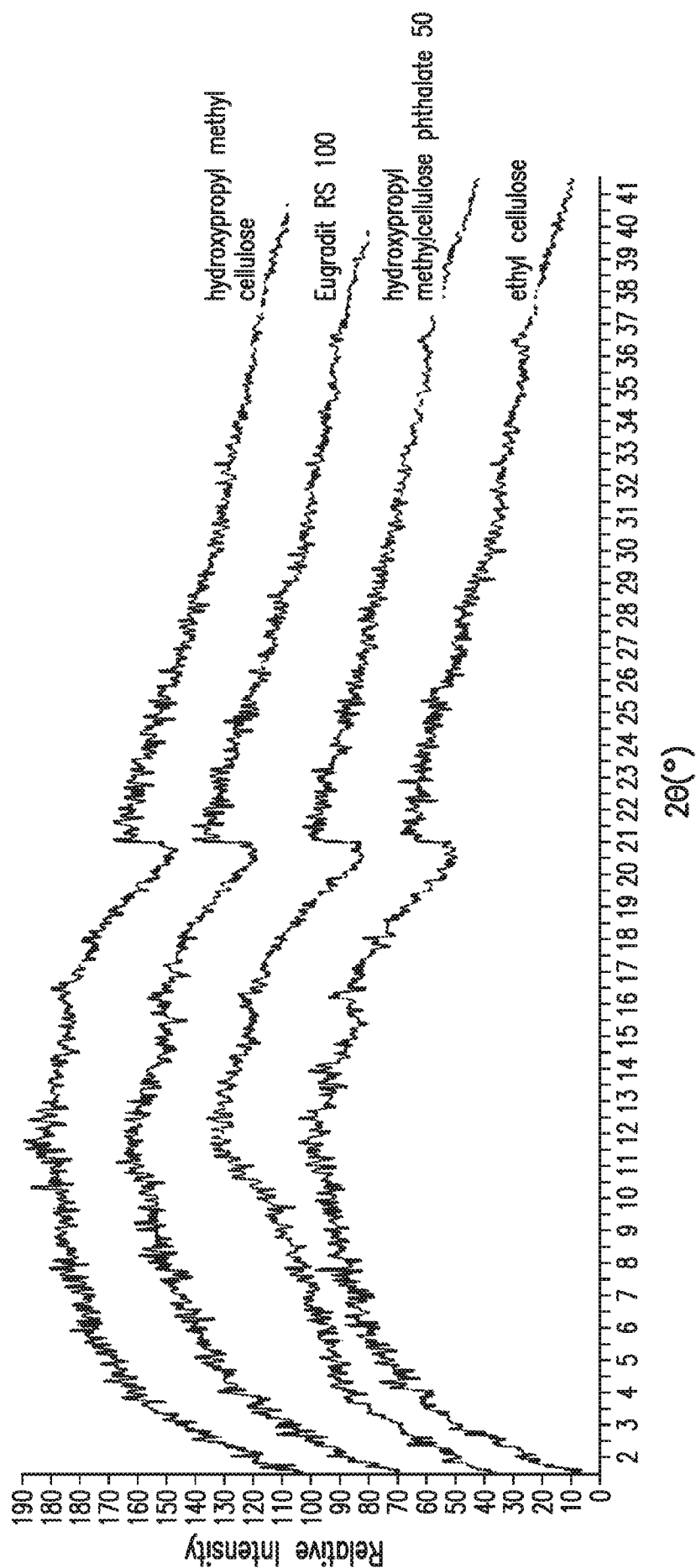


FIG. 3

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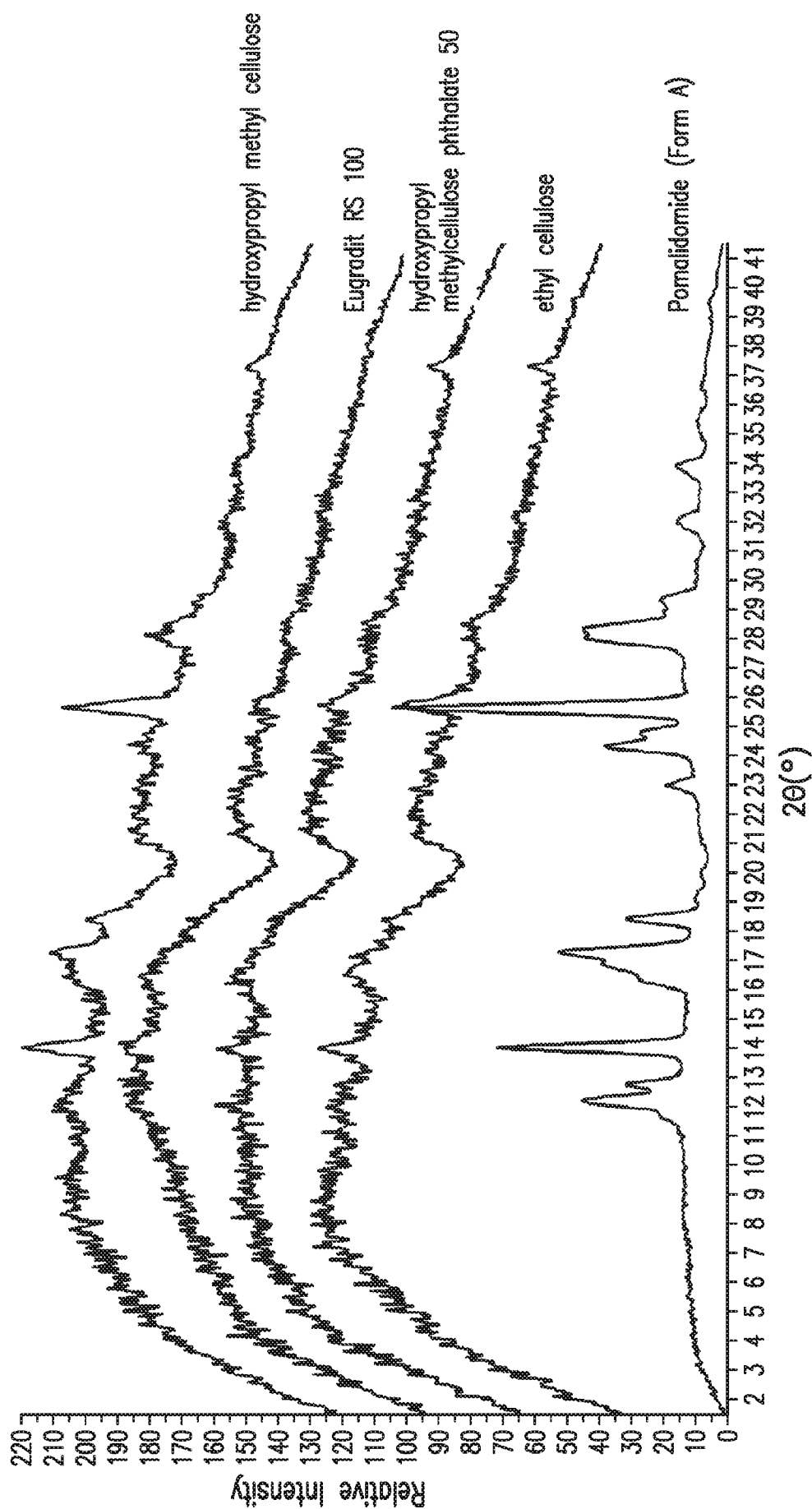


FIG. 4

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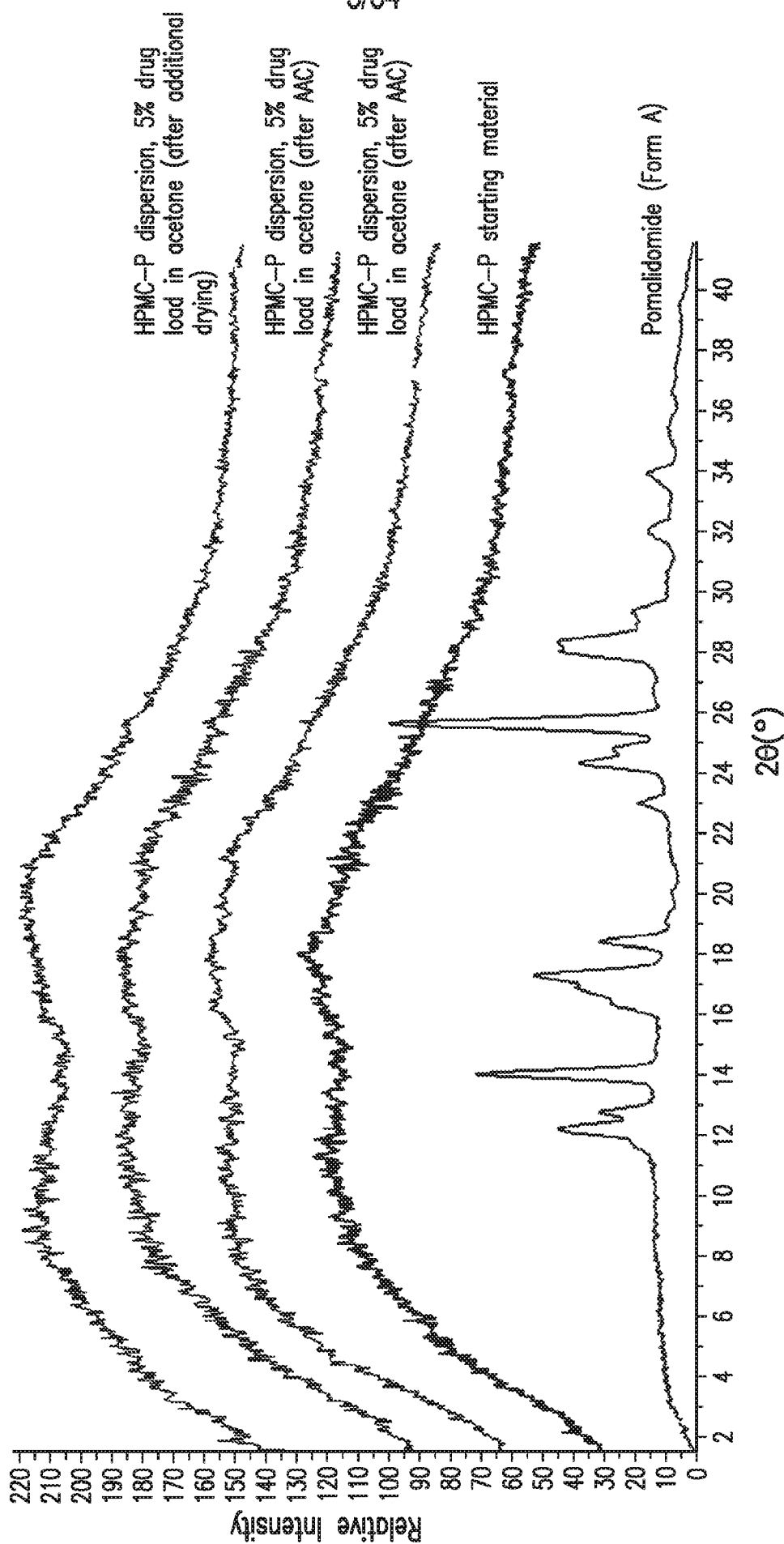


FIG. 5

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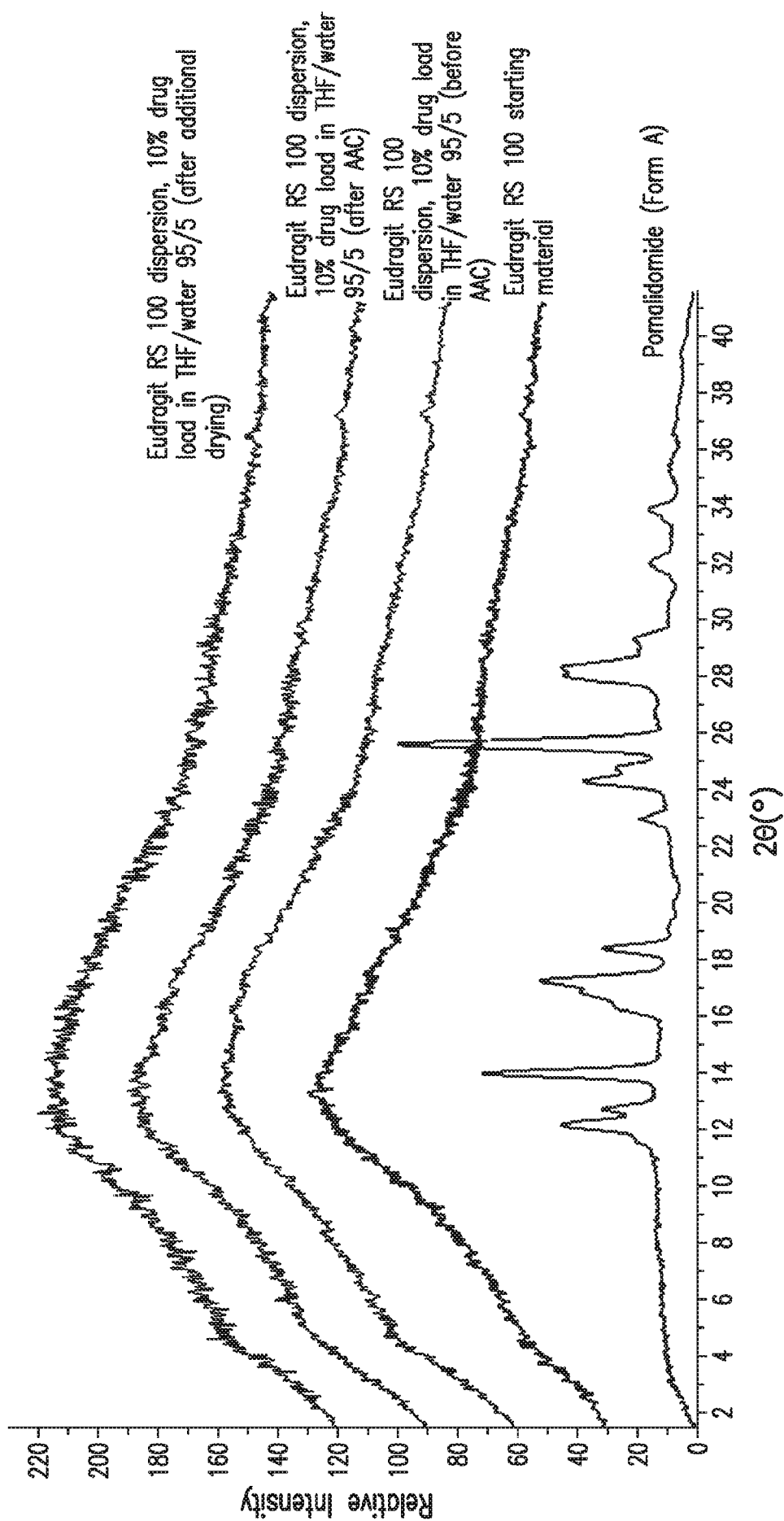


