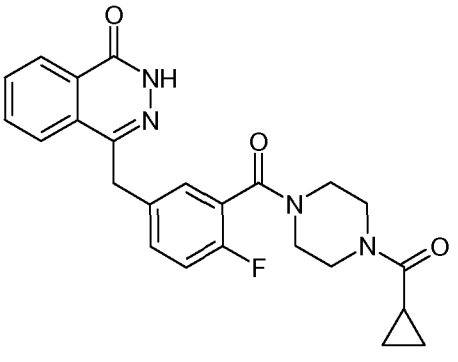
PHARMACEUTICAL FORMULATION 514

Certain embodiments of the invention disclosed herein were made under a joint Research Agreement between Abbott GMBH & Co.KG and AstraZeneca UK Ltd.

The present invention relates to novel pharmaceutical compositions with improved bioavailability and/or stability and/or drug loading, to processes for preparing these novel pharmaceutical compositions and to their use in treating cancer, either as a sole agent or in combination with other therapies.

In particular, the present invention relates to a pharmaceutical formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature. A particularly suitable matrix polymer being copovidone. The invention also relates to a daily pharmaceutical dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one provided by such a formulation. In addition, the invention relates to the use of copovidone in a solid dispersion composition with 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one for increasing the bioavailability and/or stability of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one, or for treating cancer in a patient.

4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one (Compound 1), which has the following structure:



is disclosed and exemplified in International Patent Application Publication No. WO 2004/080976, (compound 168). It is a poly(ADP-ribose)polymerase (PARP) inhibitor currently in clinical trials for treating cancers, such as breast and ovarian cancer.

According to WO2005/012524 and WO2005/053662, PARP inhibitor compounds, such as 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one, are particularly effective in treating cancers whose cells are defective in homologous recombination (HR) dependent DNA double-stranded break (DSB) repair pathway. BRCA1 (NM_007295) and BRCA 2 (NM_000059) hereditary breast / ovarian cancer genes are just 2 out of many proteins in the HR dependent DNA DSB repair pathway. Other members of the HR dependent DNA DSB repair pathway include: ATM (NM_000051), ATR (NM_001184), DSS1 (U41515), RPA 1 (NM_002945.2), RPA 2 (NM_00294.6), RPA 3 (NM_002974.3), RPA 4 (NM_013347.1), Chk1 (NM_001274.2), Chk2 (096017 GI:6685284), RAD51 (NM_002875), RAD51L1 (NM_002877), RAD51c (NM_002876), RAD51L3 (NM_002878), DMC1 (NM_007068), XRCC2 (NM_005431), XRCC3 (NM_05432), RAD52 (NM_002879), RAD54L (NM_003579), RAD54B (NM_012415), RAD50 (NM_005732), MRE11A (NM_005590) and NBS1 (NM_002485). Thus, for example, breast or ovarian cancers that are BRCA1+ and/or BRCA2+ could be much more susceptible to treatment with a PARP inhibitor compound, than cancers without a defective homologous recombination (HR) dependent DNA double-stranded break (DSB) repair pathway; potentially allowing effective monotherapy treatment, and/or treatment at lower doses with concomitant fewer or lesser side effects.

4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one (Compound 1) is a weakly acidic compound with a pKa of about 12.5 (phthalazinone moiety). It is essentially neutral across the physiological pH range. The aqueous equilibrium solubility of Compound 1 was measured to be around 0.10 mg/mL across a range of aqueous buffers (pH 1-9); this solubility is increased to 0.12-0.20 mg/mL in real and simulated gastrointestinal media with the highest solubility of 0.20 mg/mL in the fed state simulated intestinal fluid (see Example 1.1).

Compound 1 was determined to be moderately permeable, compared to the high permeability marker propranolol, when investigated using a Caco-2 cell line. The Caco-2 Papp value was 3.67×10^{-6} cm/sec, which equates to a human Peff value of 1.4×10^{-4} cm/sec. Compound 1 is at the limits of poorly soluble in terms of drug formulation being a tentative class 4 (at doses above 25mg) within the Biopharmaceutical Classification System (BCS) based on these solubility and permeability values (see Example 1).

Predictions of the bioavailability of Compound 1, made based on solubility and permeability measurements, suggested that an immediate release (IR) tablet would be suitable for Compound 1. Indeed, compounds with similar solubility, permeability and dose range have been successfully formulated as IR tablets (E.g. see Kasim et al. "Molecular properties of WHO essential drugs and provision of biopharmaceutics classification." Molecular Pharmaceutics. 1(1):85-96, 2004). When tested in dogs however, the exposure following administration of a conventional IR tablet was much lower than expected (see Example 6; Figure 13).

The oral bioavailability of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one to a patient is dependant to a certain extent upon the dissolution rate and solubility of the drug in the GI tract. The bioavailability of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one for a series of formulations can be assessed by determining the area under the curve (AUC) of a graph of plasma 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one concentration *v.* time elapsed since administration of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

The inventors were able to address the poor bioavailability of an IR tablet of Compound 1 by making a lipidic formulation (Gelucire™ 44-14), and this formulation has been used in Phase I and II clinical trials. However, at high drug loading (>10%), reduced exposure was seen with the lipidic formulation (see Example 6 and Figure 30). A potential issue with the gelucire lipidic formulation was thus only realised during dose escalation studies aimed at determining the maximum tolerated dose and, thus predicting the potential therapeutic dose. It was realized that if the therapeutic dose was 400mg, a 10% drug loaded Gelucire™ 44-14 formulation would have to be administered as 16 size 0 capsules. Not only does this present with patient compliance issues, it would also have commercial implications, e.g. increase in manufacturing, packaging, and transportation costs, etc.

In the event that 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one is required in daily dosages greater than 50mg or 100mg, (indeed dosages as high as 400mg twice daily are being tested in clinical trials), it would be desirable to to find a formulation of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2h-phthalazin-1-one with increased bioavailability and one that would allow a sufficient drug loading to be achieved so that it could be administered by means of a manageable number of units (e.g. fewer than 4 per day).

Such increased bioavailability could be useful in enabling a reduction in the daily dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one required to achieve comparable biological exposure seen with a conventional formulation, e.g. a conventional IR tablet of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

There is a desire, therefore, to find a formulation of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one with improved bioavailability and drug loading relative to a conventional IR tablet formulation, ideally a formulation with a target bioavailability of around 90% (relative to an intravenous solution), and a formulation that permits sufficient drug loading to reduce the number of units that need to be taken at any one time, for example fewer than 4 and ideally to one or two units.

The present invention aims to provide a formulation of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one that minimises the size and/or number of tablets or capsules required for the therapeutically effective dose, ideally to fewer than 4 units, preferably only one or two units.

In terms of the aim of increasing the therapeutic potential of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one, the inventors sought to increase the therapeutic potential by achieving an increase in the bioavailability of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a formulation that permitted sufficient high drug loading (e.g. greater than 10%). In distinct embodiments the drug loading will be at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60%. It will be appreciated that the greater the drug loading the greater the likelihood of instability, so although it may be feasible to generate a formulation with a 60% drug loading it may be preferable to adopt a lower drug loading so as to maintain stability.

Of the various formulation approaches available, the inventors discovered that solid dispersion formulations with particular types of polymer were a means of addressing one or more of the aims stated above. Furthermore, it was surprisingly found that the solid dispersion formulations of the invention increased the bioavailability of Compound 1 compared to the lipidic gelucire formulation.

The inventors have now surprisingly found that the therapeutic potential of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one can be increased by formulating 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature. The matrix polymer copovidone was found to be particularly suitable as it could be used in hot melt extrusion without the need of a plasticiser and it provides a product with acceptable stability, even at 30% drug loading in the final product (e.g. tablet).

It would be further desirable to identify a suitable matrix polymer that could be formulated into a solid dispersion with the drug using any of the available solid dispersion techniques without the need for additional surfactants/plasticisers as it would be appreciated that the presence of certain extraneous excipients could compromise the stability Compound 1 (e.g. the ability to remain in amorphous form).

Thus, in one embodiment the solid dispersion formulation of the invention does not comprise a surfactant/plasticiser.

According to a first aspect of the invention there is provided a pharmaceutical formulation comprising an active agent in solid dispersion with a matrix polymer, wherein the active agent is 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a salt or solvate thereof, and the matrix polymer exhibits low hygroscopicity and high softening temperature.

In one embodiment the active agent is present in the formulation in stable amorphous form. Where the active agent is present in the formulation in stable amorphous form, the formulation may stabilise the active agent in the formulation in the amorphous form and may reduce conversion or reversion to other forms.

In certain embodiments it will be desirable for the salt or solvate of Compound 1 to be a pharmaceutically acceptable salt or solvate.

As used herein, by 'polymer' we mean a macromolecule composed of repeating structural units connected by covalent chemical bonds. The term encompasses linear and branched polymers, cyclic polymers such as cyclic oligosaccharides (including cyclodextrins), homopolymers and copolymers, whether natural, synthetic or semi-synthetic in origin.

As used herein, the term 'matrix polymer' means a material that exhibits low hygroscopicity and high softening temperature comprising a polymer or a blend of two or more polymers.

As used herein, by "low hygroscopicity" we mean having an equilibrium water content < 10% at 50% relative humidity, as determined by Dynamic Vapour Sorption (DVS), disclosed in Bergren, M.S. Int. J. Pharm 103:103-114 (1994).

As used herein, by "high softening temperature" we mean that the material, in "as received" form (that is to say, without having been exposed to high humidity) exhibits a glass transition temperature (Tg) or melting point (Tm) >100°C, as determined by Differential Scanning Calorimetry (DSC). The person of ordinary skill in the art will appreciate that Tg is a measurement appropriate for polymers that are in an amorphous state or form and Tm is a measurement that is appropriate for polymers that are in a crystalline state or form.

Suitable matrix polymers for use in the invention include: copovidone, hypromellose phthalate (hydroxypropylmethylcellulose phthalate, HPMCP), hypromellose acetate succinate (hydroxypropylmethylcellulose acetate succinate, HPMCAS), -2-hydroxypropyl -β-cyclodextrin (HPBCD), hypromellose (hydroxypropylmethylcellulose, HPMC), polymethacrylates (poly(methacrylic acid, methyl methacrylate 1:1; poly(methacrylic acid, ethyl acrylate) 1:1), hydroxypropyl cellulose (HPC), and cellulose acetate phthalate (CAP).

Copovidone is a synthetic, linear, random copolymer of N-vinyl-2-pyrrolidone (VP) and vinyl acetate (VA) with the chemical formula $(C_6H_9NO)_m$ $(C_4H_6O_2)_n$ where the VA content is nominally 40% (but may vary, for example between 35-41%). The addition of vinyl acetate to the vinylpyrrolidone polymer chain reduces hygroscopicity and glass transition temperature (Tg) of the polymer relative to Povidone (polyvinyl pyrrolidone, PVP homopolymer).

The K-value for copovidone is between 25 and 31, and since the K-value is calculated from the kinematic viscosity of a 1% aqueous solution, it is related to the average molecular weight of the polymer. The average molecular weight (Mw) ranges from ~24,000 to 30,000.

According to one aspect of the invention there is provided a pharmaceutical formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with copovidone. In one embodiment the pharmaceutical formulation is one suitable for mucosal administration to a patient. A particular mucosal administration route is oral, e.g. a tablet or capsule, and the like.

The invention also provides a daily pharmaceutical dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one wherein the dose comprises a therapeutically effective amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a

matrix polymer that exhibits low hygroscopicity and high softening temperature. In one embodiment the matrix polymer is copovidone. In a further embodiment the pharmaceutical formulation is mucosally administrable to a patient.

In a particular embodiment, the therapeutically effective amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one is in the range 10 to 1000mg, in a further embodiment the dose comprises 25 to 400mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

According to a further aspect of the invention there is provided a pharmaceutical formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with copovidone, and comprising one or more additional compounds useful in the treatment of cancer. In one embodiment the pharmaceutical formulation is for mucosal administration to a patient.

