3-CYANOQUINOLINE TABLET FORMULATIONS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to formulations of certain cyanoquinoline compounds. In particular, the invention is directed to stable tablets of a 3-cyanoquinoline compound, 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, and further comprising the super-disintegrant croscarmellose sodium, a surfactant polyethylene oxide sorbitan monooleate (polysorbate/Polyoxyethylene sorbitan monooleate (Tween-80™), or both

BACKGROUND OF THE INVENTION

Certain 3-cyanoquinoline compounds and pharmaceutically-acceptable salts thereof, are protein kinase inhibitors and possess anti-tumor activity and are therefore useful for treating certain disease states, such as cancer, that result, at least in part, from deregulation of this receptor. Receptor tyrosine kinases are important in the transmission of biochemical signals, which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor receptor (EGFR) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, *Advances in Cancer Research*, 1993, 60, 43-73) based on families of growth factors, which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGFR family of receptor tyrosine kinases such as the EGFR, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to a class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumor cell motility, dissemination and invasiveness and subsequently metastatic tumor growth (Ulkich et

al., *Cell*, 1990, 61, 203-212, Bolen et al., *FASEB J.*, 1992, 6, 3403-3409, Brickell et al., *Critical Reviews in Oncogenesis*, 1992, 3, 401-406, Bohlen et al., *Oncogene*, 1993, 8 2025-2031, Courtneidge et al., *Semin. Cancer Biol.*, 1994, 5, 239-246, Lauffenburger et al., *Cell*, 1996, 84, 359-369, Hanks et al., *BioEssays*, 1996, 19, 137-145, Parsons et al., *Current Opinion in Cell Biology*, 1997, 9, 187-192, Brown et al., *Biochimica et Biophysica Acta*, 1996, 1287, 121-149 and Schlaepfer et al., *Progress in Biophysics and Molecular Biology*, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src-family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

The 3-cyanoquinoline compound 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, also referred to as SKI-606, or bosutinib, is a weak base with an intrinsic solubility of approximately 0.06 μg/mL at pH 8.0. Below pH 8, the solubility of the compound SKI-606 increases exponentially with decreasing pH due to ionization. However, degradation of SKI-606 was observed at low pH aqueous solution (pH 3 and below) through hydrolysis, although the compound is relatively stable at pH higher than 5.

Some problems with existing solid formulations of 3-cyanoquinolines include variable dissolution, which appears to depend on the active pharmaceutical ingredient's (API) particle size. Contrary to the norm, the smaller API (D_{90}~20 microns) in the PIII formulation appeared to retard dissolution, under similar processing conditions used for the larger API (D_{90}~40 microns), as a result failing dissolution specification. This was observed more so with larger tablets (higher strength).

In addition, accelerated dissolution characteristic of formulations after aging/storage was also observed at early timepoints (small yet significant shifts on in dissolution on aging at both room temperature and under accelerated conditions). Results are presented in two dissolution methods: the 0.1 N HCl method and the CTAB/pH 5 acetate method, further discussed below The latter method was selected to better show a dissolution profile at timepoints up to 30 minutes, as the 0.1 N HCl method was found to release all drug within the first 10-20 minutes.

It would therefore be desirable to provide a stable, solid formulations of 3-cyanoquinoline compounds, such as 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, which is resistant to API particle size variation, and which is more stable during aging and storage, for use in patients.

SUMMARY OF THE INVENTION

Two innovative techniques disclosed herein: Changing the disintegrant type (and disintegrant ratio) to improve dissolution and stability properties; and replacing poloxamer with liquid surfactants like polyethylene oxide sorbitan monooleate (polysorbate/Polyoxyethylene sorbitan monooleate (Tween-80)), also to improve dissolution and stability properties.