FIG. 6

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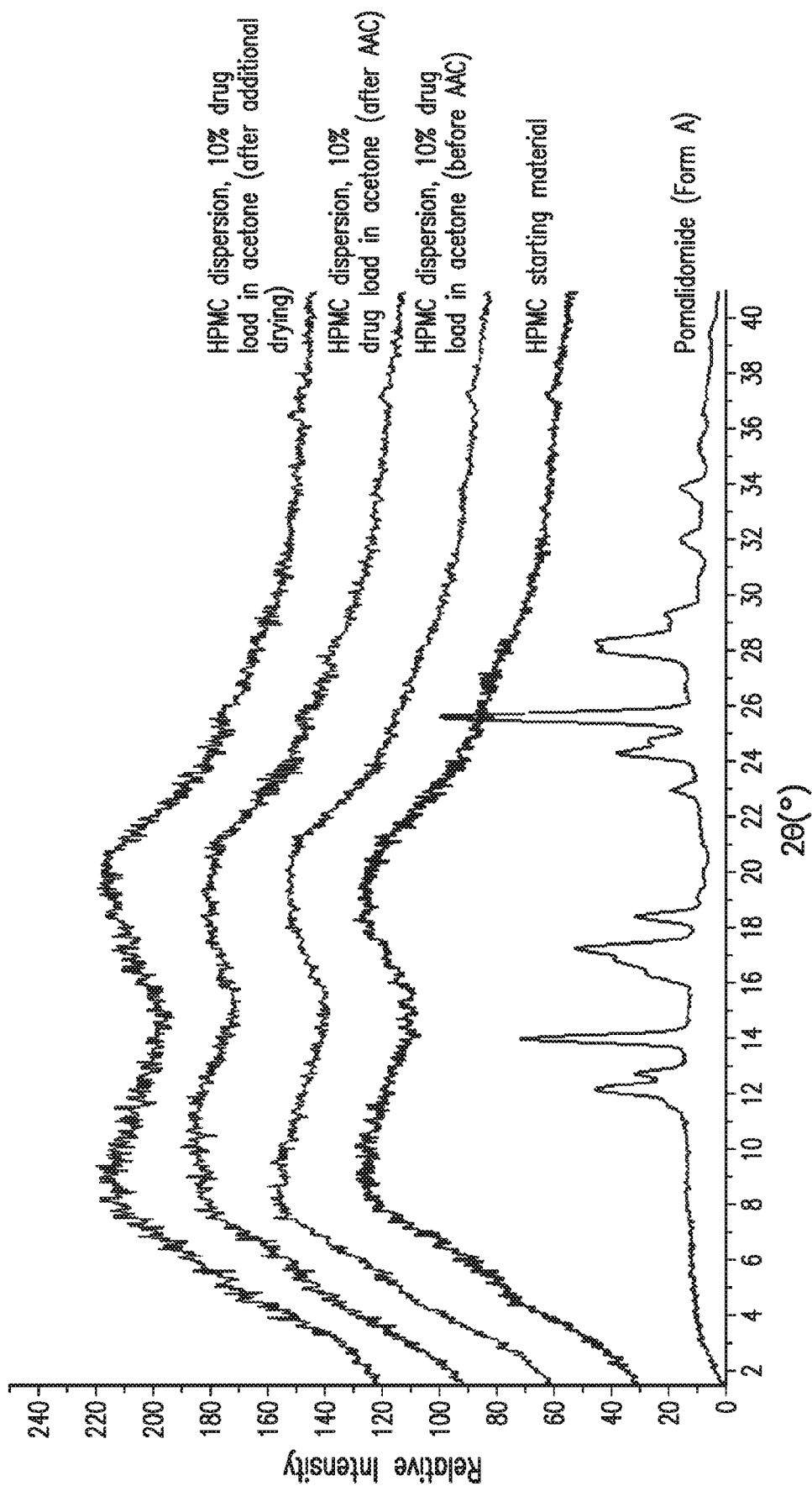


FIG. 7

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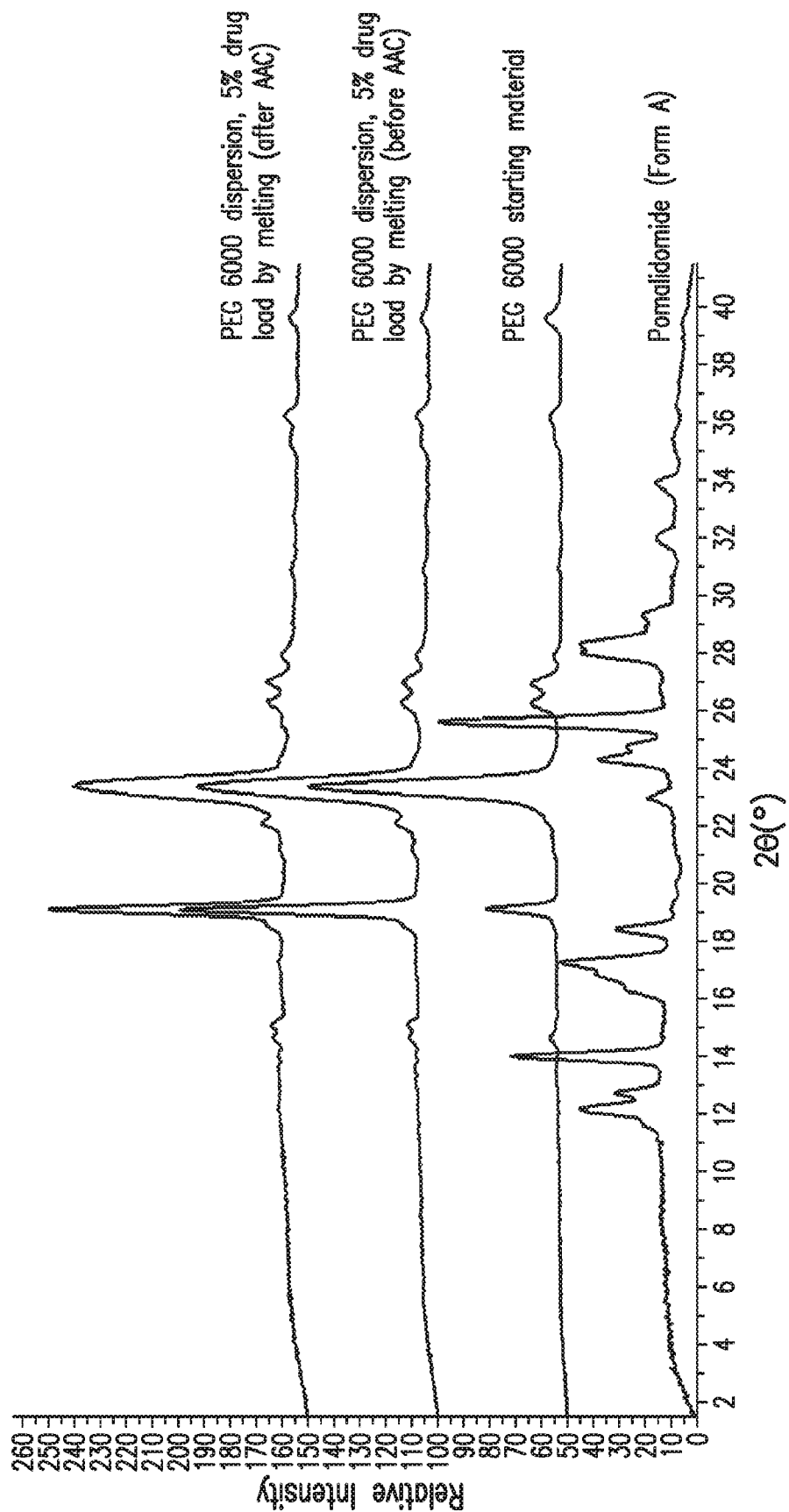


FIG. 8

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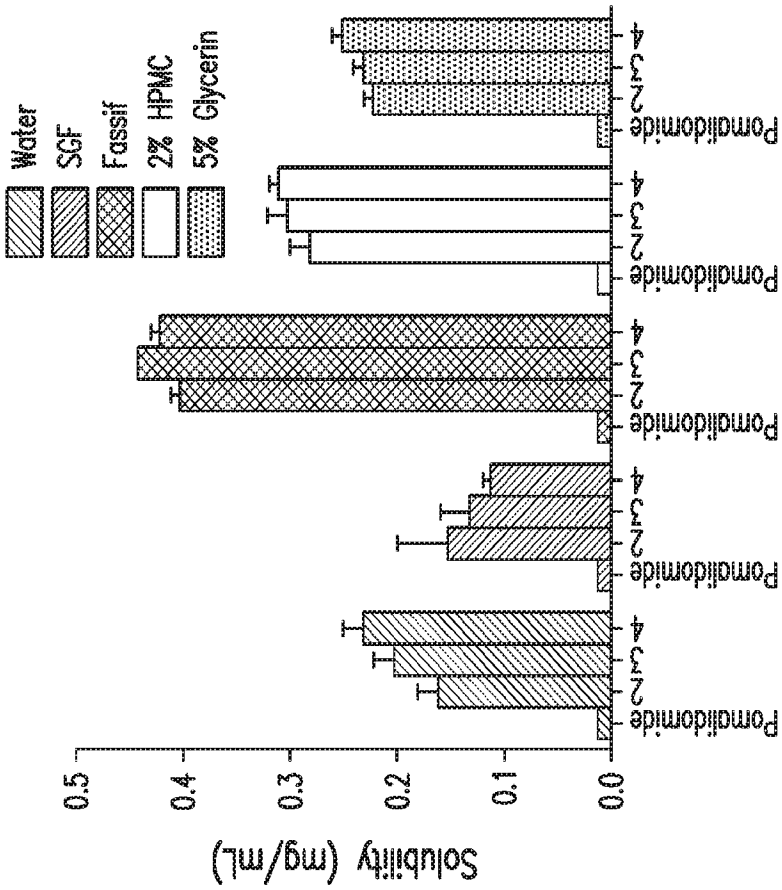


FIG. 9B

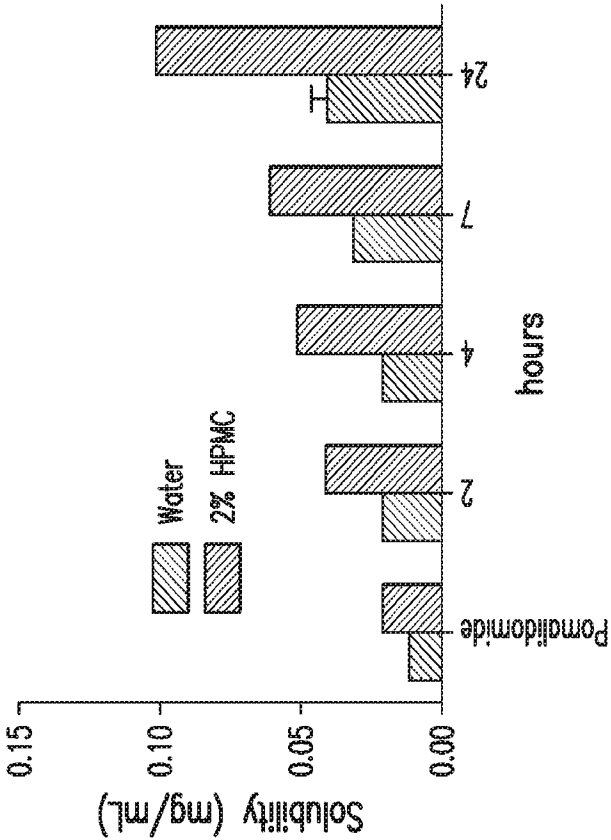


FIG. 9A

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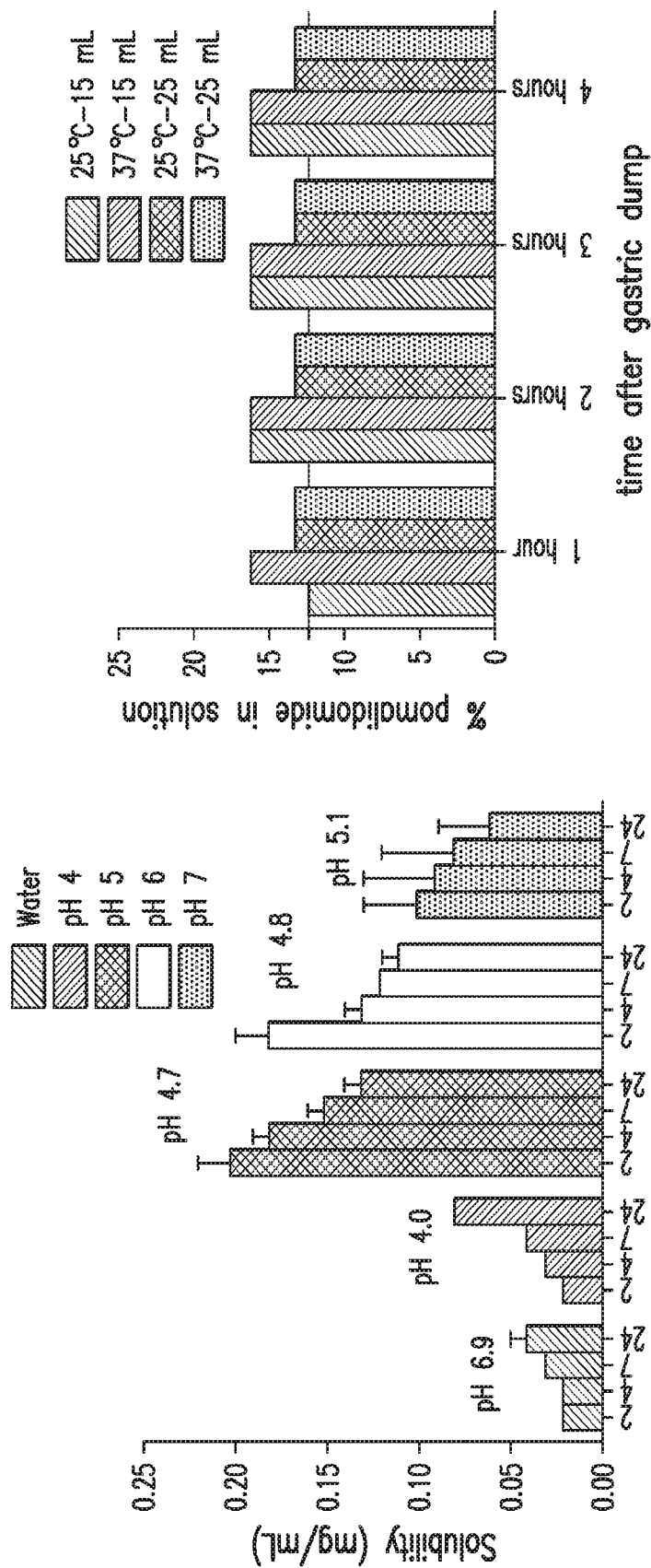


FIG. 11

FIG. 10

*pH on top of the bar is the final pH of the experiments after 24 hours.

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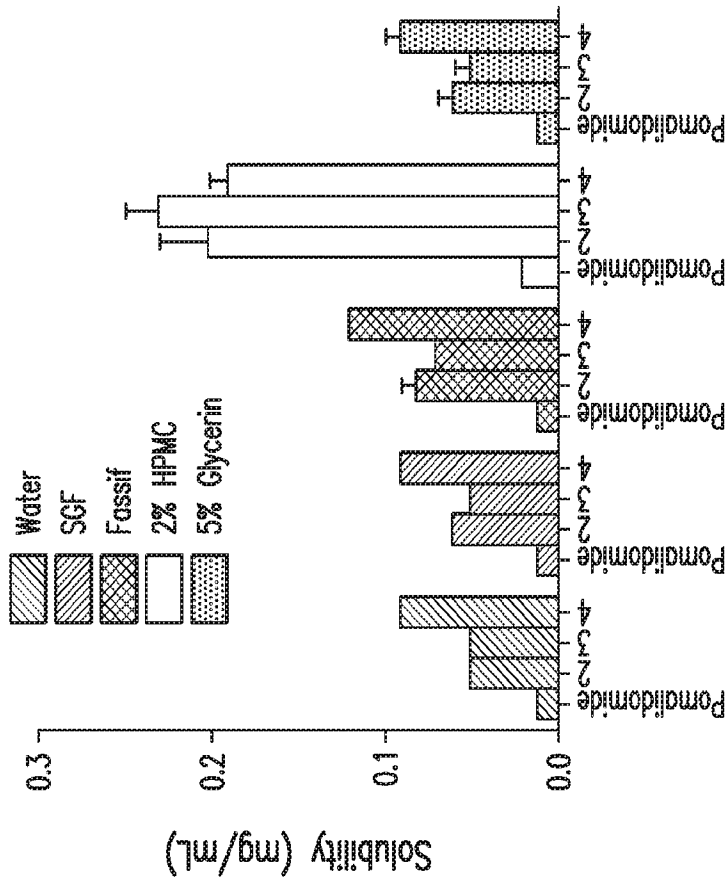