According to a further aspect of the invention there is provided an oral pharmaceutical composition comprising a solid amorphous dispersion comprising an active agent and at least one matrix polymer, wherein the matrix polymer exhibits low hygroscopicity and high softening temperature and wherein the active agent is 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof.

Further aspects of the invention relate to the use of a matrix polymer that exhibits low hygroscopicity and high softening temperature, such as copovidone, in solid dispersion with 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament, particularly for treating cancer; and, a method of treating cancer comprising administration to a patient in need thereof of a therapeutically effective amount of a formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof, in solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature, such as copovidone. In such aspects, the medicament may comprise from 10 to 1500mg of Compound 1, such as from 10 to 1000mg and from 25 – 400mg.

Further aspects of the invention relate to: a method for increasing the bioavailability of the drug 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a patient in need of said drug, comprising administering to said patient a formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-

benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature; and, a daily pharmaceutical dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4 fluoro-benzyl]-2H-phthalazin-1-one for treating cancer in the patient, wherein the dose comprises 10 to 1000mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature. In a particular embodiment of these aspects the matrix polymer is copovidone.

According to a further aspect of the invention there is provided a method of producing a solid amorphous dispersion of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one comprising:

(i) mixing a suitable amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof with a desired amount of at least one matrix polymer, wherein the matrix polymer exhibits low hygroscopicity and high softening temperature;

(ii) increasing the temperature of the mixture to produce a melt; and

(iii) extruding the melt to produce a solid product.

In step (iii) the melt may be extruded as a solid rod which may then be further processed, for example by milling, to produce a powder suitable for use in a pharmaceutical formulation. Alternatively, the melt may be extruded into one or more moulds. Such moulds may, for example provide for shaped products such as elliptical or tablet shapes.

In step (ii) the melt could be produced by applying thermal heat and/or mechanical stress.

According to the various aspects of the invention a particular ratio of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one: matrix polymer by weight is from 1:0.25 to 1:10. More preferably the lower limit of the range is 1:≥4, 1:5 or 1:7. Preferably, the upper limit of this range is 1:≤2, 1:1, 1:0.5 or 1:0.3. Suitable ratios are 1:2, 1:3 and 1:4. In one embodiment, the range is 1:≥2 to 1:10. In another embodiment, the solid dispersion includes a surface-active agent and/or a plasticiser. Further discussion of surface-active agents and plasticisers appears below.

As used herein, the phrase "therapeutically effective amount" means the drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a

therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art. By way of example, the therapeutically effective amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one could be 25mg, 50mg, 100mg, 150mg, 200mg, 250mg, 300mg, 400mg, 500mg, 600mg or 750mg once or twice a day.

The solid dispersion formulations of the invention exhibit increased bioavailability and drug loading potential and are thus likely to require fewer dose units compared to conventional/immediate release 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one formulations.

One aspect of the invention provides a daily pharmaceutical dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one for treating cancer in a patient, wherein the dose comprises 10 to 1500mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature, such as copovidone. In one embodiment the pharmaceutical dose is administrable to a patient mucosally. In another embodiment the dose comprises 25 to 600mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

In various embodiments, the dose comprises 1500, 1250, 1000, 800, 700, 600, 500, 450, 400, 300, 250, 225, 200, 175, 150, 125, 100, 75, 50, 25, 15 or 10mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one. In particular embodiments, the dose comprises 25, 50, 100, 200 or 400mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one.

Additional excipients may be included in the formulation or dose. For example, the formulation or dose may comprise one or more fillers, binders, disintegrants and/or lubricants.

Suitable fillers include, for example, lactose, sugar, starches, modified starches, mannitol, sorbitol, inorganic salts, cellulose derivatives (e.g. microcrystalline cellulose, cellulose), calcium sulphate, xylitol and lactitol.

Suitable binders include, for example, lactose, starches, modified starches, sugars, gum acacia, gum tragacanth, guar gum, pectin, wax binders, microcrystalline cellulose, methylcellulose, carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxyethyl

cellulose, hydroxypropyl cellulose, copolyvidone, gelatine, polyvinylpyrollidone (PVP) and sodium alginate.

Suitable disintegrants include, for example, crosscarmellose sodium, crospovidone, polyvinylpyrrolidone, sodium starch glycollate, corn starch, microcrystalline cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

Suitable lubricants include, for example, magnesium stearate, magnesium lauryl stearate, sodium stearyl fumarate, stearic acid, calcium stearate, zinc stearate, potassium benzoate, sodium benzoate, myristic acid, palmitic acid, mineral oil, hydrogenated castor oil, medium-chain triglycerides, poloxamer, polyethylene glycol and talc.

Additional conventional excipients, which may be added, include preservatives, stabilisers, anti-oxidants, silica flow conditioners, antiadherents or glidants.

Other suitable fillers, binders, disintegrants, lubricants and additional excipients which may be used are described in the Handbook of Pharmaceutical Excipients, 5th Edition (2006); The Theory and Practice of Industrial Pharmacy, 3rd Edition 1986; Pharmaceutical Dosage Forms 1998; Modern Pharmaceutics, 3rd Edition 1995; Remington's Pharmaceutical Sciences 20th Edition 2000.

In certain embodiments, the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one will be present in an amount of 10 to 70%, and preferably from 15 to 50% (more preferably 20 to 30% or 25 to 35%) by weight of the solid dispersion.

In certain embodiments, one or more fillers will be present in an amount of 1 to 70% by weight of the formulation or dose.

In certain embodiments, one or more binders will be present in an amount of 2 to 40% by weight of the formulation or dose.

In certain embodiments, one or more disintegrants will be present in an amount of 1 to 20%, and especially 4 to 10% by weight of the formulation or dose.

It will be appreciated that a particular excipient may act as both a binder and a filler, or as a binder, a filler and a disintegrant. Typically the combined amount of filler, binder and disintegrant comprises, for example, 1 to 90% by weight of the formulation or dose.

In certain embodiments, one or more lubricants will be present in an amount of 0.5 to 3%, and especially 1 to 2% by weight of the formulation or dose.

In certain embodiments, one or more surface-active agents will be present in the solid dispersion in an amount of 0.1 to 50%, preferably $\leq$5% (eg, 1 to 2%) by weight of the solid dispersion. The presence of a surface-active agent provides a further enhancement of the

increase in therapeutic potential achieved with the present invention. Examples of suitable surface-active agents include: anionic surfactants such as sodium dodecyl sulphate (sodium lauryl sulphate); docusate sodium; cationic surfactants such as cetrimide, benzethonium chloride, cetylpyridinium chloride and lauric acid; nonionic surfactants such as polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, e.g. polysorbates 20, 40, 60 and 80; polyoxyethylene castor oil derivatives, e.g. Cremophor RH40™; polyoxyethylene stearates and poloxamers.

In certain embodiments, one or more plasticisers will be present in the solid dispersion in an amount of 0.1% to 50%, preferably ≤5% (e.g. 1 to 2%) by weight of the solid dispersion. The presence of a plasticiser may enhance processability of the solid dispersion, for example when a melt extrusion process is used. Examples of suitable plasticisers include: acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, chlorbutanol, dextrin, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, glycerine, glycerine monostearate, mannitol, mineral oil, lanolin alcohols, palmitic acid, polyethylene glycol, polyvinyl acetate phthalate, propylene glycol, 2-pyrrolidone, sorbitol, stearic acid, triacetin, tributyl citrate, triethanolamine and triethyl citrate.

The term "solid dispersion" as used herein means systems in which an active agent is dispersed in an excipient carrier. With respect to the state of the drug in the systems, solid dispersions in this sense can include compositions in which the drug is dispersed as discrete domains of crystalline or amorphous drug, or as individual molecules within an excipient carrier. With respect to the complete drug-excipient composite, solid dispersions can be relatively large solid masses such as pellets, tablets, films or strands; or they can exist as free flowing powders consisting of micro- or nano-sized primary particles or aggregates thereof. The bulk state of the solid dispersion composition depends largely upon the mode of processing (Miller, D. A., McGinty, J. W., Williams III, R. O. Solid Dispersion Technologies. Microencapsulation of Oil-in-Water Emulsions 172 (2008) pp 451-491).

In the present invention the definition of a solid dispersion does not encompass physical mixtures from dry or wet mixing or dry blending operations.

Methods for preparing solid dispersions are known in the art and typically comprise the steps of dissolving the drug and the polymer in a common solvent and evaporating the solvent. The solvent can be routinely selected according to the polymer used. Examples of solvents are: acetone, acetone/dichloromethane, methanol/dichloromethane, acetone/water, acetone/methanol, acetone/ethanol, dichloromethane/ethanol or ethanol/water. Methods for

evaporating solvent include rotary evaporation, spray drying, lyophilisation and thin film evaporation. Alternatively solvent removal may be accomplished by cryogenic freezing followed by lyophilisation. Other techniques may be used such as melt extrusion, solvent controlled precipitation, pH controlled precipitation, supercritical fluid technology and cryogenic co milling.

This invention further discloses a method of making the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one: copovidone solid dispersion. Such a method comprises (i) dissolving a suitable amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one and matrix polymer in a common solvent; and (ii) removing the solvent. Pharmaceutical compositions comprising the dispersion can be made, for example by adding such things as stabilizers and/or additional excipients as required. In a particular embodiment, the solvent is removed by spray drying.

According to another aspect of the invention the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one:copovidone solid dispersion is made by melt extrusion. Such a method comprises adding the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one, or a pharmaceutically acceptable salt or solvate thereof, and copovidone polymer, and any additional optional excipients, including plasticisers, to a melt extrusion apparatus which then heats and mixes and finally extrudes the solid dispersion product. The extruder heats the mixture to a temperature high enough to melt the mixture but low enough so as to not degrade the constituents.

According to another aspect of the invention there is provided a method of producing a solid amorphous dispersion of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one comprising simultaneously exposing 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof and at least one matrix polymer, wherein the matrix polymer exhibits low hygroscopicity and high softening temperature, to hot melt extrusion.

According to another aspect of the invention there is provided a method of making a solid dispersion product of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2h-phthalazin-1-one, comprising:

(a) providing a powdered or granulated premix comprising:

(i) 5-60% by weight of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2h-phthalazin-1-one; and,

(ii) 40-95% copovidone;

(b) melting the premix, without addition of solvent, in a kneader or an extruder extruder to obtain a homogeneous melt , and

(c) shaping and solidifying the melt to obtain a solid dispersion product.

In one embodiment, the solid dispersion product is formed into a suitable dosage form ready for oral administration.

In another embodiment, the solid dispersion product is ground up, mixed with one or more additional excipients or ingredients, and tabletted or encapsulated into a suitable dosage form.

When referring to a solid dispersion we do not exclude the possibility that a proportion of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one may be dissolved within the matrix polymer, the exact proportion, if any, will depend upon the particular polymer selected.

In the formulations of the invention, at least some of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one may be present in amorphous form in the solid dispersion with the matrix polymer. The provision of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in amorphous form is additionally advantageous, since it further increases the solubility and dissolution rate of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one, thereby enhancing the increase in therapeutic potential achieved with the present invention. Whether or not drug is present in amorphous form can be determined by conventional thermal analysis or X-ray diffraction. In one embodiment, at least 25% of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in the formulation is present in amorphous form, as measured using XRPD. More preferably, this amount is at least 30%, 40%, 50%, 75%, 90%, 95%, as measured using XRPD. The most preferred embodiment is where 100% of the 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in the formulation is in amorphous form. In reality, current XRPD tools and techniques may only be able to detect >5% crystalline form, and thus the inability to detect crystalline form may mean that the sample is between 95% and 100% amorphous.

XRPD may be augmented by emerging nanometer-scale characterisation techniques: Pair-wise Distribution Function (transformation of the X-ray diffraction pattern to a normalised scattering function) may facilitate the detection of nanocrystallinity; Solid State NMR proton spin diffusion studies may be used to detect phase separation, as may Atomic Force Microscopy and Nanothermal analysis. Such techniques are comparative rather than absolute but are useful tools in the development and optimisation of pharmaceutical solid dispersion formulations.