In a first embodiment, the present invention provides pharmaceutically acceptable solid compositions of 3-cyanoquinolines comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile. In certain embodiments, such solid compositions are provided as a tablet. In some embodiments, the present invention provides a unit dosage form comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The present invention provides a pharmaceutically acceptable composition comprising: (a) 20-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; and (b) 0.1-20 weight percent of one or more wetting agents, as intragranular components, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: (a) 25-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; and (b) 0.1-20 weight percent of one or more wetting agents, as an intragranular component, based on the weight of the composition, wherein the intragranular components of the composition further comprise 82.5 weight percent of the composition and the extragranular components comprise 17.5 weight percent of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) 25-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.1-5.0 weight percent of one or more binders; (c) 1–25 weight percent of one or more fillers; (d) 0.1-5 weight percent of one or more disintegrants, (e) 0.1-5 weight percent of one or more wetting agents, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of one or more fillers; and (g) 0.1-5 weight percent of one or more lubricants, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) 25-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of povidone; (c) 1–25 weight percent of microcrystalline cellulose; (d) 0.2-5 weight percent of croscarmellose sodium, (e) 0.5-5 weight percent of poloxamer, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of microcrystalline cellulose; and (g) 0.5-5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) about 2 weight percent of povidone; (c) about 6.5 weight percent of microcrystalline cellulose; (d) about 2 weight percent of croscarmellose sodium; (e) about 3 weight percent of poloxamer, based on the weight of the composition; and extragranular components (f) about 15 weight percent of microcrystalline cellulose; and (g) about 0.5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a fast dissolving pharmaceutically acceptable composition comprising: intragranular components (a) 25-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of one or more binders; (c)

1–25 weight percent of one or more fillers; (d) 0.5-5 weight percent of one or more disintegrants; (e) 0.2-5 weight percent of one or more wetting agents, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of one or more fillers; (g) 0.5-5 weight percent of one or more disintegrants; and (h) 0.5-5 weight percent of one or more lubricants, based on the weight of the composition.

The present invention provides a fast dissolving pharmaceutically acceptable composition comprising: intragranular components (a) 50-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of povidone; (c) 1–25 weight percent of microcrystalline cellulose; (d) 0.5-5 weight percent of croscarmellose sodium, (e) 0.2-5 weight percent of poloxamer, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of microcrystalline cellulose; (g) 0.5-5 weight percent of croscarmellose sodium; and (h) 0.5-5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) about 2 weight percent of povidone; (c) about 6.5 weight percent of microcrystalline cellulose; (d) about 2 weight percent of croscarmellose sodium; (e) about 3 weight percent of poloxamer, based on the weight of the composition; and extragranular components (f) about 15 weight percent of microcrystalline cellulose; (g) about 2 weight percent of croscarmellose sodium; and (h) about 0.5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) 25-80, or 30-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) povidone; (c) microcrystalline cellulose; (d) 0.2-5 weight percent of croscarmellose sodium, (e) poloxamer, based on the weight of the composition; and extragranular components (f) microcrystalline cellulose; and (g) magnesium stearate.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) povidone; (c) microcrystalline cellulose; (d) about 2 weight percent of croscarmellose sodium; (e) poloxamer, based on the weight of the composition; and extragranular components (f) microcrystalline cellulose; and (g) magnesium stearate.

The present invention provides a fast dissolving pharmaceutically acceptable composition comprising: intragranular components (a) 50-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) povidone; (c) microcrystalline cellulose; (d) 0.5-5 weight percent of croscarmellose sodium, (e) poloxamer, based on the weight of the composition; and extragranular components (f) microcrystalline cellulose; (g) 0.5-5 weight percent of croscarmellose sodium; and (h) magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) povidone; (c) microcrystalline cellulose; (d) about 2 weight percent of croscarmellose sodium; (e) poloxamer, based on the weight of the composition; and extragranular components (f) microcrystalline cellulose; (g) about 2 weight percent of croscarmellose sodium; and (h) magnesium stearate, based on the weight of the composition.

The present invention further provides a pharmaceutically acceptable compositions, for instance compositions suitable for pediatric use, comprising as low as about 25 weight percent, 20 weight percent, or even 15 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, and about 0.25-5 weight percent, 0.5-5 weight percent, 1-3 weight percent, 3 weight percent, 2 weight percent or 1 weight percent croscarmellose sodium as intragranular components, and about .25-5 weight percent, 0.5-5 weight percent, 1-3 weight percent, 3 weight percent, 2 weight percent or 1 weight percent croscarmellose sodium as an extragranular component, with additional intra- and extra-

granular components such as those described above comprising the remaining portions of the composition.