FIG. 12B

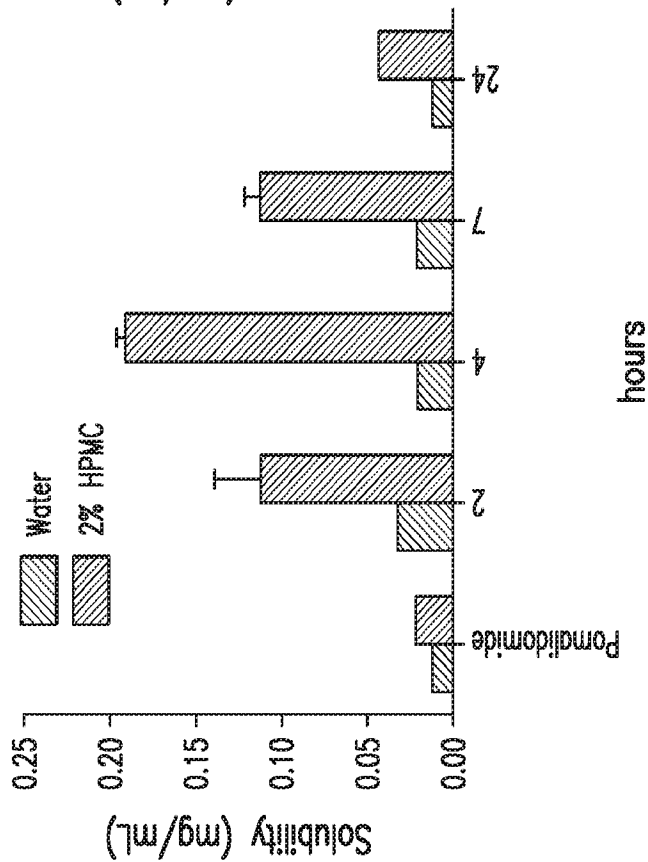


FIG. 12A

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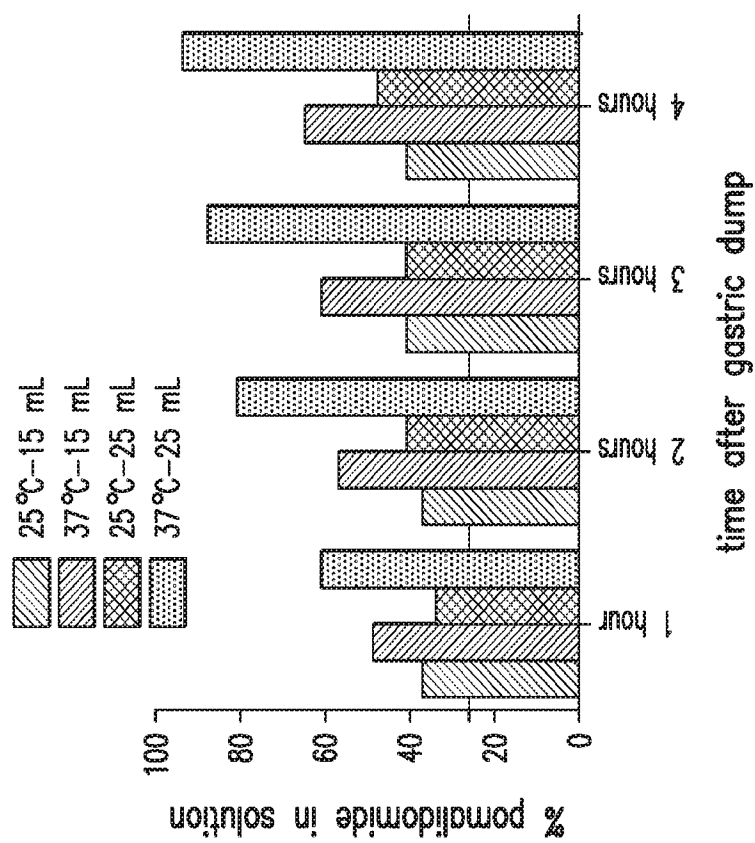


FIG. 14

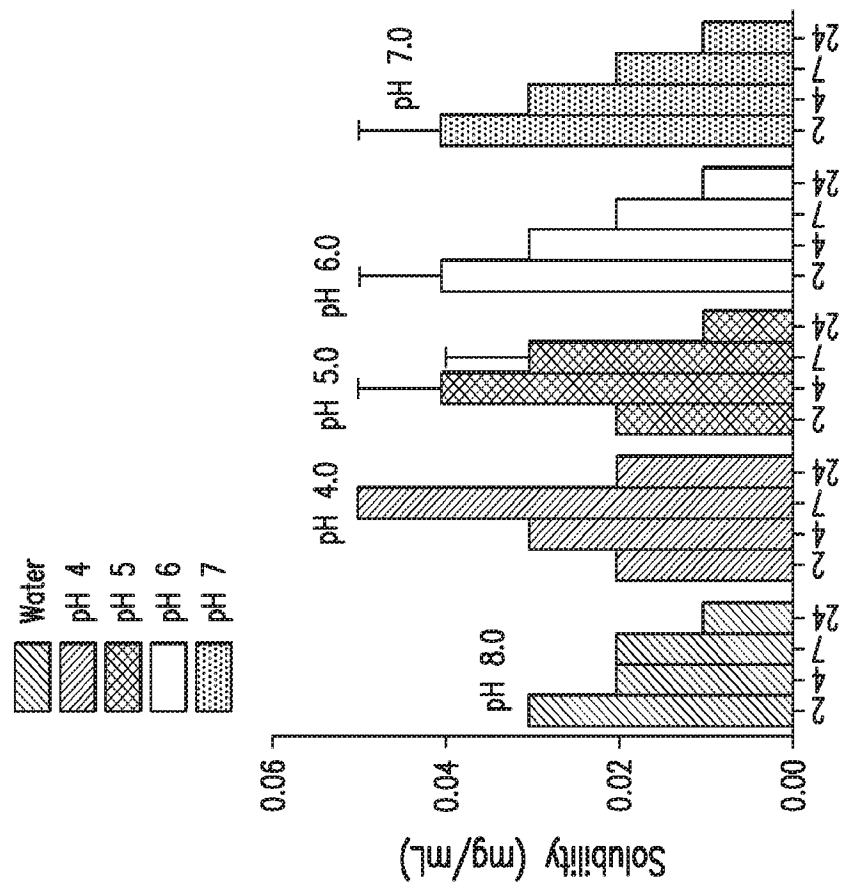


FIG. 13

*pH on top of the bar is the final pH of the experiments after 24 hours.

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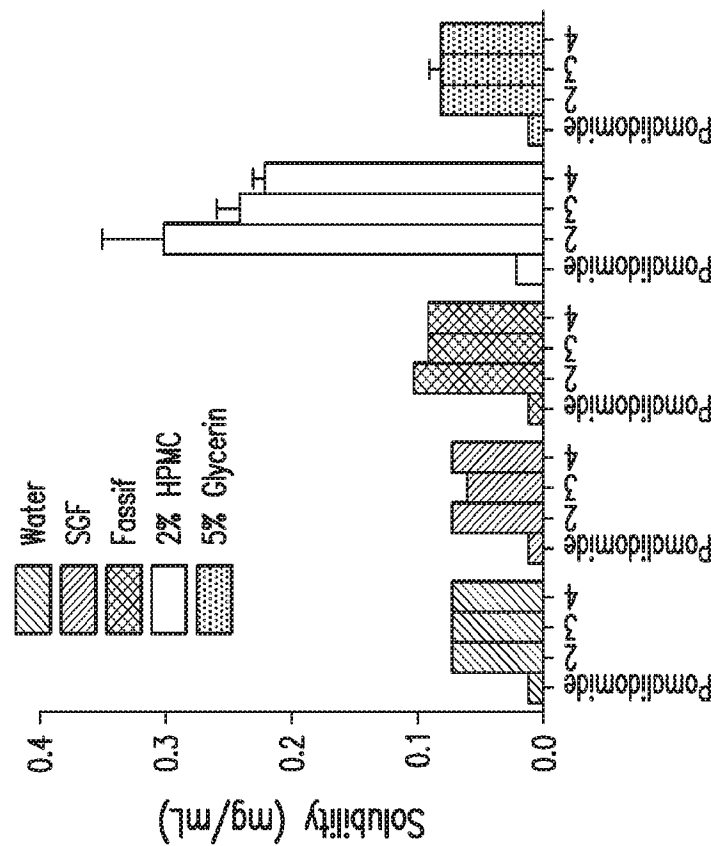


FIG. 15B

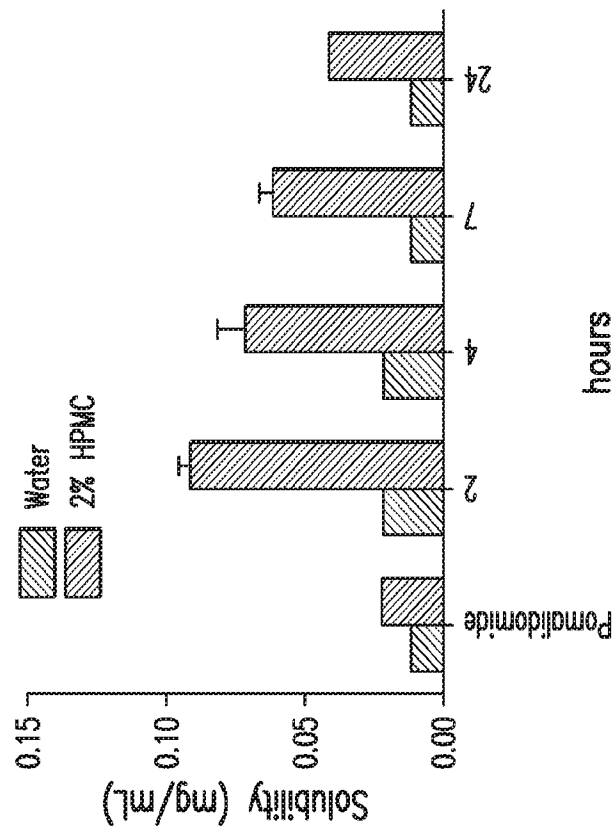


FIG. 15A

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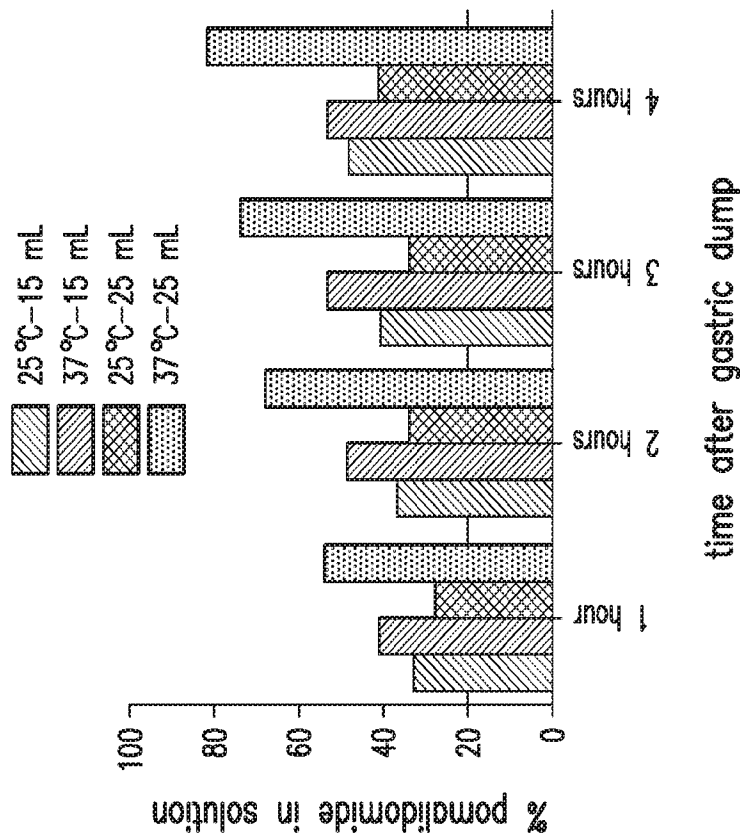


FIG. 17

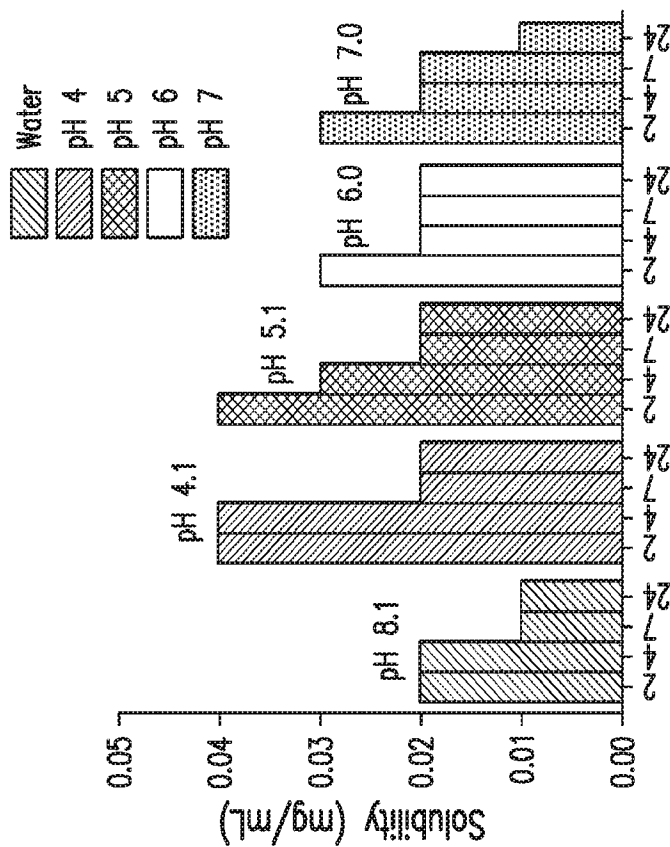


FIG. 16

*pH on top of the bar is the final pH of the experiments after 24 hours.

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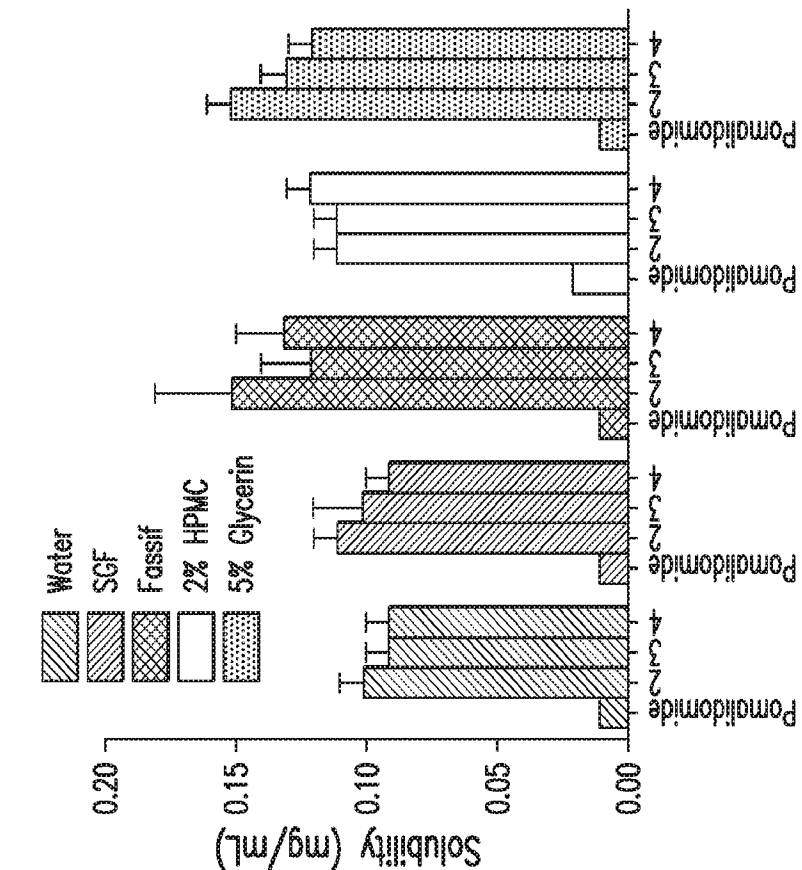