In a further embodiment, the drug is in stable amorphous form, by which is meant that the stability (ability to remain in amorphous form and resist converting to crystalline form) of the amorphous state of Compound 1 is extended in the solid dispersion formulation of the invention relative to the stability of the amorphous state of Compound 1 on its own.

In a preferred embodiment, the formulations and doses are mucosally administrable, i.e. administrable to mucosal membranes for absorption across the membranes. To this end, suitable routes of administration include administration by inhalation, as well as oral, intranasal and rectal administration. Oral administration is particularly preferred. A tablet, capsule or other form of the formulation would be chosen by the skilled addressee according to the route of administration. Other routes of administration, e.g. parenteral are however not excluded.

The 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one is useful to provide a poly-ADP-ribose polymerase (PARP) inhibitory effect. This effect is useful for treating cancer, for example breast or ovarian cancer, and particularly cancers that possess a defective homologous recombination (HR) dependent DNA double-stranded break (DSB) repair pathway, such as BRCA1+ and/or BRCA2+ve cancers.

Another aspect of the invention is directed to a 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one composition, comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in solid dispersion with copovidone, and comprising one or more additional compounds useful in the treatment of cancer.

Particularly, useful "additional" anti-cancer compounds include DNA damage promoting agents. A DNA damage promoting agent is a compound (such as a small organic molecule, peptide or nucleic acid) which increases the amount of DNA damage in a cell, either directly or indirectly, for example through inhibition of DNA repair. The DNA damage promoting agent is often a small organic molecule compound.

Suitable DNA damage promoting agents include agents which damage DNA in a cell (i.e. DNA damaging agents), for example alkylating agents such as methyl methanesulfonate (MMS), temozolomide, dacarbazine (DTIC), cisplatin, oxaliplatin, carboplatin, cisplatin-doxorubicin-cyclophosphamide, carboplatin-paclitaxel, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, etoposide, teniposide, amsacrine, irinotecan, topotecan and rubitecan and nitrosoureas, topoisomerase-1 inhibitors like Topotecan, Irinotecan, Rubitecan, Exatecan, Lurtotecan, Gimetecan, Diflomotecan (homocamptothecins); as well as 7-substituted non-silatecans; the 7-silyl camptothecins, BNP 1350; and non-camptothecin topoisomerase-I inhibitors such as indolocarbazoles, topoisomerase-II inhibitors like Doxorubicin, Danorubicin, and other rubicins, the acridines (Amsacrine, m-AMSA), Mitoxantrone, Etopside, Teniposide and AQ4, dual topoisomerase-I and II inhibitors like the benzophenazines, XR 11576/MLN 576 and benzopyridoindoles, and antimetabolites such as gemcitabine, antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea, and arsenic trioxide.

The patient can be a human, e.g. an adult or a child, but the treatment of other mammals is also contemplated.

Aspects of the present invention will now be illustrated with reference to the accompanying figures described below and experimental exemplification, by way of example and not limitation. Further aspects and embodiments will be apparent to those of ordinary skill in the art.

Figure 1 shows permeability of Compound 1 across Caco-2 monolayers (n=3, ±s.d.)

Figure 2 shows in vitro dissolution of various Compound 1 formulations.

Figure 3 shows a thermogram of a solid dispersion exhibiting a melt transition due to the presence of crystalline Compound 1

Figure 4 shows an image of a tablet which exhibits a single crystal of Compound 1 in the hot-stage microscopy method

Figure 5 shows PDF spectra for solid dispersions of Compound 1 and copovidone at various drug loadings

Figure 6 shows a comparison of PDF spectra for solid dispersions of Compound 1 and copovidone with simulated spectra for physical mixtures at various drug loadings

Figure 7 shows TM-AFM topographic (height), tip-deflection (error) and phase (mechanical property) images from 50 μm × 50 μm and 10 μm × 10 μm scans for solid dispersions of Compound 1 and copovidone at 10% drug loading

Figure 8 shows TM-AFM topographic (height), tip-deflection (error) and phase (mechanical property) images from 50 μm × 50 μm and 10 μm × 10 μm scans for solid dispersions of Compound 1 and copovidone at 30% drug loading

Figure 9 shows TM-AFM topographic (height), tip-deflection (error) and phase (mechanical property) images from 50 μm × 50 μm and 10 μm × 10 μm scans for solid dispersions of Compound 1 and copovidone at 40% drug loading

Figure 10 shows an XRPD diffractogram for Compound 1 Form H

Figure 11 shows a representative DSC trace for Compound 1 Form H

Figure 12 shows an XRPD diffractogram for Opadry

Figure 13 shows an infrared spectrum of Compound 1

Figure 14 shows infrared spectra of Aqoat MG, HP55S, Pharmacoat, Povidone and Copovidone

Figure 15 shows a synchronous spectrum of Aqoat MG annotated with correlation squares

Figure 16 shows an asynchronous spectrum of Aqoat MG

Figure 17 shows a synchronous spectrum of HP55S

Figure 18 shows an asynchronous spectrum of HP55S

Figure 19 shows an a synchronous spectrum of HP55S (high sensitivity)

Figure 20 shows a synchronous spectrum of Pharmacoat

Figure 21 shows an asynchronous spectrum of Pharmacoat

Figure 22 shows an asynchronous spectrum of Pharmacoat (high sensitivity)

Figure 23 shows a synchronous spectrum of Povidone

Figure 24 shows a synchronous spectrum of Povidone (high sensitivity)

Figure 25 shows an asynchronous spectrum of Povidone

Figure 26 shows a synchronous spectrum of Copovidone

Figure 27 shows a synchronous spectrum of Copovidone (high sensitivity)

Figure 28 shows an asynchronous spectrum of Copovidone

Figure 29 shows an asynchronous spectrum of Copovidone (high sensitivity)

Figure 30 shows a plot of plasma concentration vs time for the various Compound 1 formulations.

Example 1. Characteristics of Compound 1

1.1 Solubility

The solubility of crystalline Form A of Compound 1 was measured in water and a range of pH buffered solutions representing the physiological pH range. The physical form of any undissolved (or precipitated) Compound 1 was not assessed by XRPD after solubility determination. Solubility data are summarised in Table 1. The Form A crystalline form of Compound 1 is disclosed in WO2008/047082.

Table 1. Solubility of crystalline Compound 1 (Form A) in a range of buffers representing the physiological pH range (mg.mL^{-1})

Media	1 hr	pH	24 hr	pH
Water	0.124	5.6	0.109	6.0
0.1 M HCl	0.128	1.2	0.114	1.2
pH 3 Citrate Buffer	0.124	2.9	0.112	2.9
pH 6.8 Phosphate Buffer	0.111	6.9	0.096	6.9
pH 9 Buffer	0.116	8.9	0.102	8.8
0.1M NaOH	0.650	12.5	0.599	12.4

The solubility of Compound 1 was also measured in real and simulated gastrointestinal media (Table 2). Solubility in HIF and FeSSIF was notably higher than buffer solubilities reported in Table 1.

Table 2. Solubility of crystalline Compound 1 (Form A) real and simulated gastrointestinal media

Media	Equilibrium solubility (mg.mL^{-1}), 24 hr
Simulated Gastric Fluid (SGF)[1]	0.12
Human Gastric Fluid (HGF)[2]	0.15
Fed State Simulated Intestinal Fluid (FeSSIF)[3]	0.2
Fasted State Simulated Intestinal Fluid (FaSSIF)[3]	0.13
Human Intestinal Fluid (HIF)[2]	0.17

[1] SGF contains 3.2g pepsin, 2.0g sodium chloride, and 7.0mL hydrochloric acid per litre.

[2] Pooled from healthy volunteers; supplied by Uppsala Universitet, Box 256, 751 05 Uppsala, Sweden

[3] Marques, M. Dissolution media simulating fasted and fed states. Dissolution Technologies (May 2004) pp 16.

1.2 Permeability

Compound 1 was determined to be moderately permeable when compared to the high permeability marker propranolol, investigated using a validated Caco-2 cell line, results are summarised in Table 3 and Figure 1. Compound 1 was shown to have propensity for efflux by P-gp at low concentrations (10 μM), which was inhibited by the selective P-gp inhibitor Elacridar (GF120918; GG918; N-(4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolyl)ethyl]phenyl)-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide, hydrochloride salt.

Table 3. Permeability of Compound 1 across Caco-2 monolayers (n=3, ±S.D.), compared to the high permeability marker propranolol and the efflux marker digoxin

	P_{app} ($cm.sec^{-1}$)		Efflux Ratio
Concentation (μM)	A-to-B	B-to-A	
10	3.67±0.34	23.70±2.84	6.5
10 with Elacridar	10.34±1.38	14.29±0.93	1.4
260	7.75±0.88	17.75±1.19	2.3
700	8.4±0.41	15.06±1.42	1.8
Propranolol	19.97±2.57	21.48±0.33	1.1
Digoxin	1.34±0.03	12.22±1.37	9.1

Key: A = apical; B = basolateral

See Figure 1.

Example 2. Polymer characteristics

Table 4. Characteristics of polymers used in pharmaceutical solid dispersion formulations

Polymer	Grade	Supplier	Hygro-scopicity (%w/w)[a]	Softening Point[b]	
				Tg (°C)	Tm (°C)
Copovidone	Kollidon VA64	BASF SE	5	106	N/A
Povidone	Kollidon 17PF		16	136	N/A
	Kollidon 25			155	N/A
	Kollidon 30			168	N/A
Hypromellose phthalate (HPMCP)	HP55S	Shin-Etsu Chemical Co., Ltd	4	145	N/A
	HP55			145	N/A
Hypromellose acetate succinate (HPMCAS)	Aqoat LF		4	120	N/A
	Aqoat LG			120	N/A
	Aqoat MG			130	N/A
2-hydroxypropyl-β-cyclodextrin (HPBCD)	Kleptose HP	Roquette Freres	7	278	N/A
Hypromellose (HPMC)	Pharmacoat 606	Shin-Etsu Chemical Co., Ltd	4	175	N/A
Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit L100-55	Evonik Degussa GmbH	4	115	N/A
Poly(methacrylic acid, methyl methacrylate) 1:1	Eudragit L100		6	160[#]	N/A
Poly(butylmethacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1 acid, ethyl acrylate) 1:1	Eudragit E100		1	48	N/A
Poly(methacrylic acid, methyl methacrylate) 1:2	Eudragit S100		11	160[#]	N/A

Polymer	Grade	Supplier	Hygro-scopicity (%w/w)[a]	Softening Point[b]	
				Tg (°C)	Tm (°C)
Polyethylene glycol (PEG)	PEG 6000	Fluka AG	2	N/A	55-63
Poloxamer	Pluronic (Lutrol) F68	BASF SE	2	N/A	52-57
	Pluronic (Lutrol) F127			N/A	52-57
Hydroxypropyl cellulose (HPC)	Klucel EF	Hercules, Inc.	5	130	N/A
Cellulose acetate phthalate (CAP)	Aquacoat CPD	FMC Biopolymer	6	176	N/A

Key: N/A= Not Applicable

[a] Equilibrium water content at 50% Relative Humidity (literature values)

[b] Softening temperature expressed as glass transition temperature (Tg) or melting point (Tm) – suppliers data