The present invention further provides a pharmaceutically acceptable compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, and about 0.25-5 weight percent, 0.5-5 weight percent, 1-3 weight percent, 3 weight percent, 2 weight percent or 1 weight percent croscarmellose sodium as intragranular components, and about .25-5 weight percent, 0.5-5 weight percent, 1-3 weight percent, 3 weight percent, 2 weight percent or 1 weight percent croscarmellose sodium as an extragranular component, with additional intra- and extra-granular components such as those described above comprising the remaining portions of the composition.

A further embodiment of the invention includes tablets or tablet cores formed by compressing the above granules, wherein said cores are optionally coated by conventional means, for instance with an up to 4 % polymer film coating, said polymer comprised of conventional coating polymers. An exemplary polymer coating is applied using polyvinyl alcohol and PEG 3350 (Opadry red II and Yellow II)

The present invention also provides a fast dissolving pharmaceutically acceptable solid compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The present invention also provides methods of preparing stable, pharmaceutically acceptable solid compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The present invention also provides methods for treating cancer comprising administering to a subject an effective amount of a pharmaceutically acceptable solid compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The inventive solid compositions of SKI-606 are useful, among other things, for administering to human or animal subjects, including but not limited to pediatric, juvenile, adult and geriatric subjects.

In a second embodiment, the present invention provides a pharmaceutically acceptable composition comprising: (a) 25-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; and (b) 0.1-20 weight percent of one or more wetting agents, as intragranular and or extragranular components, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) 25-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of one or more binders; (c) 1–25 weight percent of one or more fillers; (d) 0.5-5 weight percent of one or more disintegrants, (e) 0.2-5 weight percent of one or more wetting agents, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of one or more fillers; (g) 0.5-5.0 weight percent of one or more wetting agents; and (h) 0.5-5 weight percent of one or more lubricants, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) 50-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of povidone; (c) 1–25 weight percent of microcrystalline cellulose; (d) 0.5-5 weight percent of crospovidone; (e) 0.5-5 weight percent of Polyoxyethylene sorbitan monooleate (Tween-80)™, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of microcrystalline cellulose; (g) 0.5-5 weight percent of crospovidone; and (h) 0.1-5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) about 2 weight percent of povidone; (c) about 19.5 weight percent of

microcrystalline cellulose; (d) about 3 weight percent of crospovidone, (e) about 1 weight percent of Polyoxyethylene sorbitan monooleate (Tween-80)™, based on the weight of the composition; and extragranular components (f) about 4 weight percent of microcrystalline cellulose; (g) about 1 weight percent of crospovidone and (h) about 0.5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) about 2 weight percent of povidone; (c) about 19.5 weight percent of microcrystalline cellulose; (d) about 3 weight percent of crospovidone, (e) about 1 weight percent of Polyoxyethylene sorbitan monooleate (Tween-80)™, based on the weight of the composition; and extragranular components (f) about 4 weight percent of microcrystalline cellulose; (g) about 1 weight percent of crospovidone and (h) about 0.5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention provides a pharmaceutically acceptable composition comprising: intragranular components (a) about 69 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) about 2 weight percent of povidone; (c) about 19.5 weight percent of microcrystalline cellulose; (d) about 1 weight percent of crospovidone, (e) about 1 weight percent of Polyoxyethylene sorbitan monooleate (Tween-80)™, based on the weight of the composition; and extragranular components (f) about 4 weight percent of microcrystalline cellulose; (g) about 3 weight percent of crospovidone and (h) about 0.5 weight percent of magnesium stearate, based on the weight of the composition.

The present invention also provides methods of preparing stable, pharmaceutically acceptable solid compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The present invention also provides methods for treating cancer comprising administering to a subject an effective amount of a pharmaceutically acceptable solid

compositions comprising 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

The inventive solid compositions of SKI-606 are useful, among other things, for administering to human or animal subjects, including but not limited to pediatric, juvenile, adult and geriatric subjects.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 summarizes tablet dissolution rates for SKI-606 formulations comparing different disintegrating agents (croscarmellose sodium versus crospovidone).