FIG. 19

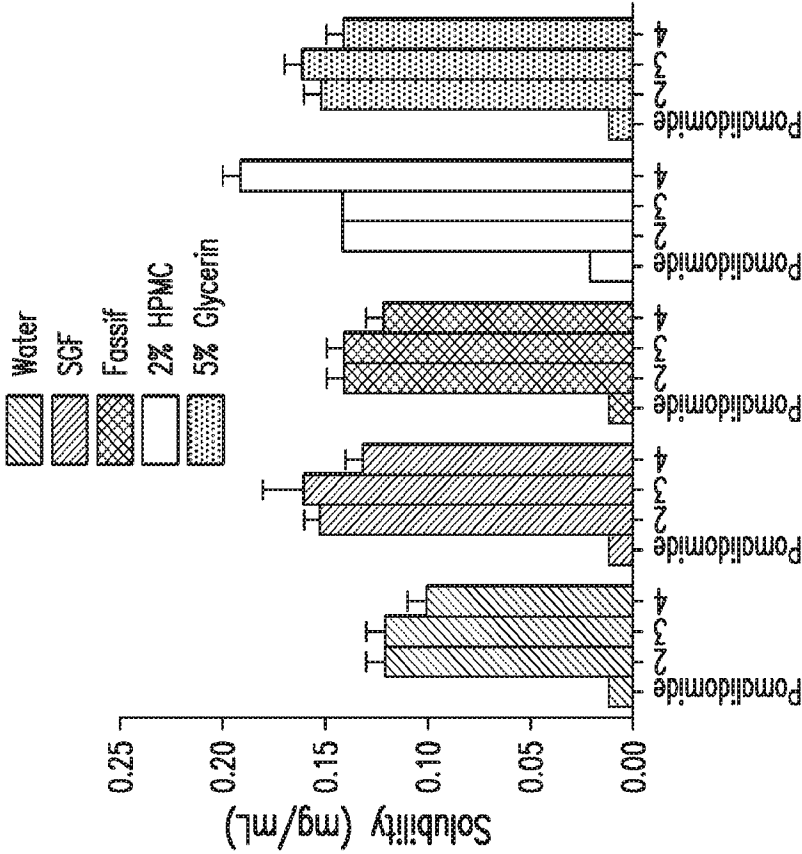


FIG. 18

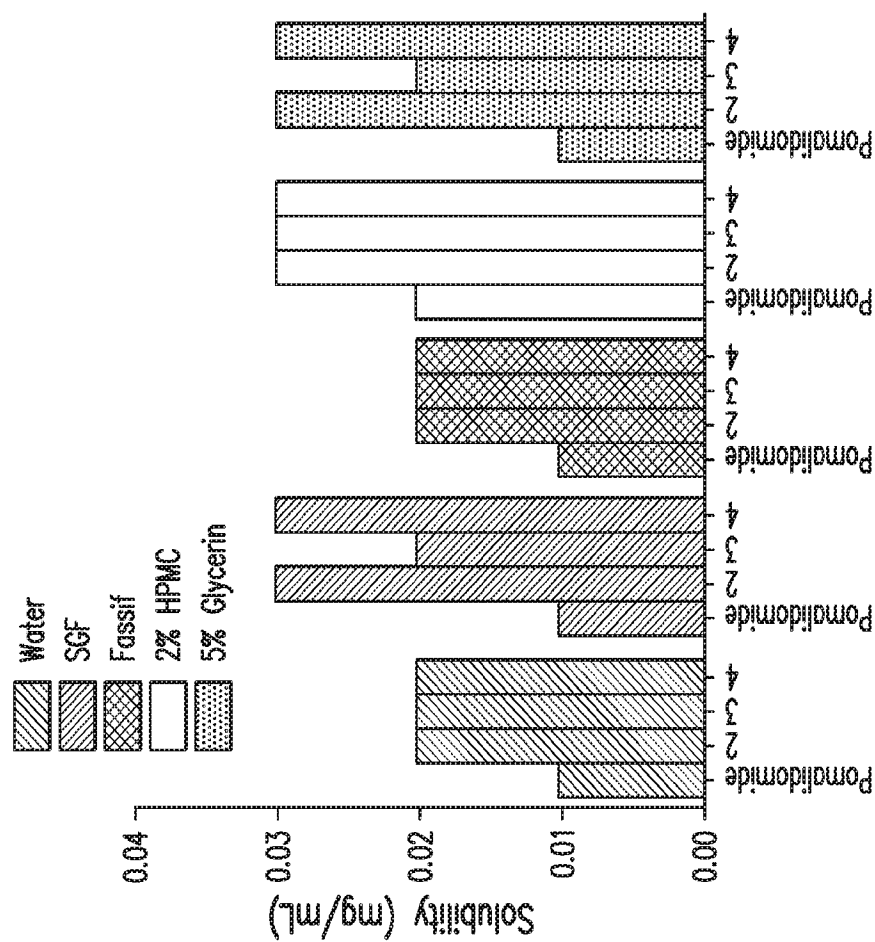


FIG. 20

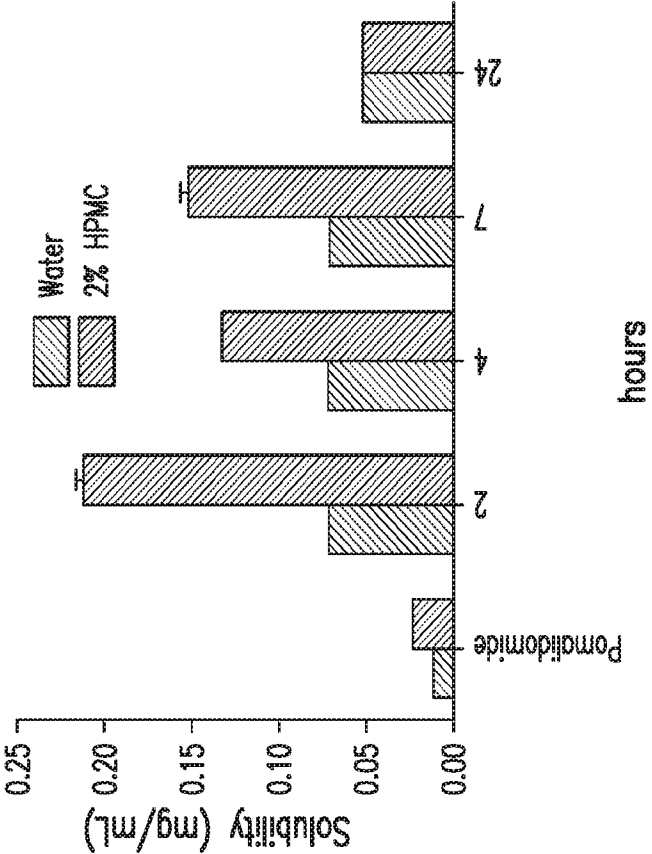


FIG. 22

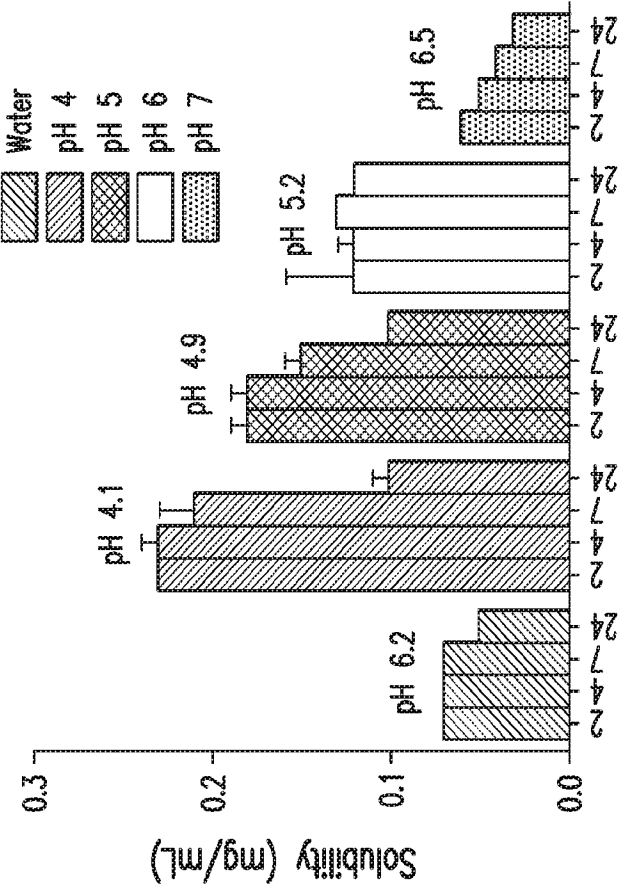


FIG. 21

*pH on top of the bar is the final pH of the experiments after 24 hours.

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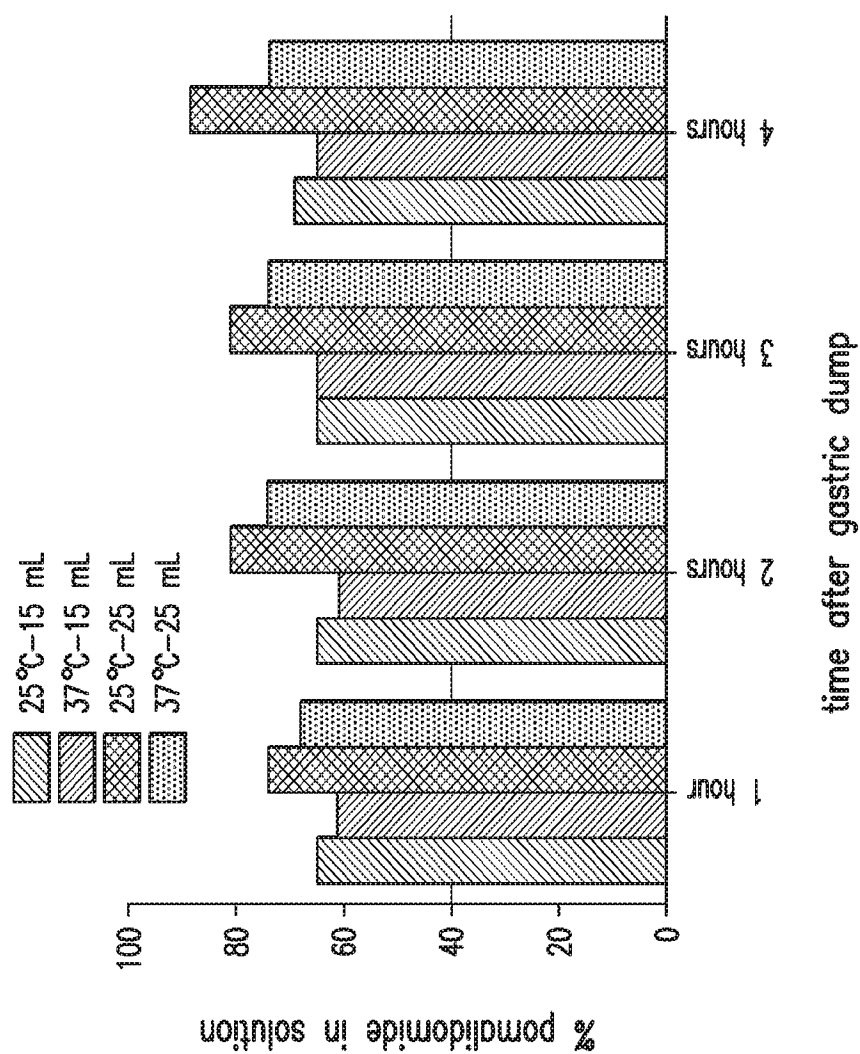


FIG. 23

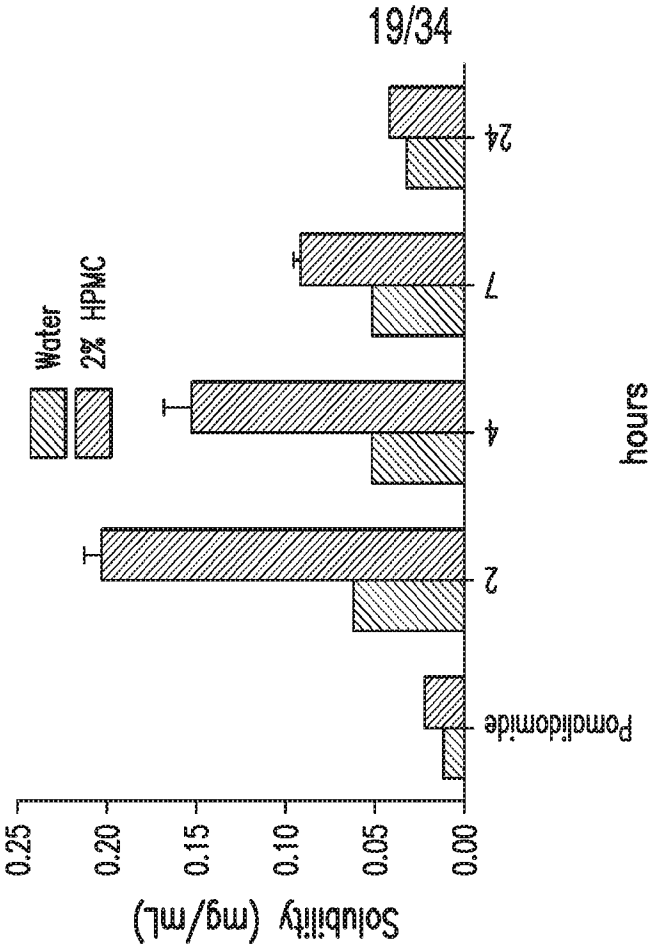


FIG. 25

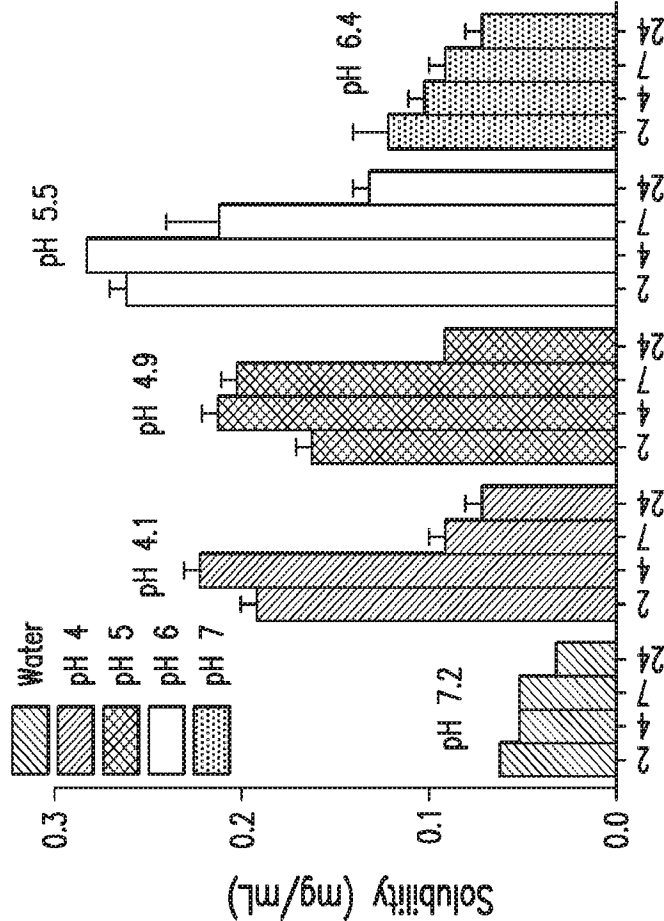


FIG. 24

*pH on top of the bar is the final pH of the experiments after 24 hours.

