PHARMACEUTICAL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising an active pharmaceutical ingredient, a polyethylene glycol having a freezing point of at least about 30 °C, and a crystallisation rate inhibitor, and solid dosage forms comprising said pharmaceutical formulations. The invention also relates to processes to prepare such pharmaceutical formulations and to the use of such pharmaceutical formulations for the treatment of a disease, syndrome, condition, or disorder.

BACKGROUND OF THE INVENTION

Many active pharmaceutical ingredients (API) have properties such as hydrophobicity and instability leading to challenges in providing suitable pharmaceutical formulations.

MALT1 (mucosa-associated lymphoid tissue lymphoma translocation 1) is a key mediator of the classical NFKB signaling pathway. WO 2018/119036 discloses a class of active pharmaceutical agents which are MALT1 inhibitors that may provide a therapeutic benefit to patients suffering from cancer and/or immunological diseases.

There exists a need for improved pharmaceutical formulations of active pharmaceutical ingredients, such as the MALT1 inhibitors described in WO 2018/119036. In particular there exists a need for pharmaceutical formulations with an acceptable bio-availability, in particular in a solid dosage form.

SUMMARY

The present disclosure, in one aspect, is directed to a pharmaceutical formulation, comprising:

a) a polyethylene glycol having a freezing point of at least about 30 °C;

b) an active pharmaceutical ingredient that is soluble in molten polyethylene glycol wherein the polyethylene glycol is as defined in a); and

c) a crystallisation rate inhibitor.

Examples of the disclosure include a pharmaceutical formulation as described herein, wherein the active pharmaceutical ingredient is a MALT1 inhibitor.

The disclosure, in another aspect, provides a solid dosage form comprising a pharmaceutical formulation described herein.

In examples in which the active pharmaceutical ingredient is a MALT1 inhibitor, the disclosure provides methods for treating or ameliorating a disease, syndrome, condition, or disorder in a subject, including a mammal and/or human in which the disease, syndrome, condition, or disorder is affected by the inhibition of MALT1, including but not limited to, cancer and/or immunological diseases, using pharmaceutical formulations and solid dosage forms described herein.

The present disclosure is also directed to the use of such pharmaceutical formulations in the preparation of a medicament wherein the medicament is prepared for treating a disease, syndrome, disorder or condition that is affected by the inhibition of MALT1, such as cancer and/or immunological diseases.

The disclosure, in another aspect, provides use of a pharmaceutical formulation described herein for the preparation of a medicament for treating a disease, syndrome, disorder or condition in a subject in need thereof, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1.

Exemplifying the disclosure are methods of treating a disease, syndrome, condition, or disorder mediated by MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL), B-cell NHL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa- associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor), comprising, consisting of, and/or consisting essentially of, administering to

a subject in need thereof a therapeutically effective amount of the pharmaceutical formulation or solid dosage form.

The disclosure, in another aspect, provides a pharmaceutical formulation described herein for use in the treatment of a disease, syndrome, disorder or condition in a subject in need thereof, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1.

In another example, the present disclosure is directed to pharmaceutical formulations and solid dosage forms described herein for use in the treatment of a disease, syndrome, condition, or disorder affected by the inhibition of MALT1, such as cancer

and/or immunological disease. The disease, syndrome, condition, or disorder may be selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma (NHL), B-cell NHL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia, lymphoblastic T cell leukemia, chronic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocyte leukemia, promyelocytic leukemia, erythroleukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

The disclosure, in another aspect, provides a process for preparing a pharmaceutical formulation described herein, the process comprising the steps of:

a) forming a melt comprising polyethylene glycol having a freezing point of at least about 30 °C, an active pharmaceutical ingredient, and a crystallisation rate inhibitor, wherein the forming a melt step comprises heating polyethylene glycol to a temperature above its freezing point; and

b) cooling the melt below the freezing point of the polyethylene glycol;

to provide a pharmaceutical formulation described herein.

The disclosure also provides a process for preparing a solid dosage form described herein, the process comprising the steps of:

a) forming a melt comprising polyethylene glycol having a freezing point of at least about 30 °C, an active pharmaceutical ingredient, and a crystallisation rate inhibitor, wherein the forming a melt step comprises heating polyethylene glycol to a temperature above its freezing point;

b) filling a hard capsule with the melt; and

c) cooling the filled capsule below the freezing point of the polyethylene glycol;

to provide a solid dosage form described herein.

The disclosure, in another aspect, provides a solid dosage form comprising

a) a polyethylene glycol having a freezing point of at least about 30 °C; and

b) an active pharmaceutical ingredient that is soluble in molten polyethylene glycol wherein the polyethylene glycol is as defined in a);

wherein the solid dosage form is a capsule acting as crystallisation rate inhibitor, e.g. a HPMC capsule.

BRIEF DESCRIPTION OF THE DRAWINGS

The summary, as well as the following detailed description, is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings exemplary embodiments of the invention; however, the invention is not limited to the specific disclosure of the drawings. In the drawings:

Figure 1 is an X-ray powder diffraction (XRPD) pattern of the crystalline form of Compound A monohydrate as obtained in Example 1.

Figure 2 is an XRPD of the precipitate formed when a supersaturated solution of Compound A in NMP is added to Fasted state simulated intestinal fluid (FaSSIF) containing 1% PVPVA64.

DETAILED DESCRIPTION OF THE INVENTION

The disclosure may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. It is to be appreciated that certain features of the disclosed pharmaceutical formulations and methods which are, for clarity, described herein in the context of separate aspects, may also be provided in combination in a single aspect. Conversely, various features of the disclosed pharmaceutical formulations and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any sub-combination.

Some of the quantitative expressions given herein are not qualified with the term "about. " It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to

refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", mean "including but not limited to", and are not intended to (and do not) exclude other components.