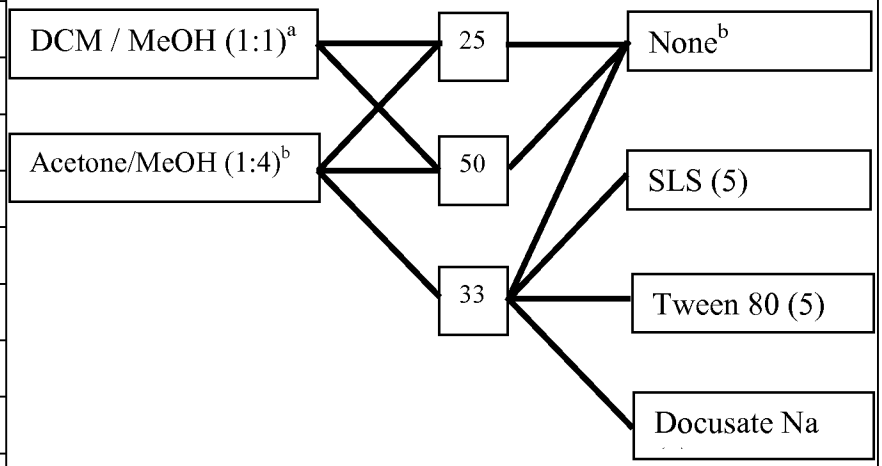
Accurate determination not possible due to chemical degradation

Example 3. Screening study – polymeric dispersions

3.1 Protocol

Table 5. Protocol for the screening study of Compound 1 solid dispersions

Polymer	Solvent System	Drug Loading (%w/w)	Additive (%w/w)
PEG 6000			
Poloxamer F68			
Poloxamer F127			
PVP K25			
PVP K30			
HPMC 606			
HPMC Phthalate			
Eudragit L100-55			
Eudragit E100			
Kleptose			
HPC			
Copovidone			
Polyacrylic acid			
Kleptose / PVP K25[c]			
Kleptose / HPMC606[d]			



[a] Poloxamer F127, PVP K30, Hydroxypropyl cellulose, Copovidone and Polyacrylic acid were not assessed in DCM / MeOH

[b] Only PVP K25, HPMC Phthalate and Kleptose were assessed without additive at 33% loading

[c] Kleptose / PVP K25 blend assessed using Acetone / MeOH solvent system only in ratios 5:70 and 10:65 at 25% drug loading and in ratios 5:45 and 10:40 at 50% drug loading, without additive

[d] Kleptose / HPMC606 blend assessed as described above for Kleptose / PVP K25 blend

3.2 Methodology

A series of 4%w/w solutions, comprising binary mixtures of Compound 1 and each of the polymers in the proportions specified in the protocol, were prepared by weighing into

1.8mL vials and dissolving in the specified solvent system. Further solutions comprising ternary mixtures of Compound 1, polymer and surfactant were prepared in a similar manner. Solvent was removed by evaporation at 40°C under nitrogen (10mL/min flow, 0.7 bar pressure) for 15 minutes followed by drying overnight under full vacuum to produce a solid dispersion.

The resulting samples were assessed using XRPD (Bruker GADDS diffractometer; data collection at room temperature using CuK_α radiation in the 2θ region between 1.5 and 41.5°), immediately after preparation and after storage for up to 1 month at 30°C and 60% RH.

3.3 Results

Table 6. Results for the screening study of Compound 1 solid dispersions

Polymer	Solvent System	Drug (%w/w)	Additive	XRPD (crystalline Compound 1)		
				After Prep.	30°C/60%RH	
					1 week	1 month
PEG6000	DCM/MeOH	25	None	N/D	Present	N/T
PEG6000	DCM/MeOH	50	None	N/D	Present	N/T
PEG6000	Acetone/MeOH	25	None	N/D	Present	N/T
PEG6000	Acetone/MeOH	50	None	N/D	Present	N/T
PEG6000	Acetone/MeOH	33	SLS	N/D	N/T	Present
PEG6000	Acetone/MeOH	33	Tween 80	N/D	N/T	Present
PEG6000	Acetone/MeOH	33	Doc. Na	N/D	N/T	Present
Poloxamer F68	DCM/MeOH	25	None	N/D	Present	N/T
Poloxamer F68	DCM/MeOH	50	None	N/D	Present	N/T
Poloxamer F68	Acetone/MeOH	25	None	N/D	Present	N/T
Poloxamer F68	Acetone/MeOH	50	None	N/D	N/D	N/T
Poloxamer F68	Acetone/MeOH	33	SLS	N/D	N/T	Present

Polymer	Solvent System	Drug (%w/w)	Additive	XRPD (crystalline Compound 1)		
				After Prep.	30°C/60%RH	
					1 week	1 month
Poloxamer F68	Acetone/MeOH	33	Tween 80	N/D	N/T	Present
Poloxamer F68	Acetone/MeOH	33	Doc. Na	N/D	N/T	Present
Poloxamer F127	Acetone/MeOH	25	None	N/D	Present	N/T
Poloxamer F127	Acetone/MeOH	50	None	N/D	Present	N/T
PVP K25	DCM/MeOH	25	None	N/D	N/D	N/T
PVP K25	DCM/MeOH	50	None	N/D	N/D	N/T
PVP K25	Acetone/MeOH	25	None	Not harvested		
PVP K25	Acetone/MeOH	33	None	N/D	N/D	N/T
PVP K25	Acetone/MeOH	50	None	Not harvested		
PVP K25	Acetone/MeOH	33	SLS	N/D	N/T	N/D
PVP K25	Acetone/MeOH	33	Tween 80	N/D	N/T	N/D
PVP K25	Acetone/MeOH	33	Doc. Na	N/D	N/T	N/D
PVP K30	Acetone/MeOH	25	None	N/D	N/D	N/T
PVP K30	Acetone/MeOH	50	None	N/D	N/D	N/T
HPMC-606	DCM/MeOH	25	None	N/D	N/D	N/T
HPMC-606	DCM/MeOH	50	None	N/D	N/D	N/T
HPMC-606	Acetone/MeOH	25	None	Not harvested		
HPMC-606	Acetone/MeOH	50	None	Not harvested		
HPMC-606	Acetone/MeOH	33	SLS	N/D	N/T	N/D
HPMC-606	Acetone/MeOH	33	Tween 80	N/D	N/T	N/D
HPMC-606	Acetone/MeOH	33	Doc. Na	N/D	N/T	N/D
HPMC Phthalate	DCM/MeOH	25	None	N/D	N/D	N/T
HPMC Phthalate	DCM/MeOH	50	None	N/D	N/D	N/T

Polymer	Solvent System	Drug (%w/w)	Additive	XRPD (crystalline Compound 1)		
				After Prep.	30°C/60%RH	
					1 week	1 month
HPMC Phthalate	Acetone/MeOH	33	None	Not harvested		
HPMC Phthalate	Acetone/MeOH	33	None	Not harvested		
HPMC Phthalate	Acetone/MeOH	33	SLS	N/D	N/T	N/D
HPMC Phthalate	Acetone/MeOH	33	Tween 80	Not harvested		
HPMC Phthalate	Acetone/MeOH	33	Doc. Na	N/D	N/T	N/D
Eudragit L100-55	DCM/MeOH	25	None	N/D	Present	N/T
Eudragit L100-55	DCM/MeOH	50	None	N/D	Present	N/T
Eudragit L100-55	Acetone/MeOH	25	None	N/D	N/D	N/T
Eudragit L100-55	Acetone/MeOH	50	None	N/D	N/D	N/T
Eudragit L100-55	Acetone/MeOH	33	SLS	N/D	N/T	N/D
Eudragit L100-55	Acetone/MeOH	33	Tween 80	N/D	N/T	N/D
Eudragit L100-55	Acetone/MeOH	33	Doc. Na	N/D	N/T	N/D
Eudragit E100	DCM/MeOH	25	None	N/D	N/D	N/T
Eudragit E100	DCM/MeOH	50	None	N/D	N/D	N/T
Eudragit E100	Acetone/MeOH	25	None	N/D	N/D	N/T

Polymer	Solvent System	Drug (%w/w)	Additive	XRPD (crystalline Compound 1)		
				After Prep.	30°C/60%RH	
					1 week	1 month
Eudragit E100	Acetone/MeOH	50	None	Present[1]	N/T	Present[1]
Eudragit E100	Acetone/MeOH	33	SLS	N/D	N/T	N/D
Eudragit E100	Acetone/MeOH	33	Tween 80	N/D	N/T	N/D
Eudragit E100	Acetone/MeOH	33	Doc. Na	N/D	N/T	N/D
Kleptose HP	DCM/MeOH	25	None	N/D	N/D	N/T
Kleptose HP	DCM/MeOH	50	None	N/D	N/D	N/T
Kleptose HP	Acetone/MeOH	25	None	N/D	N/D	N/T
Kleptose HP	Acetone/MeOH	33	None	N/D	N/T	N/D
Kleptose HP	Acetone/MeOH	50	None	N/D	N/D	N/T
Kleptose HP	Acetone/MeOH	33	None	N/D	N/T	N/D
Kleptose HP	Acetone/MeOH	33	None	N/D	N/T	N/D
Kleptose HP	Acetone/MeOH	33	None	N/D	N/T	N/D
HPC	Acetone/MeOH	25	None	N/D	N/D	N/T
HPC	Acetone/MeOH	50	None	N/D	N/D	N/T
Copovidone	Acetone/MeOH	25	None	N/D	N/D	N/T
Copovidone	Acetone/MeOH	50	None	Present	Present	N/T
Kleptose / PVP K25 (70:5)	Acetone/MeOH	25	None	N/D	N/T	N/D
Kleptose / PVP K25 (45:5)	Acetone/MeOH	50	None	N/D	N/T	N/D
Kleptose / PVP K25 (65:10)	Acetone/MeOH	25	None	N/D	N/T	N/D

Polymer	Solvent System	Drug (%w/w)	Additive	XRPD (crystalline Compound 1)		
				After Prep.	30°C/60%RH	
					1 week	1 month
Kleptose / PVP K25 (40:10)	Acetone/MeOH	50	None	N/D	N/T	N/D
Kleptose / HPMC-606 (70:5)	Acetone/MeOH	25	None	N/D	N/D	N/T
Kleptose / HPMC-606 (45:5)	Acetone/MeOH	50	None	N/D	N/D	N/T
Kleptose / HPMC-606 (65:10)	Acetone/MeOH	25	None	N/D	N/D	N/T
Kleptose / HPMC-606 (40:10)	Acetone/MeOH	50	None	N/D	N/D	N/T

Key: N/D = not detected

N/T = not tested

[1] Test performed in a separate study from other Eudragit E100 entries

The results of the screening study demonstrate that preparation of amorphous solid dispersions was possible for all of the polymers evaluated. However, solid dispersions produced using the low-melting poloxamers and polyethylene glycol were highly unstable, leading to the formation of crystalline drug within 1 month when stored at 30°C / 60% relative humidity. No further evaluation of these polymers was performed. Solid dispersions produced with Eudragit E100 at 25% drug loading appeared to be amorphous and stable; however, crystallisation was immediately apparent at 50% drug loading. Literature reports indicate that dispersions produced with Eudragit E may exhibit significant crystallinity (e.g. see Qi et al. Int. J. Pharm. 354:158-167, 2008); and, in a comparative study, may be less chemically stable than solid dispersions produced using Povidone K25 (Dargel, E., Mielck, J.B. Acta Pharm. Technol. 35(4):197-209. 1989). No further evaluation of Eudragit E100 was performed. Solid dispersions produced with Eudragit L100-55 using a DCM/MeOH solvent

system exhibited crystallisation after 1 week at 30°C / 60% relative humidity, but those produced using an acetone / MeOH solvent system were stable. We found that solid dispersions produced with copovidone at 50% drug loading exhibited some crystallisation after 1 week at 30°C / 60% relative humidity, but those produced at 25% drug loading were stable.

Example 4. Compound 1 formulations

4.1 Immediate Release Tablet

4.1.1 Composition

Table 7. Composition of an immediate release tablet

Ingredient	mg / tablet	% of core weight	Function
Compound 1	100.00	25.00	Drug substance
Lactose	238.00	59.50	Filler
Microcrystalline cellulose	40.00	10.00	Filler
Croscarmellose Na	16.00	4.00	Disintegrant
Sodium Lauryl Sulphate	2.00	0.50	Surfactant
Magnesium stearate	4.00	1.00	Lubricant
Core tablet weight	400.00		

4.1.2 Method of Preparation

Standard immediate release tablets were manufactured using a direct compression process. Crystalline compound 1 and the lactose, microcrystalline cellulose, Croscarmellose Na and Sodium Lauryl Sulphate were weighed into a glass vial to occupy approximately 75% of the volume of the vial and then mixed together in a tumble mixer for 30 minutes. The blended material was sieved through a 40 mesh (425μm) sieve, then tumble mixed for a further 15 minutes. The magnesium stearate was then added and the blend was shaken manually for about 20 seconds. The resultant mixture was then dispensed into 400mg portions and compressed into tablet cores, using a hand press equipped with 10mm tooling and with a target compression force of 0.5 tonnes.