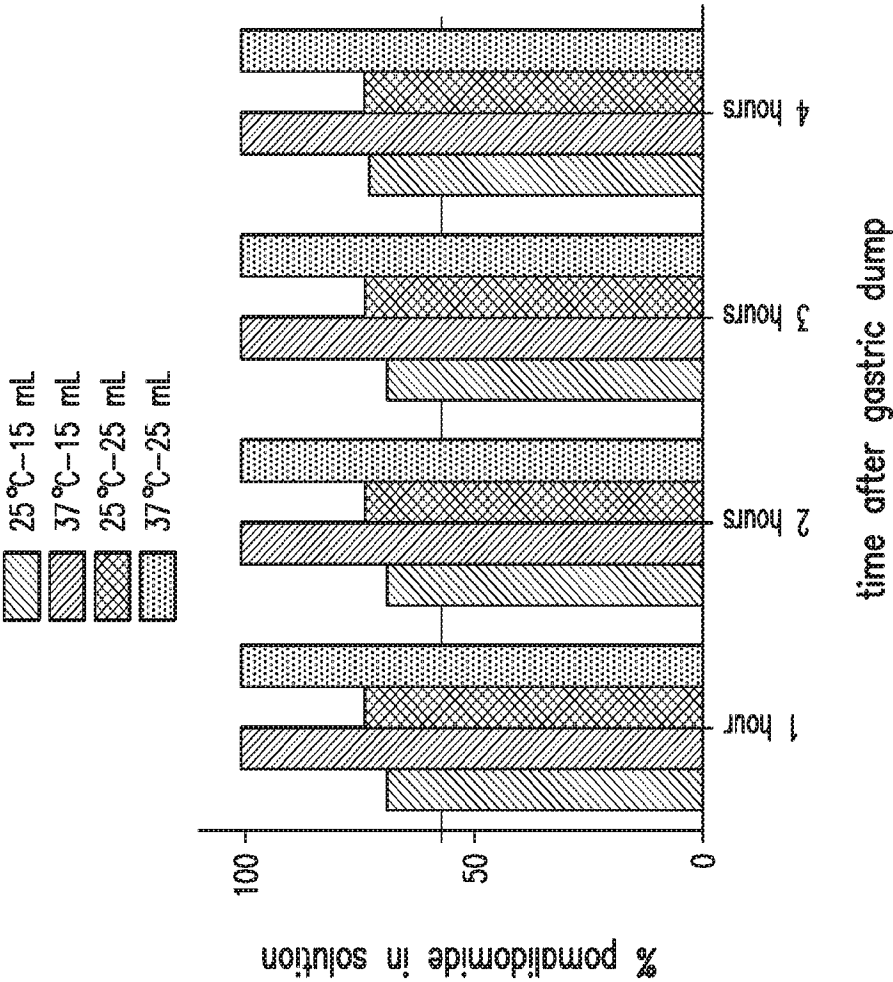


FIG. 26

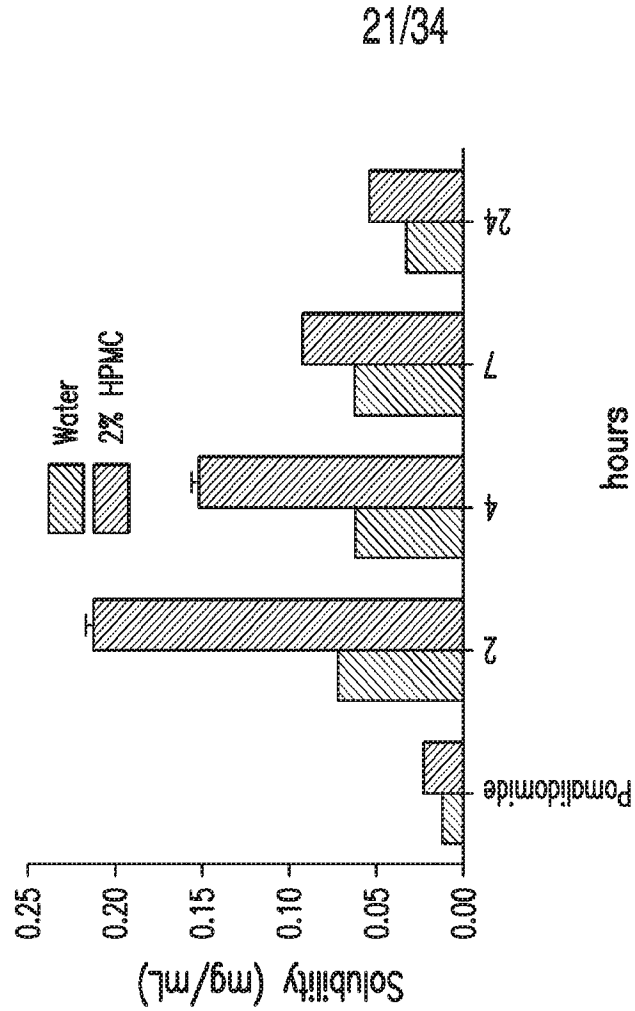


FIG. 28

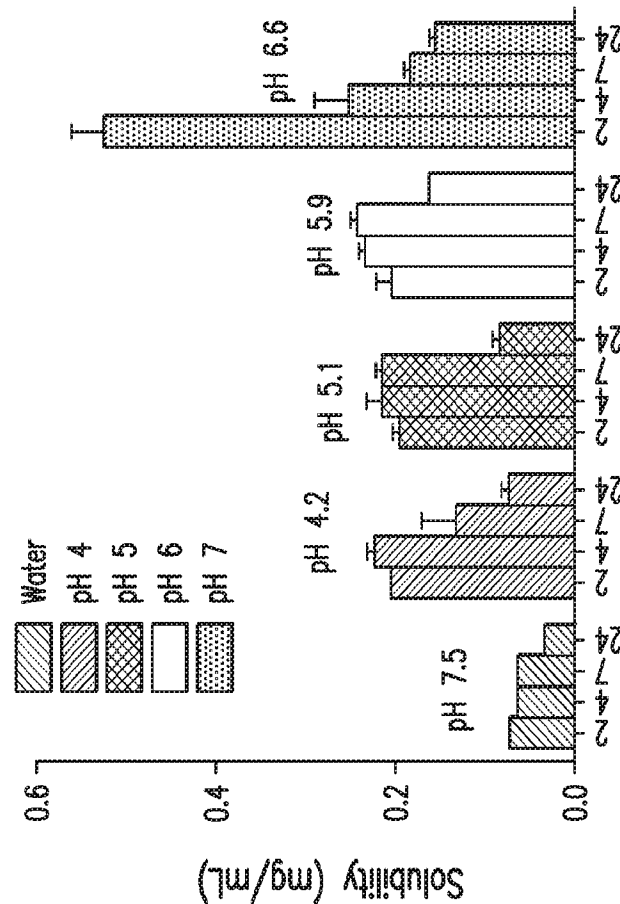


FIG. 27

*pH on top of the bar is the final pH of the experiments after 24 hours.

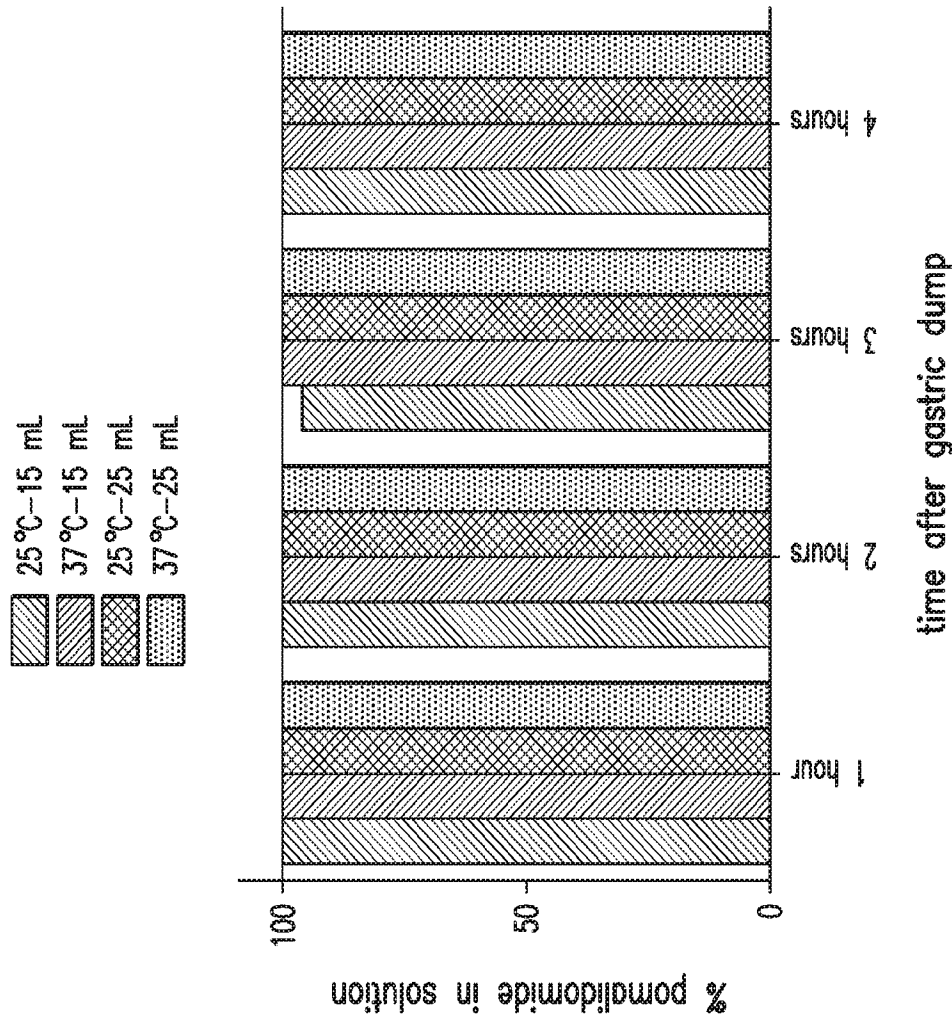


FIG. 29

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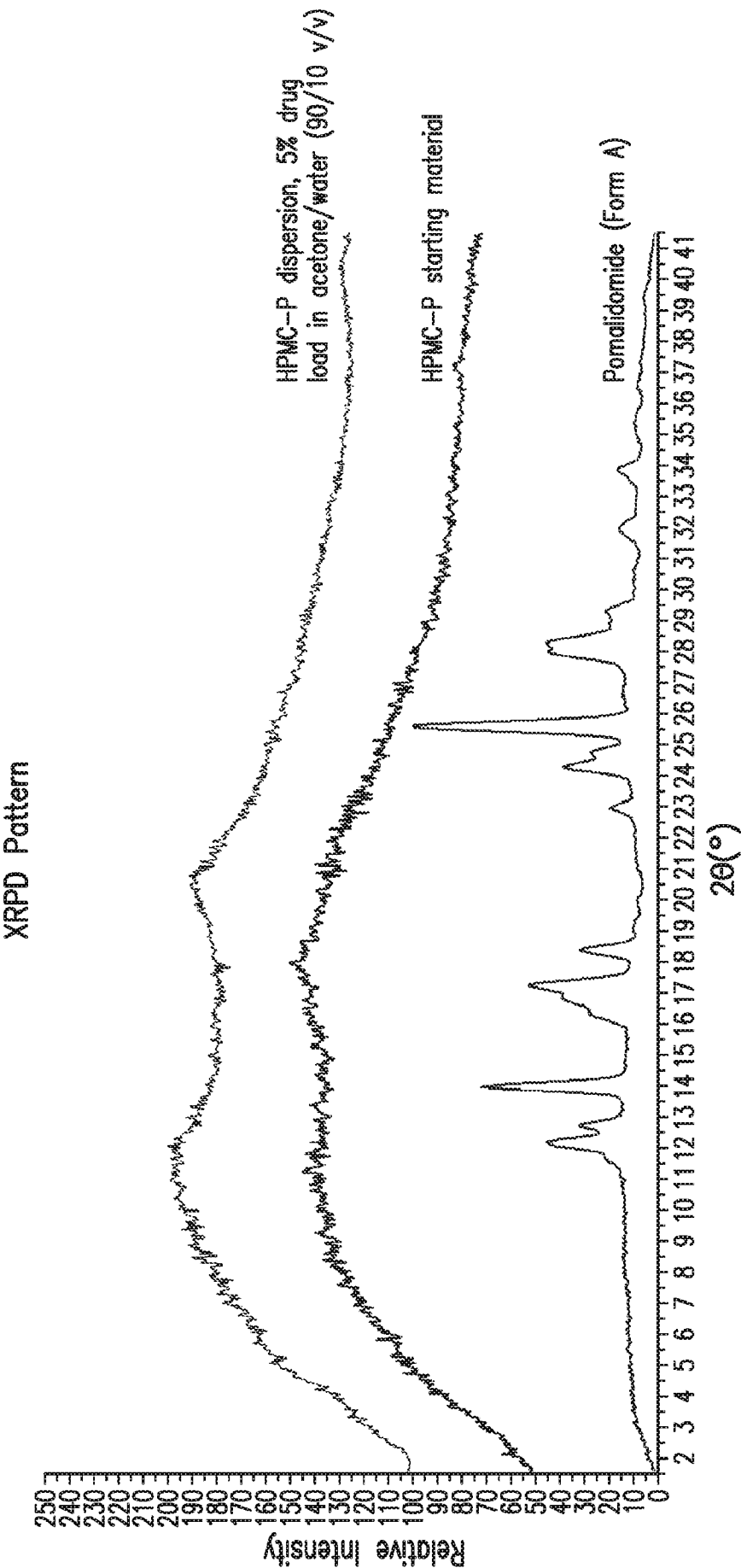


FIG. 30

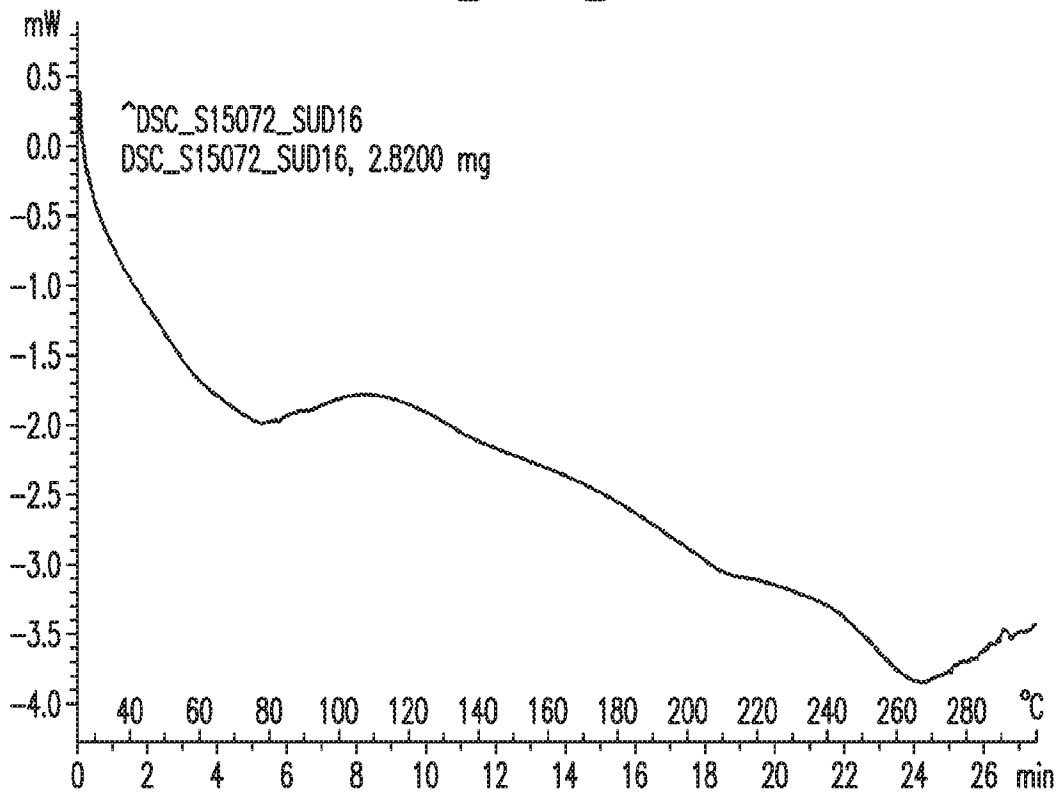
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DSC_S15072_SUD16