Figure 2 summarizes dissolution on accelerated stability for a SKI-606 formulation including crospovidone. There appears to be a significant shift in tablet dissolution especially at early timepoints.

Figure 3 summarizes dissolution on accelerated stability for a SKI-606 formulation including croscarmellose sodium. No shift (compared to Figure 2) is observed in this case.

Figure 4 summarizes effects of varying Intra and Extragranular (IG and EG) Croscarmellose sodium concentrations in a SKI-606 formulation on tablet dissolution rates.

Figure 5 summarizes effects of varying Intra and Extragranular (IG and EG) Crospovidone concentration in a SKI-606 formulation on tablet dissolution rates. A wider dissolution is observed here showing strong concentration dependency of dissolution on ratios of Crospovidone. The formulation containing API of D90 appears to be markedly different in dissolution from the rest containing API of D90= 40 or 60 microns.

Figure 6 summarizes effects of active pharmaceutical ingredient (API) particle size on Dissolution for Crospovidone containing SKI-606 Formulation containing 2% binder, and 2% intragranular and extragranular disintegrant.

Figure 7A and B summarizes the lack of effect of API particle size in both CTAB/acetate and 0.1 N HCl medias for the croscarmellose sodium based SKI-606 formulations. The CTAB/acetate media was considered a more discriminating media than the 0.1 N HCl. Compare this to Figure 9A and B that clearly show the disparate effect of API particle size on tablet dissolution in a Crospovidone based tablet formulation.

Figure 8 summarizes the lack of dissolution dependency of croscarmellose based SKI-606 formulations (Runs A, B and C) on tablet hardness within a range of 120-190 N thus attesting to the dissolution robustness of the formulation. Hardness of a tablet may routinely need to be modified in a manufacturing setting and this formulation clearly offers that ability to do so.

Figure 9A and B summarizes effect of API particle size on tablet (100 and 500 mg strengths) dissolution for Crospovidone based formulations in 0.1 N HCl. Compare and contrast this to Figure 7A and B that do not show this dependency.

Figure 10 summarizes upward shift in tablet dissolution a 500 mg Crospovidone based SKI-606 formulation on open dish accelerated stability upto 2 weeks. Dissolution data is shown for 2 formulations with varying binder percentages and disintegrant ratios. Significant dissolution differences are observed early on during tablet dissolution for both batches, indicating a lack of dissolution reproducibility on accelerated stability. Compare and contrast this to croscarmellose sodium based formulation in Figure 11 that does not show any differences on stability

Figure 11 summarizes the lack of any dissolution shift of croscarmellose sodium (CCS) based formulation on stability under similar conditions as the Crospovidone (CPV) batches in Figure 10

Figure 12 Shows additional dissolution shift data for Crospovidone (CPV) SKI-606 formulation in 0.1 N HCl under accelerated aging conditions for 500 and 100 mg strength tablets. A consistent upward trend is observed for both the strengths in 0.1 N HCl.

Figure 13 summarizes comparative dissolution profiles for SKI-606 formulations with varying concentrations of a wetting agent (poloxamer). It is observed that poloxamer has the unexpected effect of decreasing tablet dissolution in a concentration dependent manner.

Figure 14 summarizes effects of wetting agent on granule dissolution in SKI-606 formulations. This effect shows that increases in poloxamer concentration resulted in increase in granule dissolution.

Figure 15 summarizes effects of accelerated aging uto 6 weeks open dish conditions at both 40 deg C and 40 deg C/75% RH for the SKI-606 formulations containing Polyoxyethylene sorbitan monooleate (Tween-80) as a wetting agent (API D_{90} = 38 microns).It is observed that there appears to be negligible shift even under the rigorous stability conditions in an open dish.

Figure 16 summarizes effects of accelerated aging uto 6 weeks open dish conditions at both 40 deg C and 40 deg C/75% RH for the SKI-606 formulations containing Polyoxyethylene sorbitan monooleate (Tween-80) as a wetting agent (API D_{90} = 18 microns).It is observed that there appears to be negligible shift even under the rigorous stability conditions in an open dish.

Figure 17 summarizes the lack of effect of API particle size on tablet dissolution in an SKI-606 formulation containing Polyoxyethylene sorbitan monooleate (Tween-80).