4.2 Microsuspension

4.2.1 Method of Preparation

Approximately 1g of crystalline Compound 1 was weighed into a 10mL volumetric flask and 0.5% HPMC (hydroxypropyl methyl cellulose or Hypromellose, USP substitution type 2910 having nominal apparent viscosity 4000cP, such as DOW Methocel E4M or

equivalent) solution was added to volume. The mixture was stirred overnight then quantitatively diluted to 100mL with 0.5% HPMC solution to give a 10mg/mL microsuspension. The mean volume diameter of the Compound 1 was determined to be 4.54 μm by laser diffraction using a Sympatec particle size analyser (Sympatec GmbH).

4.3 Gelucire capsule

4.3.1 Formulation

Table 8. Quantitative composition of Compound 1 50 mg capsules

Constituent	Amount per capsule (mg)	Amount (% w/w)	Function	Standard
Capsule contents				
Compound 1	50.0	10.0	Active	AstraZeneca
Lauroyl macrogolglyceride (Lauroyl polyoxylglyceride)[a]	450.0	90.0	Excipient, pharmaceutical aid	PhEur (NF[c])
Capsule				
Hypromellose capsule shell[b]	Size 0	Each unit	Dosage form presentation	USP, Ph Eur
Titanium dioxide	1.84	Each unit	Opacifier	
Opacode black ink (S-1-7822/S-1-7823)	0.0332	Each unit		

[a] Supplied as Gelucire 44/14 grade.

[b] Supplied as Capsugel V Cap capsules

4.3.2 Method of Preparation

The lauroyl macrogolglyceride (lauroyl polyoxylglyceride) was melted at about 50 - 70°C then weighed into a stainless steel vessel. Crystalline Compound 1 was added and the contents mixed to achieve a homogeneous suspension. Mixing was continued while the mixture was dispensed into capsules to a fill weight of 500mg per capsule using a thermostatically-controlled automated capsule filling machine.

4.4 In vitro dissolution of Compound 1 preparations

4.4.1 Test Method

Dissolution was performed according to the general procedure of the United States Pharmacopeia Apparatus I (Basket). An amount of material containing approximately 100mg of Compound 1 was weighed accurately then transferred to a dissolution vessel containing 500mL of TRIS buffer (0.05M tris(hydroxymethyl)aminomethane solution adjusted to pH 7.2 with hydrochloric acid) maintained at 37°C and stirred at 100rpm. After 15, 30, 45 and 60 minures, 10mL samples were withdrawn and filtered through 0.2μm PVDF filters. Compound 1 concentration in the filtrate was determined by ultraviolet spectroscopy at a wavelength of 278nm.

4.4.2 Results

Table 9. In vitro dissolution of Compound 1 preparations

Sample	Dissolution (% Release)							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
Drug only	15	28	43	51	58	62	68	71
Tablet	72	81	85	87	89	90	91	92
Microsuspension	70	75	77	78	79	79	80	80
Gelucire capsule (10% drug loading)	37	92	97	99	99	100	100	100

See Figure 2.

4.5 Nanosuspension

4.5.1 Method of Preparation

Compound 1 was mixed with a few drops of vehicle (0.5% HPMC/0.1%Tween80) in a glass vial and "vortex" mixed for 1 minute, to wet and disperse the compound and to form a free flowing slurry. A further volume of vehicle was added to the slurry to produce a drug concentration of 50mg/ml and the resulting slurry was then "vortex" mixed for approximately 1 minute to mix. The slurry at 50mg/ml drug concentration was transferred to a zirconia milling pot. Zirconia milling beads (0.6-0.8mm diameter) were added to the pot until the level of beads and slurry was equal. The pot was then sealed with a Teflon ring and lid

(zirconia) and placed on a Fritsch P7 planetary mill. A second pot (as counter weight) was then placed on the mill. The pots were rotated on the mill at 800rpm for 4 x 30 minutes runs (with 10 minutes between each run). The pots were then allowed to cool for a further 15 minutes and a sample of the resulting bead milled suspension taken for analysis. The nanosuspension was then separated from the milling beads, and diluted to a concentration of 10mg/ml, ready for dosing. Nanosuspension particle size was measured using Fibre Optic Quasi Elastic Light Scattering (FOQUELS) from Brookhaven Instruments - laser wavelength of 635nm. A mean effective diameter of 692 +/- 8nm was measured. X-ray diffraction confirmed that the drug was essentially crystalline.

4.6 Solid Dispersion

4.6.1 Preparation by Solvent Evaporation Process

Solid dispersions having a 1:3 ratio by weight of Compound 1: polymer were prepared as follows:

0.75g of Compound 1, prepared according to Example 9 [compound 168] in WO 2004/080976, and 2.25g of polymer were weighed directly into a 250ml round bottom flask and dissolved in 75ml of methanol:dichloromethane (1:1). The solvent was removed on a rotary evaporator. The formulation was placed in a vacuum oven and dried under high vacuum at 40°C overnight.

The formulation was retrieved from the flask and dry milled if necessary using a pestle and mortar. The formulation was then stored in a vacuum desiccator until needed.

In order to produce formulations having ratios other than 1:3, weights and volumes in the process were adjusted pro-rata to those described above.

4.6.2 Preparation by Melt Extrusion Process

Compound 1 was blended with polymer and glidant in the proportions defined in the manufacturing formula. The blend was extruded in a twin-screw extruder. During extrusion, a vacuum was applied to the extruder barrel to degas the melt. The extrudate was calendered by passing through two contra-rotating calender rollers, and then cooled prior to milling.

4.6.3 Stability study

4.6.3.1 Protocol

Solid dispersions were prepared using the solvent evaporation process described previously (see 4.6.1), and amorphous Compound 1 was prepared according to Example 9 [compound 168] in WO 2004/080976. Samples were stored in closed HDPE bottles with polyethylene liners, with desiccant, for a period of 3 months under refrigeration (2-8°C), long-

term conditions (25°C / 60% relative humidity) and accelerated conditions (40°C / 75% relative humidity). In addition, samples were stored for a period of 1 month in an open petri dish at 40°C / 75% relative humidity. Samples were tested prior to set-down, after 1 month and, for the samples in closed containers under long-term and accelerated conditions only, after 3 months.

4.6.3.2 Methodology

Dissolution

Dissolution was carried out in accordance with the general procedure of the United States Pharmacopeia using Apparatus II (paddle method). An amount of the solid dispersion containing about 100mg of Compound 1 was weighed accurately then placed in 500mL pH6.5 phosphate buffer at a temperature of 37°C and a stirring speed of 75rpm. After 5, 10, 20 and 45 minutes a 2mL sample was removed and the Compound 1 content determined by HPLC.

Table 10. Chromatographic conditions for in vitro dissolution test

Apparatus	Liquid chromatograph with UV detector
Column	Waters Sunfire C18, 4.6mm x 50mm (3.5µm or equivalent)
Eluents	Eluent A: 0.1% TFA in water Eluent B: 0.1% TFA in acetonitrile
Gradient program	Time (min) %A %B 0 65 35 0.8 65 35 0.81 5 95 1.8 5 95 1.81 65 35 3.5 65 35
Flow rate	1mL / min approx.
Temperature	35°C
Wavelength	276nm
Injection volume	10µL
Run time	3.5 min.
Compound 1 retention time	1 min approx.

Determination of crystallinity by differential scanning calorimetry

The sample was heated in a differential scanning calorimeter (TA Instruments Q1000) using a programme designed to drive off any water and / or solvents present, before cooling the sample and heating at a constant rate over a temperature range encompassing the melting transition of any crystalline material which may be present (Compound 1 Tm = 210°C) (see Figure 3).

Table 11. Parameters for differential scanning calorimetry

General parameters	
Sample weight (mg)	2 – 10
Pan type	Aluminium, pierced
Atmosphere	Nitrogen, 20-30 mL/min
Temperature programme	
Equilibration (30 minutes)	30°C
Cool to	0°C
Heat at 5°C/min	120°C
Cool	0°C
Heat at 5°C/min	235°C
Cool	

4.6.3.3 Results

Table 12. Results for the stability study of Compound 1 polymeric dispersions

Formulation	Initial		2-8°C		25°C / 60%RH				40°C / 75% RH					
			Closed		Closed				Closed				Open	
			1 month		1 month		3 months		1 month		3 months		1 month	
	Diss	DSC	Diss	DSC	Diss	DSC	Diss	DSC	Diss	DSC	Diss	DSC	Diss	DSC
Kleptose 1:3	90	N/D	88	N/D	91	N/D	92	N/D	87	N/D	84	N/D	NT	N/D
PVP 1:3	92	N/D	91	N/D	91	N/D	94	N/D	90	N/D	66	X	NT	X
Amorphous Compound 1	NT	N/D	NT	X	NT	X	NT	X	NT	X	NT	X	NT	X
Kleptose 1:2	81	NT	82	N/D	82	N/D	X	N/D	76	N/D	66	N/D	81	N/D
PVP 1:2	81	N/D	81	N/D	77	N/D	86	N/D	85	N/D	55	N/D	NT	X
HPMCP 1:3	99	N/D	91	N/D	90	N/D	87	N/D	87	N/D	83	N/D	91	N/D
HPMCP 1:2	97	N/D	98	N/D	97	N/D	92	N/D	91	N/D	89	N/D	92	N/D

Key: N/D = not detected

N/T = not tested

Diss = Dissolution (cumulative release) at 45 minutes, % DSC = Crystallinity as determined by differential scanning calorimetry

The results of the stability study demonstrate that solid dispersions produced using the relatively hygroscopic polymer povidone tended to crystallise when stored at 40°C / 75% relative humidity, leading to a reduction in dissolution rate. Solid dispersions produced using 2-hydroxypropyl-β-cyclodextrin and hypromellose phthalate were stable under all tested conditions.

4.7. Copovidone Solid Dispersion (uncoated tablet formulation)

4.7.1 Formulation

Table 13. Composition of Compound 1 / copovidone solid dispersion uncoated tablet

Components	Quantity (mg)	Quantity (%)	Function	Standard
Compound 1	200.00	25.00	Active pharmaceutical ingredient	AstraZeneca
Copovidone	460.00	57.50	Polymeric carrier	NF and Ph Eur
Colloidal silicon dioxide	14.64	1.83	Glidant	NF and Ph Eur
Mannitol	117.36	14.67	Soluble filler	NF and Ph Eur
Sodium stearyl fumarate	8.00	1.00	Lubricant	NF and Ph Eur
Core tablet weight	800.00			

4.7.2 Method of Preparation

A solid dispersion of Compound 1 and copovidone was prepared using the melt extrusion process described in 4.6.2. The milled extrudate was mixed with the external excipients and compressed into tablet form using a single punch hand press to achieve hardness in the range 80-100 N.

4.7.3 Stability study –uncoated tablets

4.7.3.1 Protocol

Uncoated tablets prepared as described in 4.7.2 were stored in closed HDPE bottles with polyethylene liners, with desiccant, for a period of 4 months under long-term conditions

(25°C / 60% relative humidity) and accelerated conditions (40°C / 75% relative humidity). Samples were tested prior to set-down, then after 1, 3 and 4 months.

4.7.3.2 *In Vitro* evaluation

Crystallinity was determined by DSC as described in 4.6.3.2.