FIG. 31

TGMS_S15072_SUD16_v1

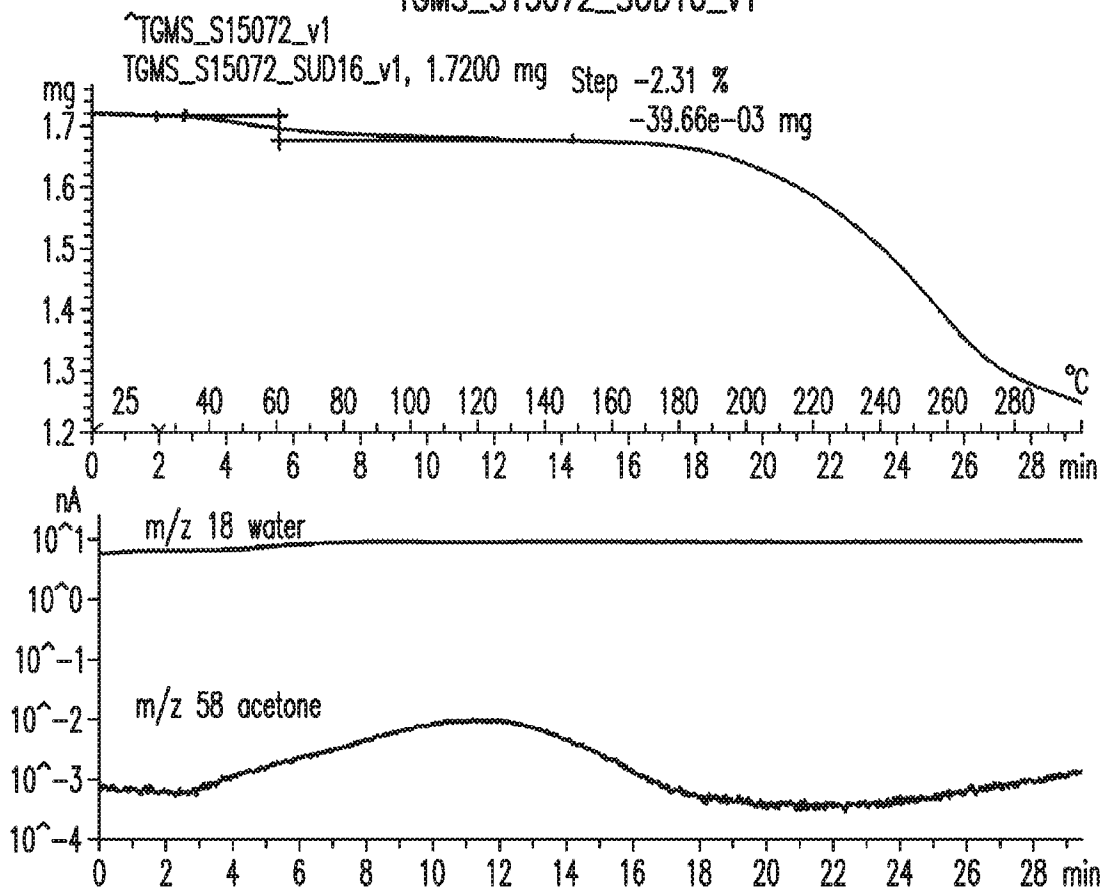


FIG. 32

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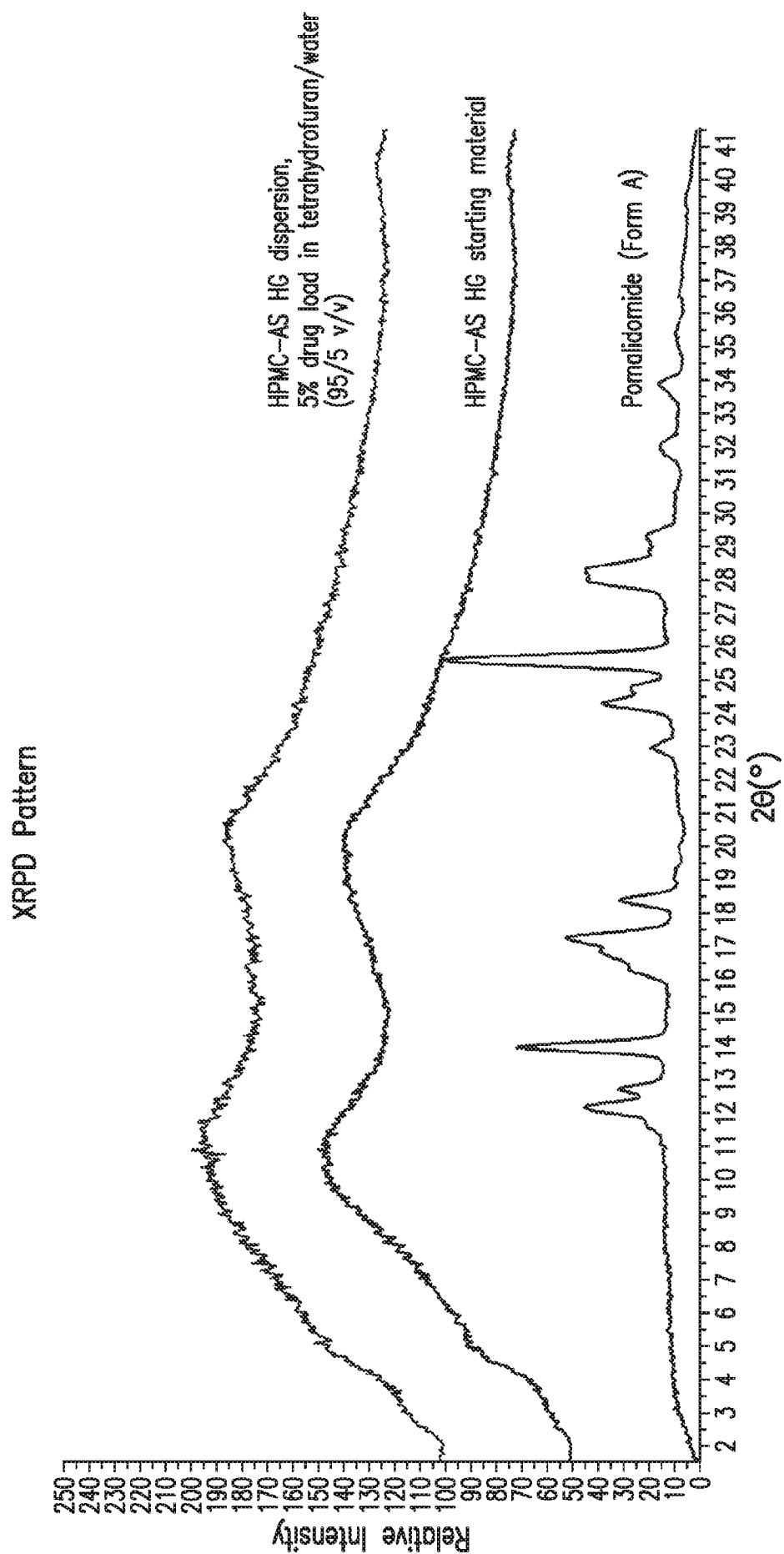


FIG. 33

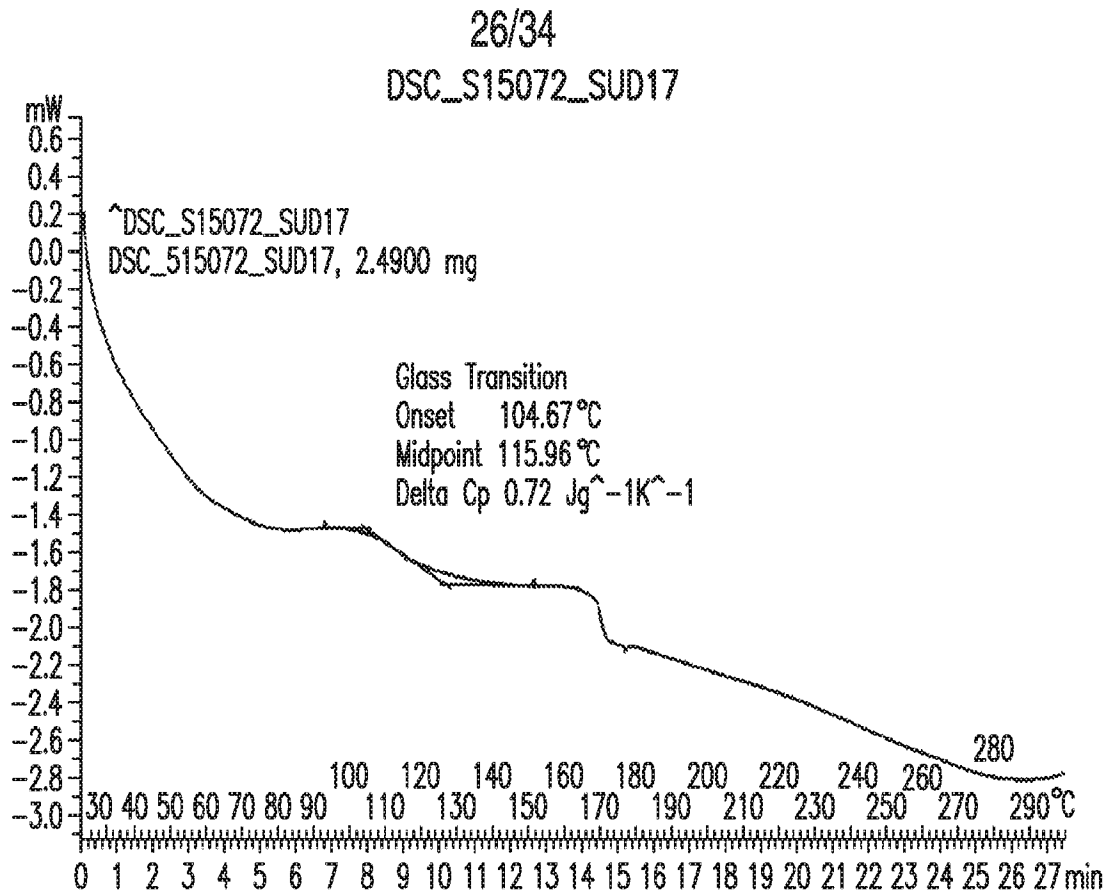


FIG. 34

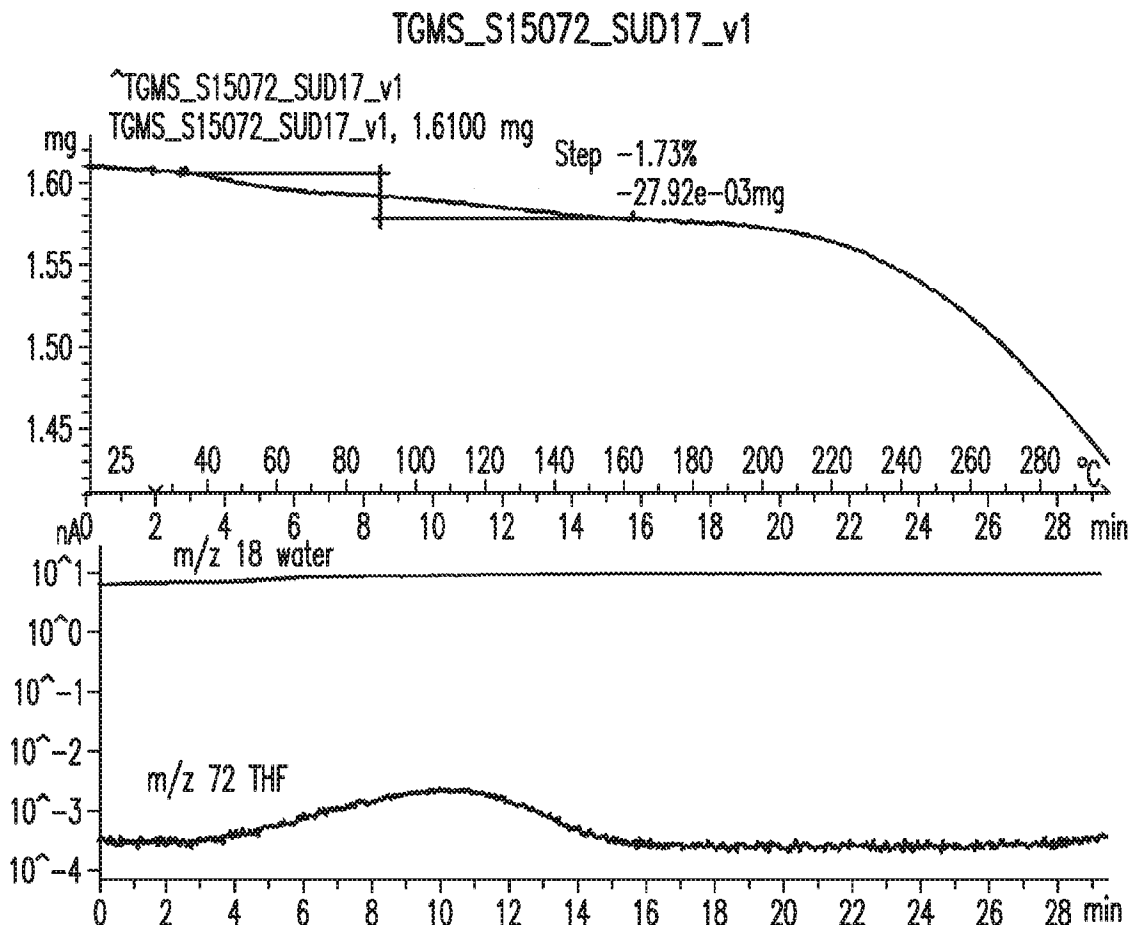


FIG. 35

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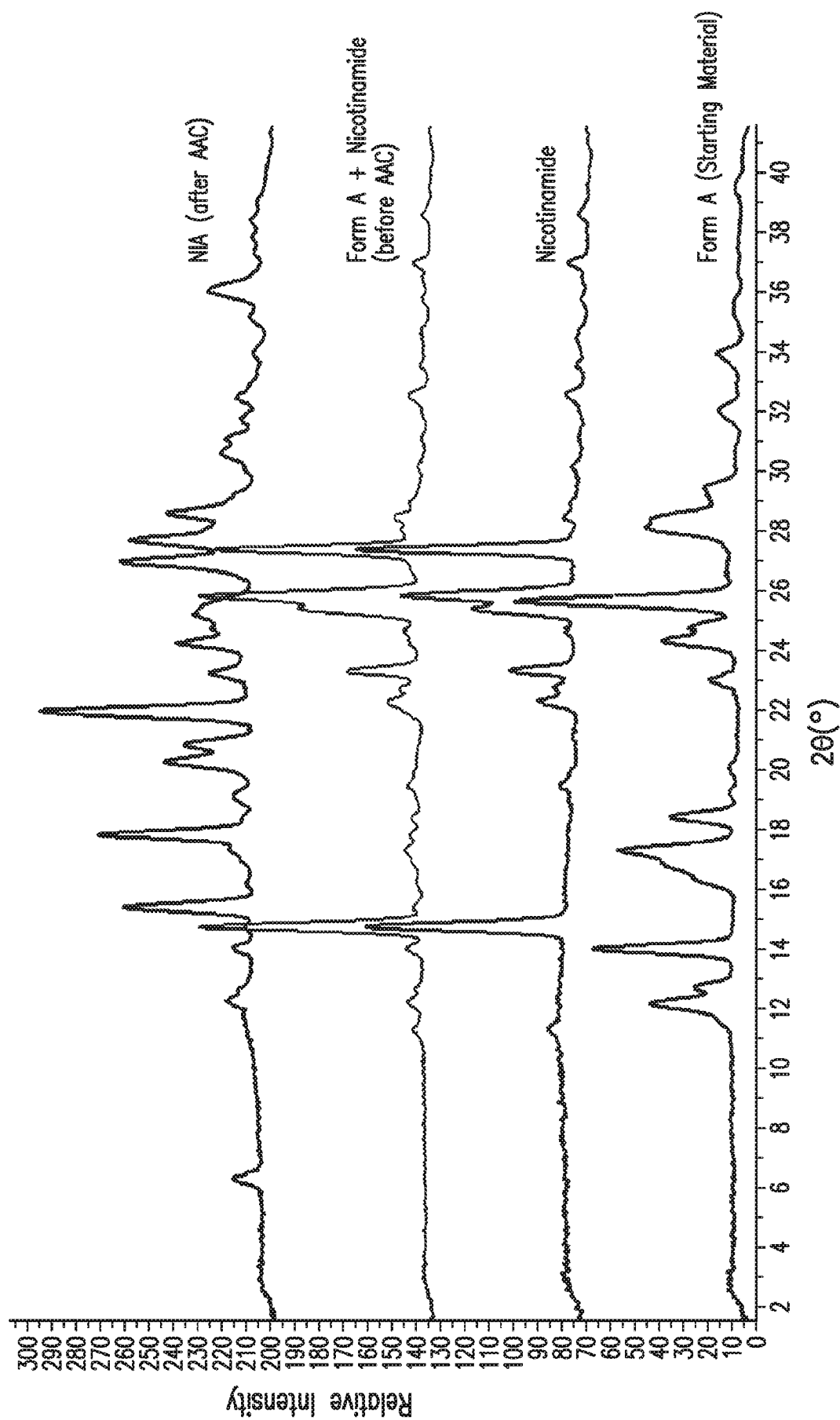


FIG. 36

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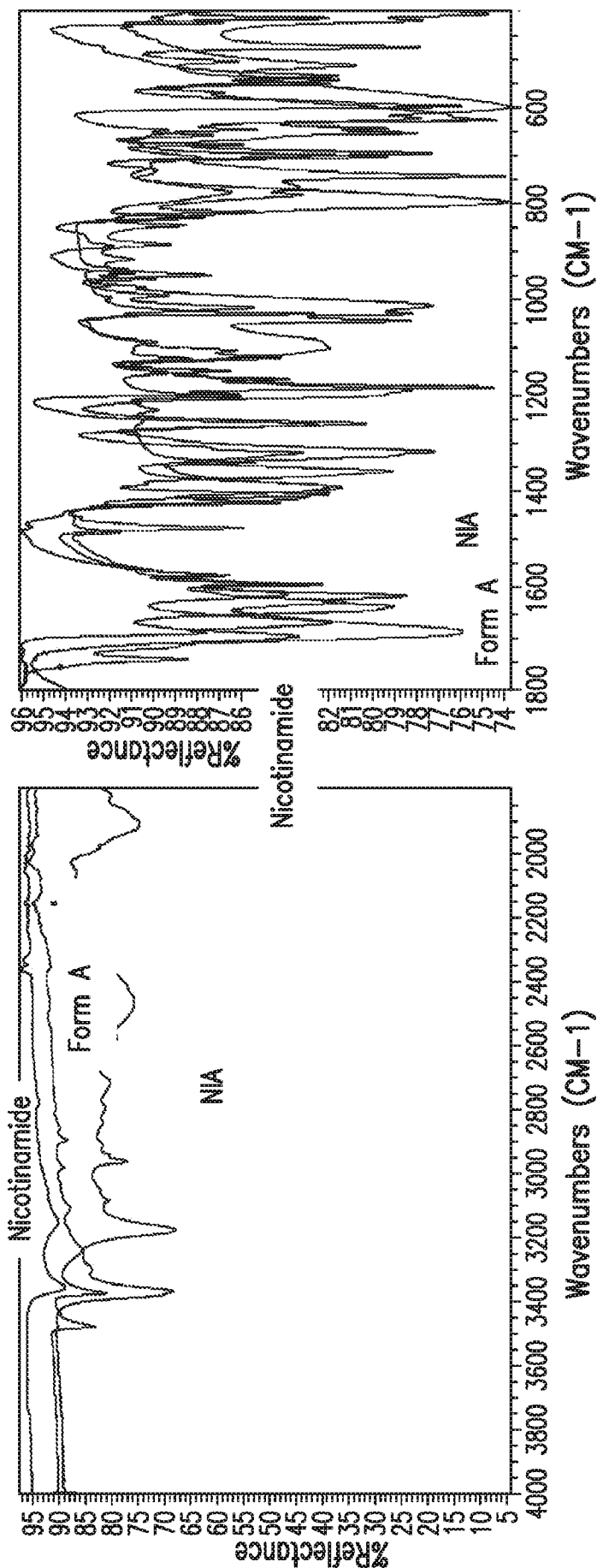


FIG. 37B

FIG. 37A

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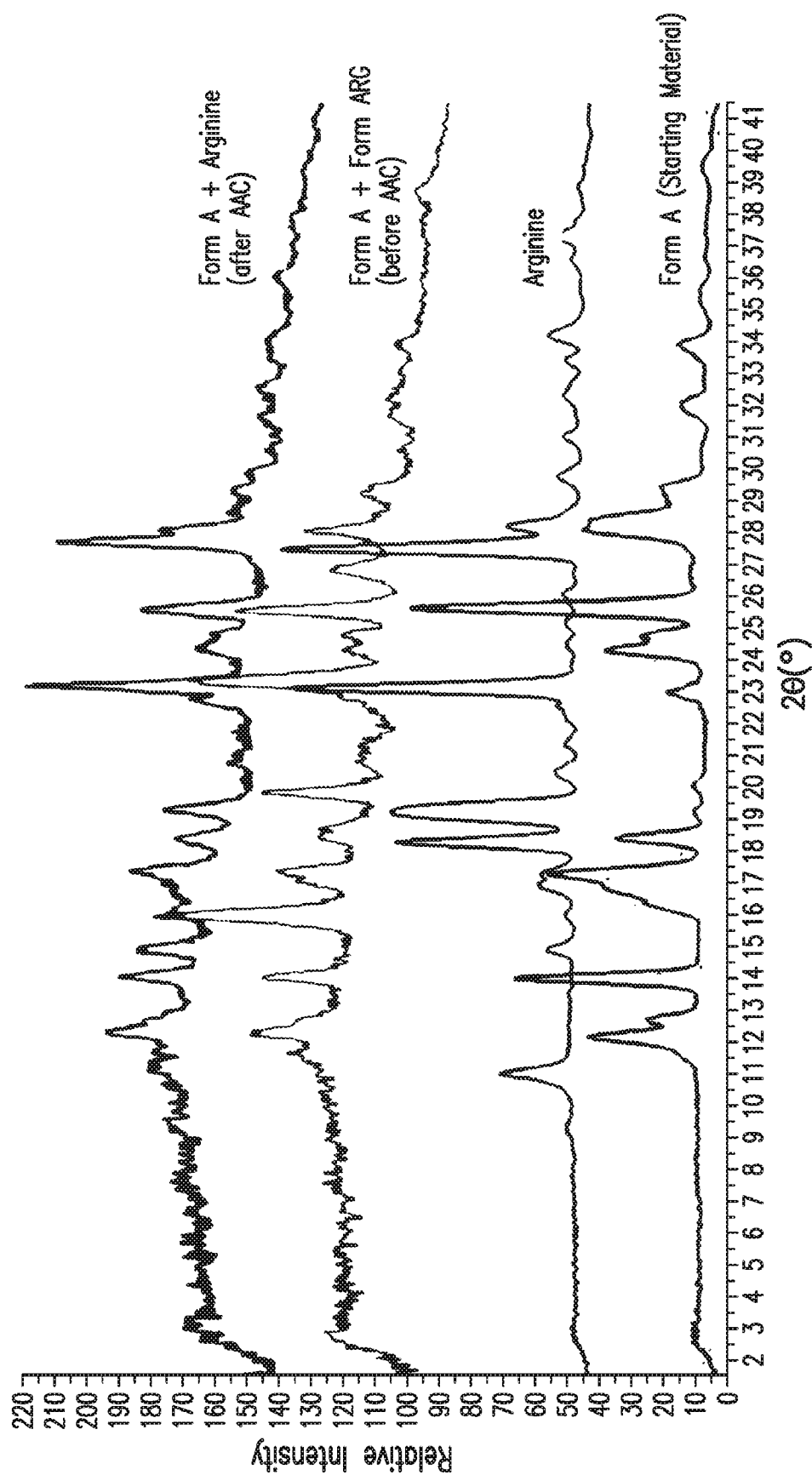


FIG. 38

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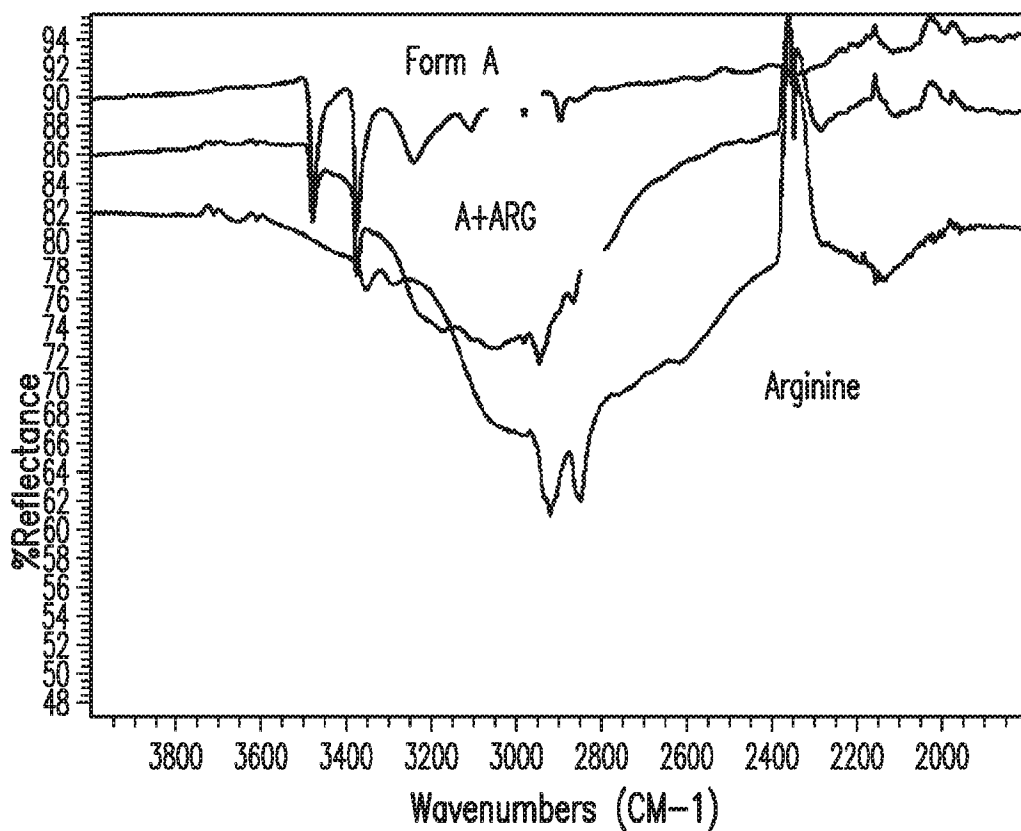


FIG. 39A

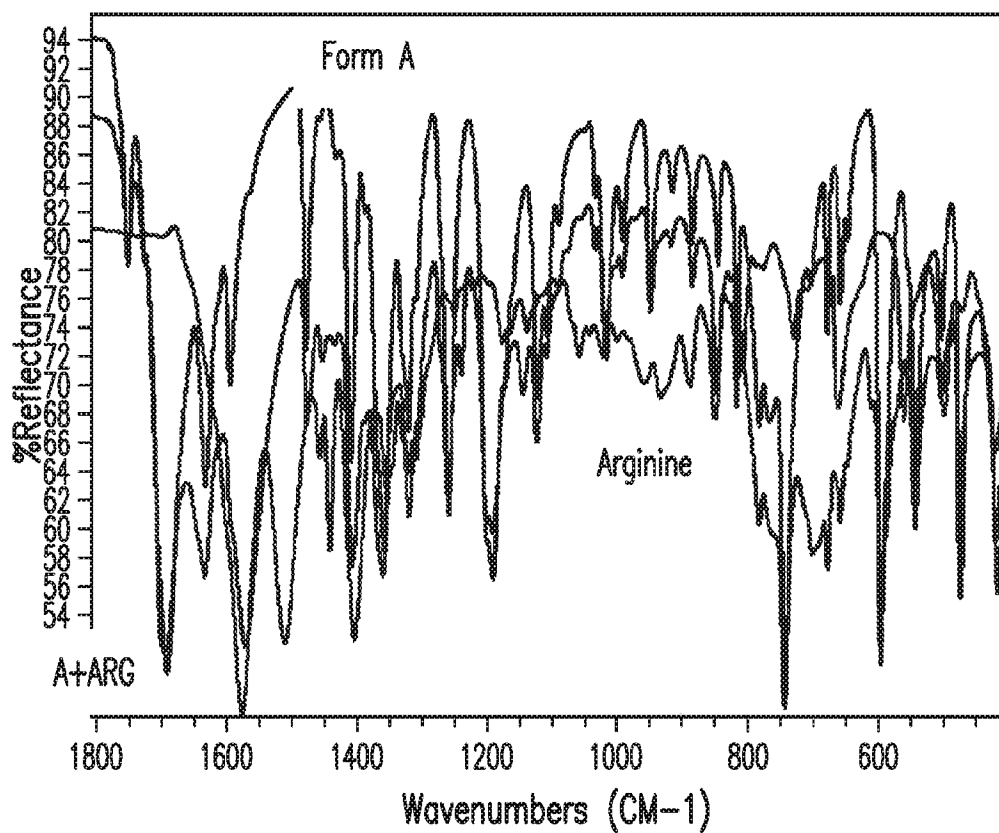


FIG. 39B

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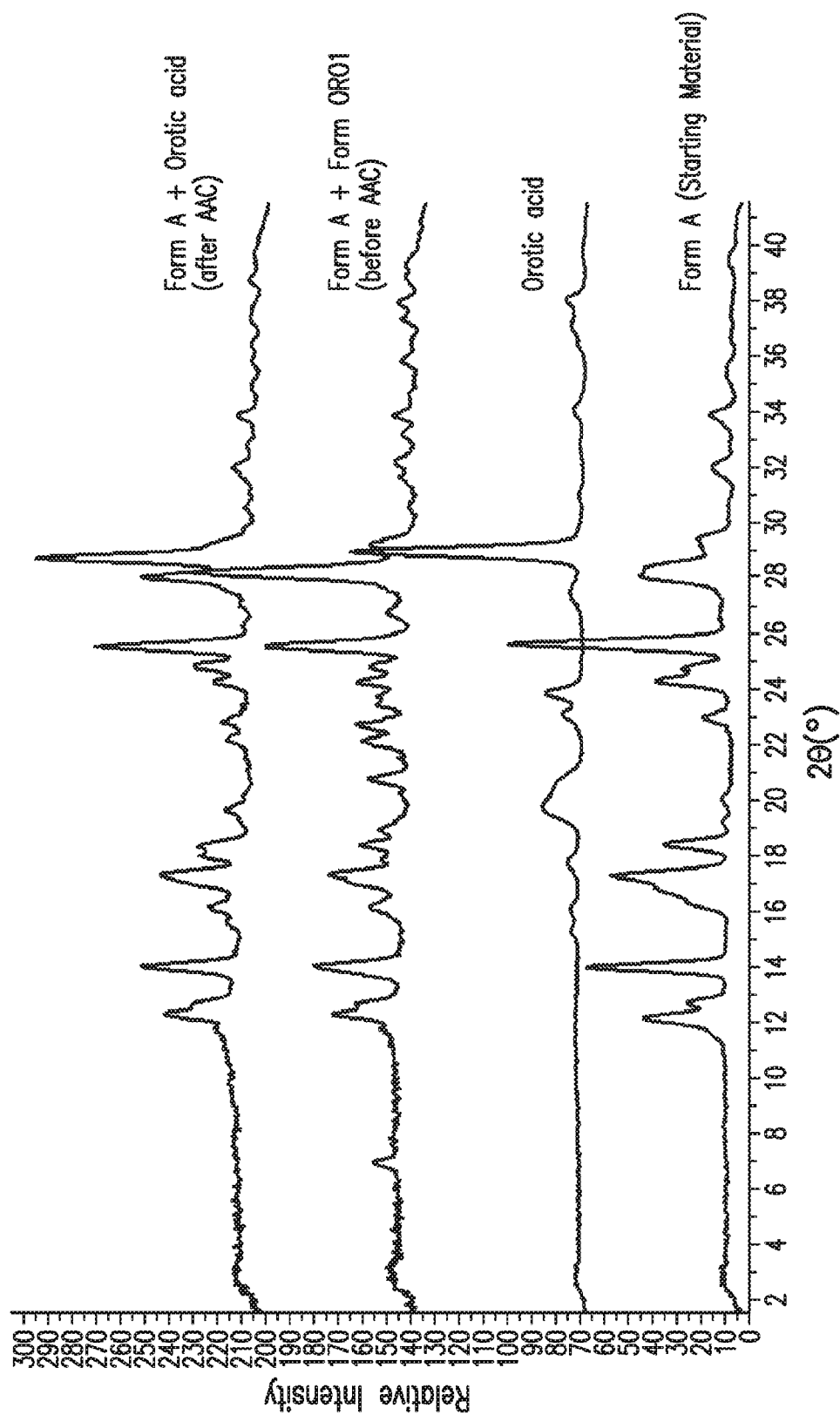