Dissolution Test

The dissolution method was adapted from that previously described for solid dispersion formulations (see 4.6.3.2). Dissolution was carried out in accordance with the general procedure of the United States Pharmacopeia using Apparatus II (paddle method). Individual dosage units were placed in 1000mL of pH6.5 phosphate buffer at a temperature of 37°C and a stirring speed of 75rpm. After 15, 30, 60, 90, 120 and 180 minutes a 1mL sample was removed and the Compound 1 content determined by HPLC:

Table 14. Chromatographic conditions for in vitro dissolution test for Compound 1 / copovidone solid dispersion tablet

Chromatographic conditions	
Apparatus	Liquid chromatograph with UV detector
Column	Waters Sunfire C18, 4.6mm x 50mm (3.5µm or equivalent)
Eluents	Eluent A: 0.1% TFA in water Eluent B: 0.1% TFA in acetonitrile
Gradient program	Time (min) %A %B 0 75 25 3.0 55 45 3.5 0 100 4.0 0 100 7.0 75 25
Flow rate	1mL / min approx.
Temperature	40°C
Wavelength	276nm
Injection volume	10µL
Run time	7 min.
Compound 1 retention time	2.9 min approx.

Compound 1 assay and impurities by HPLC

The Compound 1 and total impurities contents were determined using High Performance Liquid Chromatography (HPLC). A sample solution was prepared containing approximately 0.4 mg/mL Compound 1, using 50:50 v/v acetonitrile / water as diluent. The sample solution was filtered using a 0.2μm PVDF filter prior to analysis.

10μL sample was injected into a mobile phase comprising 0.05% trifluoroacetic acid (TFA) in water (Eluent A) / 0.05% TFA in acetonitrile (Eluent B), as defined by the gradient program in Table 15 below.

Table 15 Gradient programme - Compound 1 assay and impurities

Gradient programme	Time mins)	%A	%B
	0	90	10
	20	60	40
	28	5	95
	30	5	95
	30.1	90	10
	36	90	10

The mobile phase starts as defined at time zero, then the composition is modified by adjusting the proportion of eluents A and B gradually and linearly to the composition at each successive time-point.

Separation of impurities was performed using a column 15 cm long x 4.6 mm internal diameter packed with Waters Sunfire C18 stationary phase having 3.5 μm particle size. The mobile phase flow rate was 1.0mL/minute, temperature was controlled at 30°C, and impurity concentration was determined by comparison of absorbance at 276nm, measured using a variable wavelength uv detector, with that of an external Compound 1 reference standard.

Water content by coulometric Karl Fischer titration

Water content was determined by coulometric Karl Fischer titration using a Metrohm 684 Coulometer. Samples were ball milled prior to analysis and measurements were performed using a sample size of 200mg.

4.7.3.3 Results

Table 16. Results of the stability study for Compound 1 / copovidone solid dispersion tablet (200mg, uncoated))

		Initial		25°C / 60% Relative Humidity						40°C / 75% Relative Humidity					
				1 month		3 months		4 months		1 month		3 months		4 months	
Crystallinity by DSC		N/D		N/D		N/D		N/D		N/D		N/D		N/D	
Dissolution	(Time-point)	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2
	(15 min)	14	3	15	2	19	7	20	5	17	2	14	1	17	2
	(30 min)	32	5	33	3	41	15	45	10	38	2	33	3	37	4
	(60 min)	60	8	62	4	68	13	81	15	70	2	62	7	68	5
	(90 min)	77	5	82	8	85	6	96	7	88	3	80	7	85	2
	(120 min)	84	2	89	6	92	3	100	4	93	5	88	5	91	2
	(180 min)	87	1	91	4	93	1	NT		95	4	91	4	94	1
Water content (%w/w)		1.3		1.3		1.6		1.3		1.4		1.7		1.8	
Assay (%)		99.6		98.6		101.1		98.1		100.4		100.5		100.1	
Impurities (%)		0.44		0.44		0.44		0.43		0.44		0.44		0.44	

[1]X is the mean % release (n=3)
[2] S is the standard deviation (n=3)

4.8. Copovidone Solid Dispersion (film-coated tablet formulation)

4.8.1 Formulation

Table 17. Composition of Compound 1 / copovidone solid dispersion tablet

Components	**25mg tablet**	**100mg tablet**		**Function**
Tablet core	**Quantity (mg per tablet)**		**Quantity (% core weight)**	
Compound 1	25.00	100.00	25.00	Active pharmaceutical ingredient
Copovidone	57.50	230.00	57.50	Polymeric carrier
Colloidal silicon dioxide	1.83	7.33	1.83	Glidant
Mannitol	14.67	58.67	14.67	Soluble filler
Sodium stearyl fumarate	1.00	4.00	1.00	Lubricant
Core tablet weight	100.00	400.00		
Tablet Coating	**Quantity (mg per tablet)**		**Quantity (% coating weight)**	**Function**
Hypromellose (HPMC 2910)	2.19	8.75	62.5	Film former
Titanium dioxide (E171)	0.88	3.51	25.05	Opacifier
Macrogol / PEG 400	0.22	0.88	6.25	Plasticiser
Iron oxide yellow (E172)	0.16	0.64	4.55	Colouring agent

Components	**25mg tablet**	**100mg tablet**		**Function**
Tablet core	**Quantity (mg per tablet)**		**Quantity (% core weight)**	
Iron oxide black (E172)	0.06	0.23	1.65	Colouring agent
			% of core weight	
Nominal Coating Weight	3.50	14.00	3.50	

4.8.2 Method of Preparation

Compound 1 was blended with polymer and glidant in the proportions defined in the manufacturing formula. The blend was extruded in a twin-screw extruder. During extrusion, a vacuum was applied to the extruder barrel to degas the melt. The extrudate was calendered by passing through two contra-rotating calender rollers, and then cooled prior to milling. The extrudate was milled and subsequently mixed with the external excipients. The powder blend was compressed into tablet cores using a Rotary Press (Korsch XL 100 with 10 punch stations) to achieve a sufficient hardness (minimum 25 N).

The tablet cores were coated using a Driacoater Driam 600 coater with Opadry™ Green (Colorcon 03B21726, 130g/Kg aqueous solution). The total coating solution applied is equivalent to 35 g of Opadry™ per Kg of tablet cores.

4.8.3 Stability study –film-coated tablets

4.8.3.1 Protocol

Film-coated tablets prepared as described in 4.8.2 were stored in closed HDPE bottles with polyethylene liners, with desiccant, for a period of 4 months under long-term conditions (25°C / 60% relative humidity) and accelerated conditions (40°C / 75% relative humidity). Samples were tested prior to set-down, then after 1 month 3 and 4 months.

4.8.3.2 In Vitro evaluation

Water content, assay and impurities were determined using the methods described in Section 4.7.3.2.

Determination of crystallinity by hot-stage microscopy

Ground tablets were examined by optical microscopy under cross-polarising conditions whilst being heated steadily across the melting point range of the excipients and Compound 1 to detect the presence of drug crystals. Any particles seen to be birefringent between 180 °C and 190°C which subsequently melted at approximately 210°C were classified as Compound 1. See Figure 4 for an example of a drug crystal as seen under the microscope.

Dissolution Test

The dissolution method was adapted from that previously described for uncoated tablet formulations (see 4.7.3.2). Dissolution was carried out in accordance with the general procedure of the United States Pharmacopeia using Apparatus I (basket method). Individual dosage units were placed in 900 mL 0.3% SDS at a temperature of 37°C and a stirring speed of 100 rpm. After 15, 30, 45, 60 and 90 minutes a sample was removed and the Compound 1 content determined by HPLC:

Table 18. Chromatographic conditions for in vitro dissolution test for Compound 1 / copovidone solid dispersion tablet

Chromatographic conditions			
Apparatus	Liquid chromatograph with UV detector		
Column	Waters Symmetry C18, 4,6 mm x 75 mm x 3.5 µm		
Eluents	Eluent A: 0.1% TFA in water Eluent B: 0.1% TFA in acetonitrile		
Gradient program	Time (min)	%A	%B
	0	75	25
	3.0	55	45
	3.5	0	100
	7.0	75	25

Chromatographic conditions	
Flow rate	1 mL / min approx.
Temperature	40°C
Wavelength	276 nm
Injection volume	10 μL
Run time	7 min
Compound 1 retention time	2.9 min approx.

4.8.3.3 Results

Table 19. Results of the stability study for Compound 1 / copovidone film-coated solid dispersion tablet (25mg)

		Initial		25°C / 60% Relative Humidity						40°C / 75% Relative Humidity					
				4 weeks		13 weeks		26 weeks		4 weeks		13 weeks		26 weeks	
Crystallinity:															
Hot-Stage Microscopy		D (+)		N/D		D (++)		D (+++)		N/D		D (++)		D (+++)	
Wide-Angle X-Ray Scattering		N/D		N/T		N/D		N/D		N/T		N/D		N/D	
Dissolution	(Time-point)	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2
	(15 min)	41	3.6	38	3.2	41	3.8	41	2.9	39	2.8	41	2.1	39	3.5
	(30 min)	77	5.2	78	6.2	78	4.8	81	4.5	77	3.7	78	2.1	78	5.4
	(45 min)	98	3.9	99	3.5	99	3.4	102	2.3	98	3.9	98	1.4	101	2.4
	(60 min)	104	1.4	104	1.9	104	1.0	105	1.3	103	4.8	101	0.5	106	1.3
	(90 min)	104	1.1	104	1.4	104	1.0	105	1.5	103	4.5	101	0.4	106	1.0
Water content (%w/w)		2.3		2.1		2.2		2.0		1.9		2.1		2.2	
Assay (%)		104.0		104.3		103.5		102.5		102.0		104.1		106.0	
Impurities (%)		0.52		0.51		0.50		0.50		0.50		0.50		0.53	

Key: N/D = not detected

D = detected; (+) 1-5 birefringent spots (++) 5-30 birefringent spots (+++) more than 30 birefringent spots

N/T = not tested

[1]X is the mean % release (n=3)

[2] S is the standard deviation (n=3)

Table 20. Results of the stability study for Compound 1 / copovidone film-coated solid dispersion tablet (100mg)

		Initial		25°C / 60% Relative Humidity						40°C / 75% Relative Humidity					
				4 weeks		13 weeks		26 weeks		4 weeks		13 weeks		26 weeks	
Crystallinity:															
Hot-Stage Microscopy		D (+)		N/D		D (+++)		D (+++)		D (+)		D (+)		D (++)	
Wide-Angle X-Ray Scattering		N/D		N/T		N/D		N/D		N/T		N/D		N/D	
Dissolution	(Time-point)	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2	X^1	S^2
	(15 min)	24	0.5	24	1.0	25	1.9	26	1.1	25	1.8	25	1.2	24	1.2
	(30 min)	55	1.0	54	1.3	56	2.3	60	1.6	57	2.8	56	2.1	56	1.9
	(45 min)	80	1.6	80	1.6	81	1.9	87	1.5	83	3.1	81	2.1	83	2.1
	(60 min)	97	1.0	97	1.1	98	1.7	102	0.5	99	2.1	97	2.1	99	1.2
	(90 min)	101	0.8	101	0.5	102	0.8	104	0.8	102	1.0	101	0.8	102	0.5
Water content (%w/w)		2.0		1.7		2.5		1.6		1.8		2.2		1.5	
Assay (%)		102.5		100.5		102.8		102.2		103.6		100.8		102.1	
Impurities (%)		0.50		0.49		0.50		0.50		0.51		0.49		0.50	

Key: N/D = not detected

D = detected; (+) 1-5 birefringent spots (++) 5-30 birefringent spots (+++) more than 30 birefringent spots

N/T = not tested

[1]X is the mean % release (n=3)

[2]S is the standard deviation (n=3)

Example 5 Nanometer-scale characterisation studies

5.1 Solid state Nuclear Magnetic Resonance Study

Solid dispersions of Compound 1 and copovidone, prepared with drug loadings of 10, 25, 35 and 40% using the melt extrusion process described in 4.6.2, were evaluated by solid state nuclear magnetic resonance spectroscopy (SSNMR) using methodology disclosed in Asano, A; Takegoshi, K.; Hikichi, K. Polymer (1994), 35(26), 5630-6. ^{13}C cross-polarisation magic angle spinning SSNMR spectra were recorded at 100 MHz with a spin rate of 9 kHz using a Bruker Avance 400WB with a 4mm HFX MAS probe. For each sample, with different drug loading, a series of spectra were acquired with different contact times ranging from 500 μs to 10 ms. Peak areas from different spectral regions were measured. These areas were selected to contain peaks corresponding to Compound 1 or copovidone. With increasing contact time peak area increases to a maximum value and then decays due to a process known as proton spin diffusion. This decay is characterised by a constant $T_{1\rho}$, which represents proton spin-lattice relaxation in the rotating frame of reference. For a phase-separated system, on a length scale longer than the spin-diffusion length scale, the relaxation rates for this decay process are identical to those observed for the individual components. For a mixed system, a single value of $T_{1\rho}$ is observed as a weighted average of the individual components.