FIG. 40

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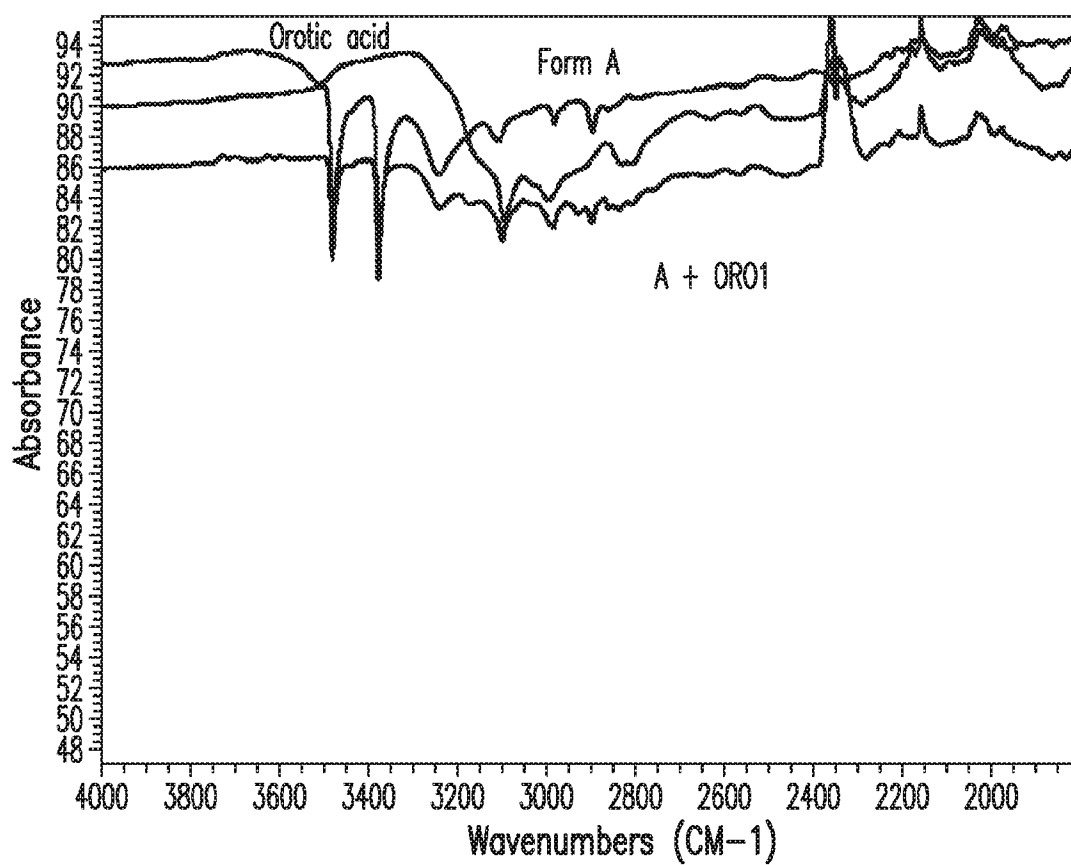


FIG. 41A

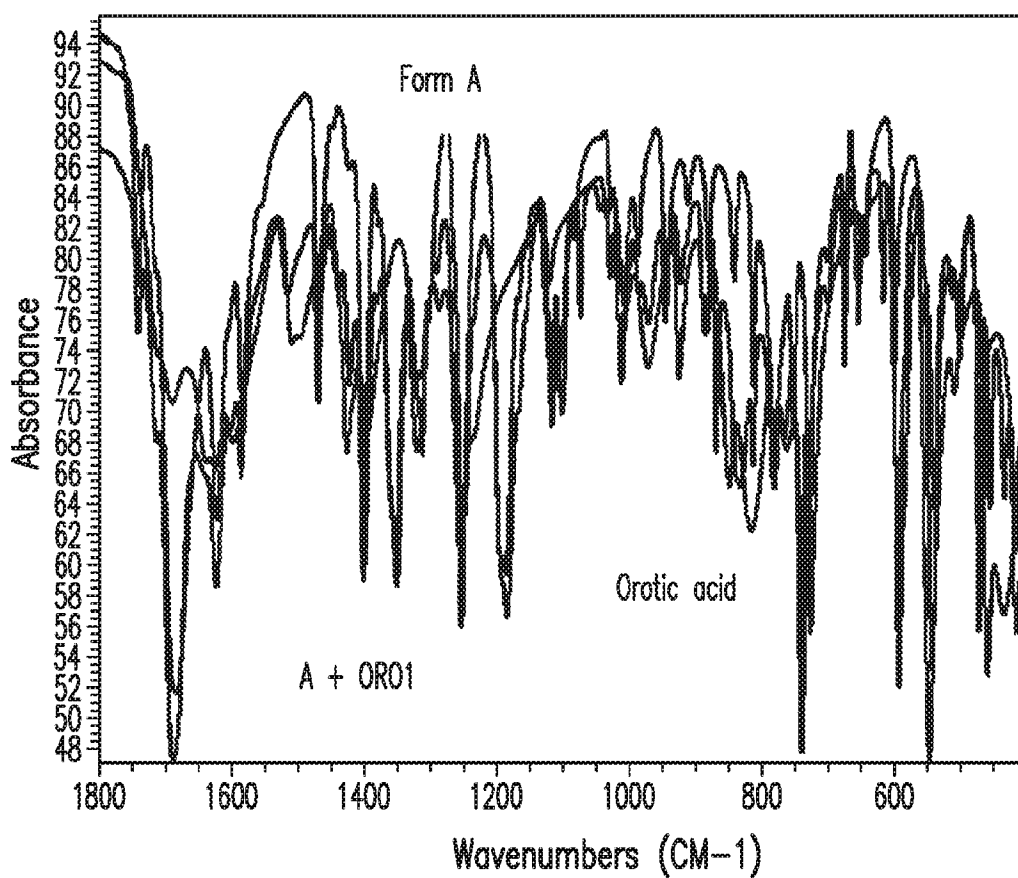


FIG. 41B

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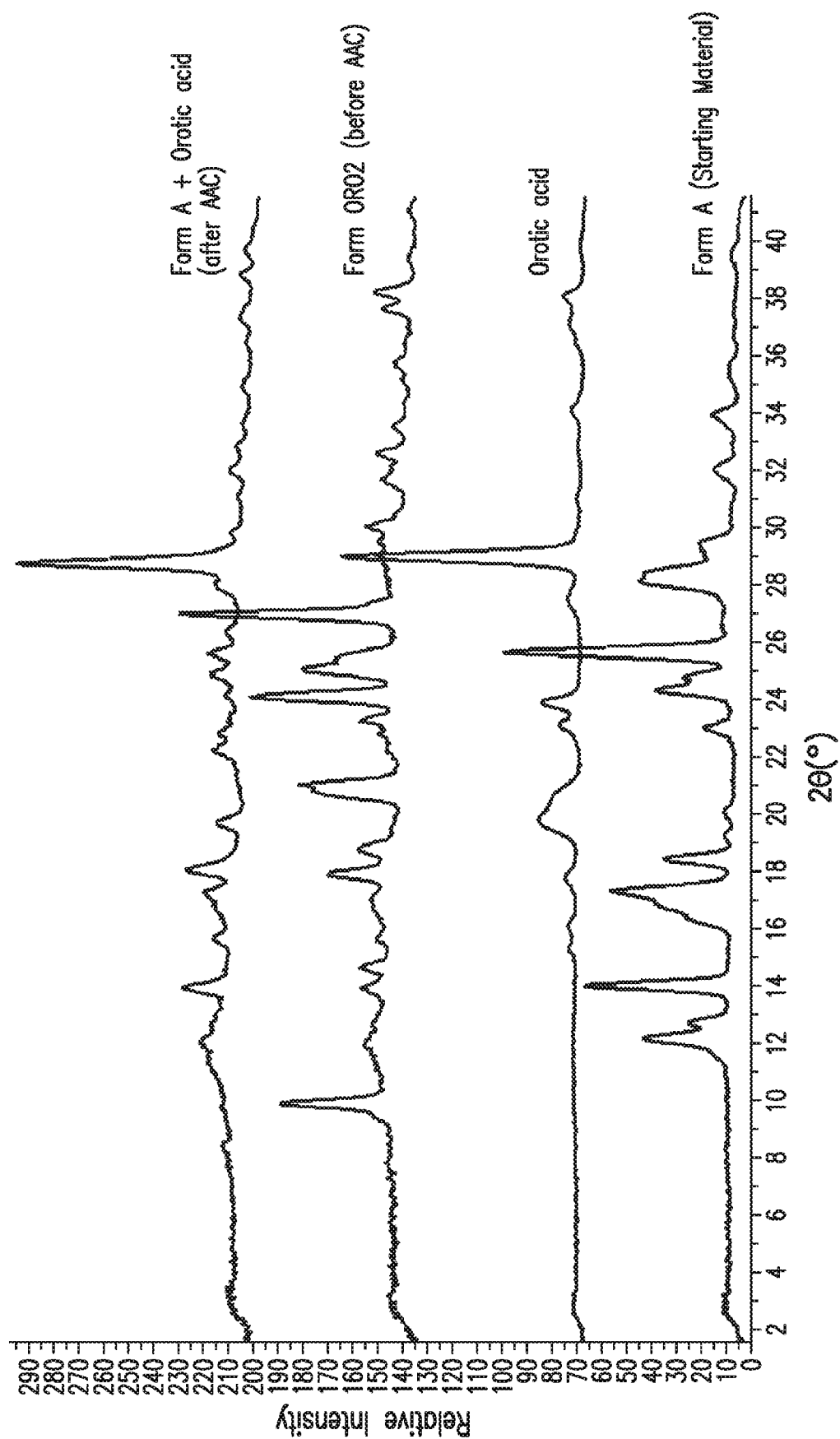


FIG. 42

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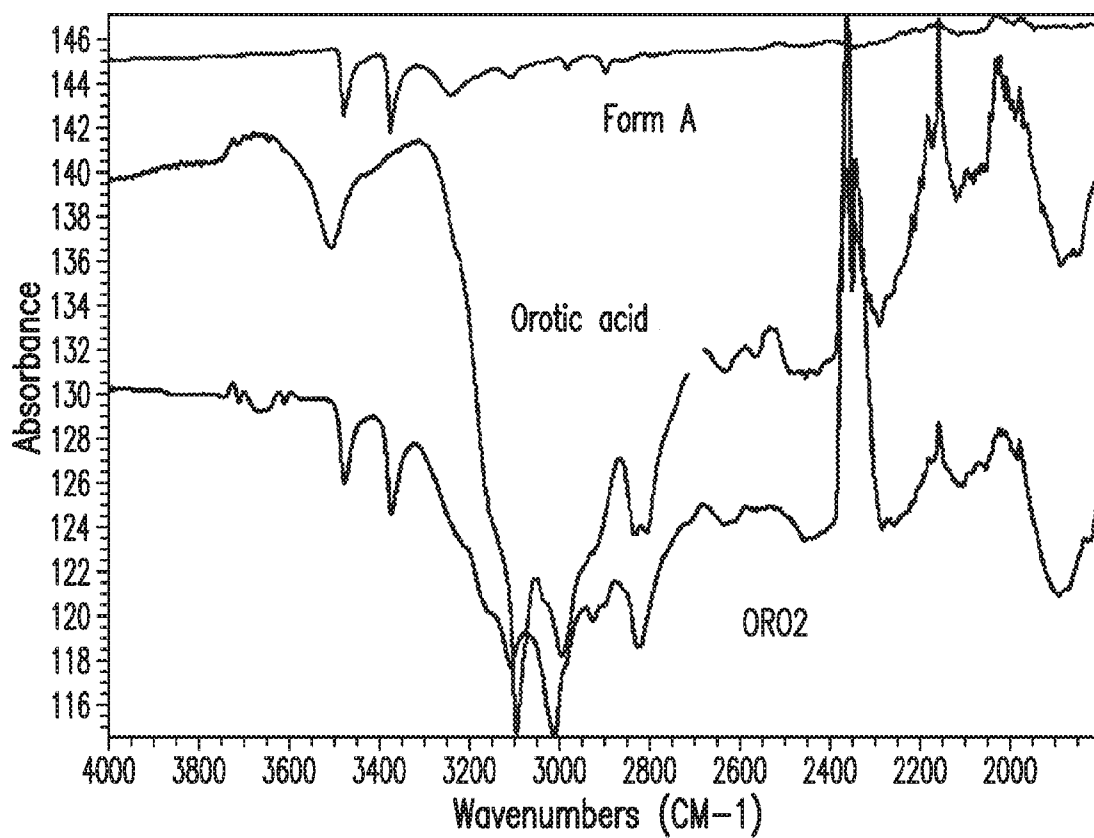


FIG. 43A

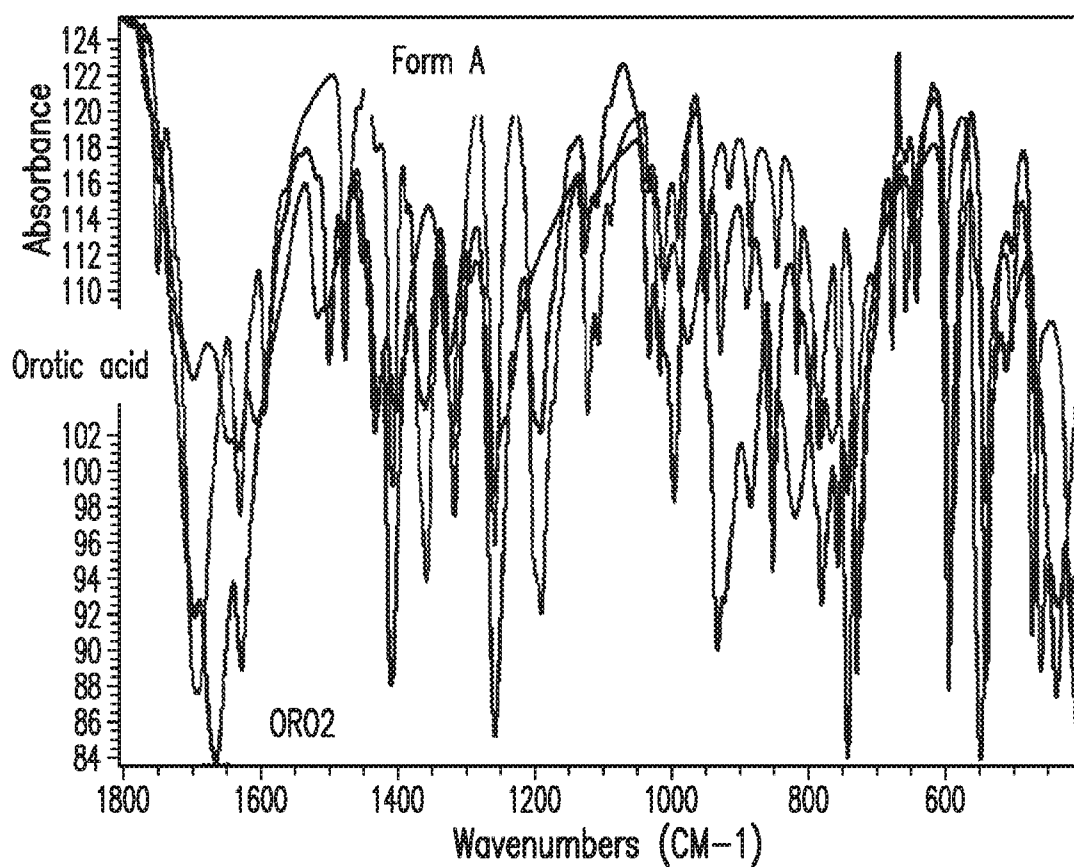


FIG. 43B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/041715

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 C07D401/04 A61K31/454
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 815 749 A1 (IP GES FÜR MAN MBH [DE]) 24 December 2014 (2014-12-24) paragraphs [0022], [0081], [0122]; claim 1	1-44
X	WO 2014/160690 A1 (CELGENE CORP [US]) 2 October 2014 (2014-10-02) paragraphs [0059], [0069]; claim 1	45-91
X	US 2014/336223 A1 (TUTINO ANTHONY J [US] ET AL) 13 November 2014 (2014-11-13) claim 1	1-91
X	CN 104 224 723 A (BEIJING COLLAB PHARMA CO LTD) 24 December 2014 (2014-12-24) claims	1-91
	----- -/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

11 September 2017

Date of mailing of the international search report

26/09/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Giese, Hans-Hermann

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/041715

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/160698 A1 (CELGENE CORP [US]) 2 October 2014 (2014-10-02) paragraph [0217]; claims 1,9 -----	45-91
A	WO 2014/071280 A1 (CELGENE CORP [US]) 8 May 2014 (2014-05-08) claim 1 -----	1-91
A	CN 105 213 392 A (UNIV ZHEJIANG) 6 January 2016 (2016-01-06) claims 1-3 -----	1-91

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/041715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2815749	A1	24-12-2014	NONE
WO 2014160690	A1	02-10-2014	US 2016039785 A1 11-02-2016 WO 2014160690 A1 02-10-2014
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/041715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 105213392	A	06-01-2016	NONE