For the samples with Compound 1 loading between 10 & 40% each magnetization decay could be fitted to a single exponential function with very similar $T_{1\rho}$ values observed. This suggests a similar relaxation pathway for the drug and polymer and infers a single phase.

Table 21. Results of the Solid State NMR study

Compound 1 loading	$T_{1\rho}$ / ms	
	Peaks due to Compound 1 (119.5 – 140.0 ppm)	Peaks due to co-povidone (167.0 – 183.0 ppm)
40%	9.9	9.7
35%	10.2	9.4
25%	13.2	8.6
10%	15.5	9.4

5.2 Pair-wise Distribution Function Study

Solid dispersions of Compound 1 and copovidone, prepared with drug loadings of 10, 25, 35 and 40% using the melt extrusion process described in 4.6.2, were evaluated using X-ray powder diffraction and Pair-wise Distribution Functions (PDFs) were derived for each sample.

5.2.1 Data collection

X-ray powder diffraction data were collected on the Bruker D8 diffractometer, which has a Copper source generating X-rays with a wavelength of 1.5418Å (Göbel mirrors used to provide parallel beam optics remove the kβ leaving a beam with an average wavelength of kα1 and kα2) using a voltage of 40kV and a filament emission of 40mA. Samples were measured in reflection mode and the diffraction pattern collected using a scanning position-sensitive detector.

A diffractogram of the zero background wafer was obtained, under vacuum. 50 mg (+/- 5mg) of each sample was weighed out and dispersed onto a zero background holder, ensuring near complete coverage. The sample was added to the TTK chamber, which was then placed under vacuum to a pressure of <5x10-2 mbar. XRPD data were collected over approximately 20-30 minutes: data acquisition parameters of 4-80°2θ in steps of 0.007091° counting for 0.2s/step were used for each sample.

A peak in the patterns at 6.6°2θ is caused by the sample holder and was removed in each case through subtraction of a blank run (i.e. an empty sample holder) which is measured on the day of the experiment.

5.2.2 Computational Methods – Pair-wise Distribution Function

PDFs were calculated for each sample (S.J.L.Billinge and M.G.Kanatzidis, Chem. Commun., 2004, 749-760; S. Bates et.al., Pharmaceutical Research, 2006, 23(10) 2333-2349; S.Bates et.al., J. Pharmaceutical Sciences, 2007, 96(5), 1418-1433) The measured X-ray diffraction pattern (known as the scattering function) was transformed to a normalized scattering function S(Q) by carrying out a number of corrections to the data related to both the sample and experimental set-up. PDFs are then generated from the sine Fourier transformation of s(Q), equation 1.

$$G(r) = \frac{2}{\pi}\int_0^{\infty} Q[S(Q)-1]\sin(Qr)dQ \qquad \textit{Equation 1}$$

Q is the magnitude of the scattering vector and is derived from $Q=4\pi\sin(q) / \lambda$

The PDF is a plot of G(r) against interatomic distance and shows the probability of finding an atom at given distance 'r' from another atom. X-ray amorphous materials which are nanocrystalline possess long range ordering and thus the probability of finding an atom out at long distances is relatively high. In contrast, truly amorphous materials do not possess any long range ordering and the probability of finding an atom out at long distances is relatively low.

PDFs were generated from each of X-ray diffraction pattern measured using the software PDFgetX2 (X. Qui et.al., J. Appl. Cryst. 2004, 37, 678)

5.2.3 Results

As shown in Figure 5. there is little evidence of ordering beyond 15Å for solid dispersions of Compound 1 and copovidone for any of the drug loadings investigated. This confirms that these solid dispersions are amorphous and do not exhibit significant long-range order.

5.2.4 Linear combination of PDFs

5.2.4.1 Method

PDFs of the separate components of the formulation, amorphous Compound 1 and copovidone, were generated. These PDFs were then combined in the correct ratios (70% copovidone and 30% amorphous Compound 1) to give a simulated PDF trace for a physical mixture of the two. The traces obtained in 5.2.2. were compared to this simulated trace.

5.2.4.2 Results

As shown in Figure 6, a physical mixture of amorphous Compound 1 and copovidone would exhibit a characteristic pattern between 1 and 5Å, comprising dual minima for G(r) at approximately 2Å and approximately 3Å ; solid dispersions of Compound 1 and copovidone exhibit a single accentuated minimum at approximately 3Å. These data indicate that solid dispersions of Compound 1 and copovidone are true molecular dispersions.

5.3 Nano-thermal characterisation study

Solid dispersions of Compound 1 and copovidone, prepared with drug loadings of 10, 30 and 40% using the melt extrusion process described in 4.6.2, were evaluated using Atomic

Force Microscopy (Gan, Y. Surface Science Reports (2009), 64(3), 99-121; Fulghum, J. E.; McGuire, G. E.; Musselman, I. H.; Nemanich, R. J.; White, J. M.; Chopra, D. R.; Chourasia, A. R. Analytical Chemistry (1989), 61(12), 243R-69R) and using localised thermal analysis (Harding, L.; King, W. P.; Dai, X.; Craig, D. Q. M.; Reading, M. Pharmaceutical Research (2007), 24(11), 2048-2054.)

5.3.1 Methods

The work was carried out on a TA Instruments 2990 Micro-Thermal Analyzer based on a Veeco Explorer atomic force microscope. Preliminary imaging of the samples was carried out in Tapping Mode (TM-AFM) using Veeco 1660-00 high resonance frequency (HRF) silicon probes. Micro-thermal analysis (micro-TA) was carried out using Wollaston wire thermal probes. Nano-thermal analysis (nano-TA) was carried out using Anasys Instruments AN2-300 ThermaLever™ doped silicon probes controlled by an Anasys Instruments NanoTA1 AFM accessory. The Wollaston probe was temperature-calibrated using poly(ethylene) terephthalate (PET) film (melting temperature = 240 °C) and room temperature. A 3-point temperature calibration was `carried out for the ThermaLever probe using polycaprolactone (PCL, Tm = 55 °C), HDPE (Tm = 115 °C) and PET melting temperature standards. The calibration of each probe was checked before and after a sample was analysed. Unless stated otherwise, the heating rate used in all the localised thermal analysis runs was 20 °C/s.

All the samples were analysed in the as-received state - i.e. the unmodified surface of the moulded pellets.

5.3.2 Results

The samples at various drug loadings all exhibited surface features to a variable degree, but none showed any evidence of phase separation within the matrix, as illustrated in Figure 7 (10% drug loading), Figure 8 (30% drug loading) and Figure 9 (40% drug loading).

5.4 Crystallisation Study

The effect of water on the crystallinity of Compound 1 was investigated for the milled extrudate prepared using the melt extrusion process described in 4.6.2 and for the tablet composition shown in Table 13 and prepared as described in 4.7.2. The study was carried out using aqueous slurries both in the absence and presence of a proprietary coating composition,

Opadry™ Green (Colorcon 03B21726, 130g/Kg aqueous solution). Tablets were ground prior to the slurry experiments commencing.

5.4.1 Experimental conditions

The following materials were weighed into 25mL vials:

Table 22. Preparation of slurries for crystallisation study

	Weight (mg)		
Exp	Ground tablet	Milled extrudate	Opadry
1	83.0		199.2
2	-	67.7	208.2
3	91.0	-	-
4	-	68.0	-

20 mL of water heated to 50°C was added to each vial. The resulting slurries remained stirring at 50°C for 48 hours.

Analysis of the resultant slurry material by XRPD identified Form H as the primary crystal form of Compound 1. Compound 1 Form H has an X-ray diffraction pattern (λ=1.5418Å) containing specific peaks at:

Table 23. XRPD data for Compound 1 Form H

Peak	2θ° (± 0.1°)
1	6.5
2	6.9
3	8.4
4	12.8

Compound 1 Form H may also have the following additional peaks an X-ray diffraction pattern (λ=1.5418Å):

Table 24. Additional XRPD data for Compound 1 Form H

Peak	2θ° (± 0.1°)
5	15.1

Peak	2θ° (± 0.1°)
6	16.5
7	16.8
8	19.9
9	20.3

Compound 1 Form H may also be characterised by any combination of three or more peaks selected from the first list of 4 peaks above.

A representative powder XRPD pattern of compound 1 Form H is shown in Figure 10.

Compound 1 Form H gives a weight loss via TGA that is consistent with a monohydrate with some additional physisorbed water. In the example given the total amount of water present is 4.7% by weight; the theoretical weight loss for a monohydrate of compound 1 is 4.0%w/w.

Compound 1 Form H may also be characterised using DSC. Compound 1 Form H when heated from 0°C to 300°C at 10°C per minute displays a broad dehydration endotherm up to 115°C, followed by phase transitions between 125 - 175°C. A sharp endotherm is observed with an onset at 208.0°C ±1°C, this being consistent with Form A. A representative DSC trace for compound 1 as Form H is shown in Figure 11.

In the absence of Opadry™ the resulting material gave strong XRPD reflections consistent with Form H, whereas in the presence of Opadry™ the intensity of the Form H XRPD diffraction pattern was considerably reduced. This is not the result of interference, as the XRPD diffraction pattern of Opadry™ shown in Figure 12 indicates there are no significant peaks present below 25 °2θ. Therefore, the very low intensity of the reflections observed indicates the presence of only small quantities of Form H. This may suggest that Opadry™ may exert a stabilising effect upon amorphous solid dispersions of Compound 1. This grade of Opadry™ was selected for use in the preparation of the film-coated tablet formulation described in 4.8.

5.5 Two-dimensional Correlation Spectroscopy Study

5.5.1 Introduction

Two-dimensional correlation spectroscopy (2D-COS) is a method in which an external perturbation is applied to a system and monitored by some spectrometric device. Spectral intensity is plotted as a function of spectral variables (e.g. wavelength, frequency or

wavenumber). Two orthogonal axes of spectral variables define the 2D spectral plane, and the spectral intensity may be plotted along a third axis (Noda, I., Dowrey, A. E., Marcott, C., Story, G. M., Ozaki, Y. Appl. Spectrosc. 54 (7) 2000 pp 236A-248A; Noda, I. Appl. Spectosc. 44 (4) 1990 pp 550-561).

In a synchronous 2D correlation spectrum, intensity is representative of the simultaneous or coincidental changes of spectral intensity variations measured across the range of perturbation. A synchronous spectrum is symmetrical with regard to the diagonal corresponding to equal values for the chosen spectral variable; correlation peaks appear at both diagonal and off-diagonal positions. The diagonal peaks, referred to as autopeaks, represent the intensity variation for specific values of the chosen spectral variable across the range of perturbation, whereas the off-diagonal peaks, referred to as cross peaks, represent simultaneous or coincidental changes of spectral intensities observed at two different values of the chosen spectral variable. Such synchronised changes may indicate a coupling or interaction.

In contrast, in the asynchronous spectrum, intensity represents sequential or successive changes. The asynchronous spectrum is anti-symmetrical with respect to the diagonal and has no autopeaks, consisting exclusively of cross peaks which develop only if the two spectral features change out of phase. This feature may be used to differentiate overlapped bands arising from spectral signals of different origins, such as different components acting independently in a complex mixture.

For both synchronous and asynchronous correlation spectra, sensitivity may be improved, at the expense of an increase in noise, by subtraction of the average spectrum from each individual spectrum in the perturbation data set

Thus 2D-COS may be used to establish the nature and extent of any correlations in the spectral variations which arise in response to the perturbation and which may be indicative of intra- or inter-molecular interactions within the sample matrix. In the context of a pharmaceutical solid dispersion, a high level of interaction between the drug and the matrix polymer will tend to promote the formation of a stable and homogeneous dispersion whereas

the absence of such interaction, or the existence of competitive intramolecular coupling, will have a contrary effect.

5.5.2 Method

The effect of a change in concentration of Compound 1 and various polymers in solid dispersions prepared by the solvent evaporation process described in 4.6.1 was studied using infrared spectroscopy. The spectra were collected on a Thermo Nicolet Magna 550 series II spectrometer. 2D-COS spectra were collected for solid dispersion compositions of Compound 1 and matrix polymers as shown in Table 25.

Table 25 List of polymers with percent of mixtures

Composition		Matrix polymer				
API %	Polymer %	Hypromellose acetate succinate (Aqoat MG)	Copovidone (Kollidon VA64)	Hypromellose phthalate (HP55S)	Hypromellose (Pharmacoat 606)	Povidone (Kollidon 25)
10	90	T	T	T	T	T
20	80	T	T	T	T	T
23	77	T	T	T	T	T
25	75	T	T	T	T	T
26	74	T	T	T	T	T
28	72	T	T	N/T	T	T
30	70	T	T	N/T	T	T

T = tested
N/T = not tested

Each spectrum was normalised to the most intense band using proprietary software (Omnic 8.0). The spectra were then converted into a comma separated value (CSV) file, transferred to MS Excel™ and formatted for Matlab® (The MathWorks™) wherein 2D synchronous and asynchronous spectra were generated.

5.5.3 Results

Hypromellose acetate succinate (Aqoat MG)

In the spectrum of Compound 1, the most intense band is located at 1630cm^{-1} (Figure 13). In the Aqoat MG spectrum the most intense band is located at 1050cm^{-1} (Figure 14). In the synchronous spectrum (Figure 15) cross peaks are evident at 1050 cm^{-1},1650 cm^{-1} and

1050 cm^{-1}, 2700cm^{-1}; however the asynchronous spectrum (Figure 16) indicates that these interactions are intramolecular (polymer / polymer) in nature.

Hypromellose phthalate (HP55S)

The Infrared spectrum for HP55S exhibits a strong spectral feature at just above 1000cm^{-1}, as shown in Figure 14. The synchronous (Figure 17) and asynchronous (Figures 18 and 19) correlation spectra indicate weak mixed intra- and inter-molecular interactions in the range 1600 to 1800cm^{-1}.

Hypromellose (Pharmacoat 606)

As for HP55S, the infrared spectrum for Pharmacoat exhibits a strong spectral feature at just above 1000cm-1, (Figure 14). The synchronous (Figure 20) and asynchronous (Figures 21 and 22) correlation spectra indicate weak mixed intra- and inter-molecular interactions in the range 1600 to 1800cm^{-1}. The intensity of intermolecular (drug-polymer) interaction for Pharmacoat is somewhat greater than for HP55S.

Povidone (Kollidon 25)

The primary band in the infrared spectrum of povidone (Figure 14) is at 1600 cm^{-1} and overlaps with the primary band in the infrared spectrum of Compound 1 (Figure 13). The synchronous (Figures 23 and 24) and asynchronous (Figure 25) correlation spectra indicate hydrogen bonding interactions.

Copovidone (Kollidon VA64)

Copovidone has many of the same infrared (Figure 2) and 2D spectral features (Figures 26-29) as Povidone but also exhibits additional factors suggesting a greater strength of hydrogen bonding.

5.5.4 Conclusions

The degree of intermolecular interaction observed in solid dispersions of Compound 1 is highly dependent upon the nature of the matrix polymer. The overall ranking of the intermolecular interactions is shown in Table 26.

Table 26 Molecular Interaction Ranking

Polymer	Interaction	Strength	Rank
Aqoat MG	Dipole-dipole	Very Weak	5
HP55S	Dipole-dipole	Weak	4
Pharmacoat	Dipole-dipole	Medium to Weak	3
Povidone	Hydrogen bonding	Strong	2
Copovidone	Hydrogen bonding	Very Strong	1

These results suggest that solid dispersions of Compound 1 and copovidone may be particularly stable and homogeneous.

Example 6. Comparative bioavailability study

6.1 Protocol

One hundred milligrams of the drug in several different presentations were orally administered to fasted beagle dogs (n=6). The formulations dosed were the IR tablet (see 4.1), microsuspension (see 4.2) and nanosuspension (see 4.5) formulations, capsules containing various drug loadings in Gelucire® 44/14 (see 4.3), capsules containing solid dispersions produced by solvent evaporation (see 4.6.1), and melt extrusion (see 4.6.2) processes, and a tablet prepared from a melt-extruded solid dispersion (see 4.7). The dosing of the tablets and capsules was followed with 20 ml of water whereas 10 mL of the suspension formulations was dosed by gavage and followed by 10 mL of water to wash the gavage tube.

Blood samples were taken post-dose at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 12, 24 and 30 hours. The samples were centrifuged at 3000rpm for 15 minutes, the plasma removed into plain blood tubes and stored at -20°C until analysis. Samples were analysed using a manual solid phase extraction (Phenomenex Strata X, 30mg) method followed by LC-MS using the conditions specified in Table 27 below

Table 27. Summary of LC-MS conditions for the determination of Compound 1 in dog plasma

Chromatographic conditions	
Apparatus	Liquid chromatograph with MS/MS detector
Column	Waters Xterra Phenyl, 2.1mm x 50mm (3.5µm) or equivalent
Eluents	Ammonium formate (1mM, pH 3.0) / Acetonitrile 73:27 v/v)
Flow rate	0.2mL / min approx.
Temperature	40°C
Wavelength	276nm
Injection volume	5µL
Run time	4 min.
Compound 1 retention time	2.7 min approx.
Mass spectrometer parameters	
Mode of operation	Ion Spray (positive ion) (MS/MS)
Voltage	4500V approx.
Temperature	450°C approx.
Ions monitored	435.3 to 281.2

6.2 Results

Table 28. Summary of pharmacokinetic data for Compound 1 formulations

Formulation	$AUC_{(0\text{-inf})}$ ($ng.hr.mL^{-1}$)	C_pmax ($ng.mL^{-1}$)	Bioavailability relative to copovidone solid dispersion capsule (%)
Immediate Release tablet (25% drug loading)	7748	1225	19
Gelucire 44/14 (capsules, 10% drug	15649	2551	38

Formulation	$AUC_{(0\text{-inf})}$ ($ng.hr.mL^{-1}$)	C_pmax ($ng.mL^{-1}$)	Bioavailability relative to copovidone solid dispersion capsule (%)
loading)			
Gelucire 44/14 (capsules, 20% drug loading)	10078	1654	25
Gelucire 44/14 (capsules, 40% drug loading)	7579	1174	18
Microsuspension (1% drug loading)	9327	1249	23
Nanosuspension (1% drug loading)	22746	3922	55
Kleptose solid dispersion[1] (capsule; 20% drug loading, 1 : 3 drug : polymer ratio)	40373	7959	98
PVP Solid dispersion[1] (capsule; 20% drug loading, 1 : 3 drug : polymer ratio)	35788	6810	87
AQOAT solid dispersion[1] (capsule; 20% drug loading, 1 : 3 drug : polymer ratio)	35450	6840	86
HPMC-606 solid dispersion[1] (capsule; 20% drug loading, 1 : 3 drug : polymer ratio)	31739	6179	77
HP55S solid dispersion[1] (capsule; 25% drug loading, 1 : 2 drug : polymer ratio)	34687	6749	84
Copovidone solid dispersion[2] (capsule; 20% drug loading; 20:46 drug : polymer ratio)	41129	7707	100
Copovidone solid dispersion (tablet; 25% drug loading; 30:70 drug : polymer ratio)	37745	7502	92

[1] Blended with crospovidone disintegrant (100mg / capsule) prior to filling

[2] Blended with mannitol / Aerosil (99:1) (167 mg / capsule) prior to filling

See Figure 30. Both $C_p$max and AUC from the polymer-based solid dispersions were significantly greater (*P<0.05)* than the immediate release tablet, Gelucire capsule and microsuspension / nanosuspension formulations.

5

CLAIMS

1. A pharmaceutical formulation comprising and active agent in solid dispersion with a matrix polymer, wherein the active agent is 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a salt or solvate thereof, and the matrix polymer exhibits low hygroscopicity and high softening temperature.

2. The formulation as claimed in claim 1, wherein the active agent is in stable amorphous form.

3. The formulation as claimed in claim 2, wherein at least 90% of the active agent is in amorphous form.

4. The formulation as claimed in any one of claims 1 to 3, wherein the matrix polymer is selected from: copovidone, hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), 2-hydroxypropyl -β-cyclodextrin (HPBCD), hydroxypropyl methylcellulose (Hypromellose, HPMC), polymethacrylates, hydroxypropyl cellulose (HPC), and cellulose acetate phthalate (CAP).

5. The formulation as claimed in any one of claims 1 to 3, wherein the matrix polymer is copovidone.

6. The formulation as claimed in claim 5, wherein the copovidone is a co-polymer of 1-vinyl-2-pyrollidone and vinyl acetate in a ratio of 6:4 by mass.

7. The formulation as claimed in any one of claims 1 to 6, wherein the ratio of active agent:matrix polymer by weight is from 1:0.25 to 1:10.

8. The formulation as claimed in claim 7, wherein the ratio of active agent:matrix polymer by weight is 1:≥2 to 1:10.

9. The formulation as claimed in any of the preceding claims wherein the amount of active agent per unit dose is at least 20%.

10. The formulation as claimed in any of any preceding claim, wherein the solid dispersion includes a surface-active agent and/or plasticiser.

11. The formulation as claimed in claim 10, wherein the surface-active agent is selected from: sodium dodecyl sulphate (sodium lauryl sulphate); docusate sodium; cetrimide; benzethonium chloride; cetylpyridinium chloride; lauric acid; polyoxyethylene alkyl ethers; polyoxyethylene sorbitan fatty acid esters, e.g. polysorbates 20, 40, 60 and 80; polyoxyethylene castor oil derivatives, e.g. Cremophor RH40™; polyoxyethylene stearates and poloxamers.

12. The formulation as claimed in any of the preceding claims, which is for mucosal administration.

13. The formulation as claimed in any of the preceding claims, wherein the solid dispersion is made by solvent evaporation or melt extrusion.

14. The formulation as claimed in claim 12, wherein the solid dispersion is made by melt extrusion.

15. Use of a matrix polymer that exhibits low hygroscopicity and high softening temperature in solid dispersion with 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament.

16. The use as claimed in claim 14, wherein the medicament is for treating cancer.

17. The use as claimed in claim 14 or 15, wherein the medicament comprises 10 to 1500mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof.

18. A method for increasing the bioavailability of the drug 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a patient in need of said drug, comprising administering to said patient a formulation comprising 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature.

19. A daily pharmaceutical dose of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4 fluoro-benzyl]-2H-phthalazin-1-one for treating cancer in the patient, wherein the dose comprises 10 to 1000mg of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one in a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature.

20. The pharmaceutical dose according to claim 19, wherein the matrix polymer is copovidone.

21. A method of producing a solid amorphous dispersion of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one comprising:

(i) mixing a suitable amount of 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a pharmaceutically acceptable salt or solvate thereof with a desired amount of at least one matrix polymer, wherein the matrix polymer exhibits low hygroscopicity and high softening temperature;

(ii) increasing the temperature of the mixture to produce a melt; and

(iii) extruding the melt to produce a solid product.

22. The method as claimed in claim 21, wherein in step (iii) the melt is extruded into one or more moulds.