Figure 18 summarizes dissolution on accelerated stability in bottles with desiccant for the 500 mg strength croscarmellose based formulation (2% binder and 2% intra and extragranular CCS) 500 mg coated in Bottles with Desiccant. There is no shift in dissolution observed at 6M at 40Deg C/75% RH.

Figure 19 summarizes dissolution on accelerated stability in bottles without desiccant for the 500 mg strength croscarmellose based formulation (2% binder and 2% intra and extragranular CCS) 500 mg coated in Bottles with Desiccant. There is very little shift in dissolution observed at 6M at 40Deg C/75% RH

Figure 20 summarizes dissolution on accelerated stability in bottles with desiccant for the 500 mg strength croscarmellose based formulation (2% binder and 2% intra and extragranular CCS) 100 mg coated in Bottles with Desiccant. There is no shift in dissolution observed at 6M at 40Deg C/75% RH.

Figure 21A summarizes Scale-up (100 Kg) batch dissolution stability in Bottles with desiccant. There is minimal to no shift in dissolution on stability in CTAB/acetate buffer (A) and no shift in 0.1 N HCl (B).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

1. Definitions:

As used herein, an "effective amount" of a compound or pharmaceutically acceptable composition can achieve a desired therapeutic and/or prophylactic effect. In some embodiments, an "effective amount" is at least a minimal amount of a compound, or composition containing a compound, which is sufficient for treating one or more symptoms of a disorder or condition associated with modulation of protein tyrosine kinases. In certain embodiments, an "effective amount" of a compound, or composition containing a compound, is sufficient for treating symptoms associated with, a disease associated with an aberrant tyrosine kinase receptor (e.g. cancer, including malignant and benign tumor growths).

The term "subject", as used herein, means a mammal and includes human and animal subjects, such as domestic animals (e.g., horses, dogs, cats, etc.).

The terms "suffer" or "suffering" as used herein refers to one or more conditions that a patient has been diagnosed with, or is suspected to have.

The terms “treat” or “treating,” as used herein, refers to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disorder or condition, or one or more symptoms of the disorder or condition.

“Therapeutically active agent” or “active agent” refers to a substance, including a biologically active substance, that is useful for therapy (e.g., human therapy, veterinary therapy), including prophylactic and therapeutic treatment. Therapeutically active agents include organic molecules that are drug compounds, peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecules linked to a protein, glycoprotein, steroid, nucleic acid, DNA, RNA, nucleotide, nucleoside, oligonucleotides, antisense oligonucleotides, lipid, hormone, and vitamin. Therapeutically active agents include any substance used as a medicine for treatment, prevention, delay, reduction or amelioration of a disease, condition, or disorder. Among therapeutically active agents useful in the formulations of the present invention are opioid receptor antagonist compounds, opioid analgesic compounds, and the like. Further detailed description of compounds useful as therapeutically active agents is provided below. A therapeutically active agent includes a compound that increases the effect or effectiveness of a second compound, for example, by enhancing potency or reducing adverse effects of a second compound.

The expression “unit dosage form” as used herein refers to a physically discrete unit of inventive formulation appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active agent employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active agent employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

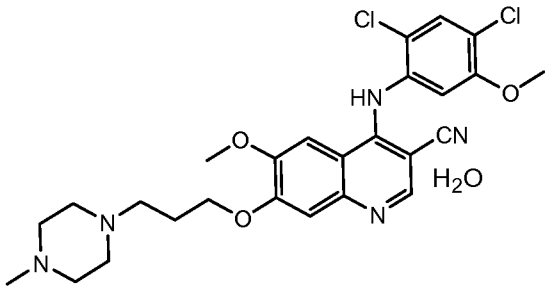
Briefly, "dry blend" materials are physically blended together before filling capsules or compressing tablets. See, Handbook of Pharmaceutical Granulation Technology, 1997, Dilip Parikh, Marcel Dekker, Inc. ISBN 0-8247-9882-1, page 309.

In dry granulation (slugging or roller compaction) intragranular materials are blended to prepare slugs or roller compaction. Material is milled and blended with extragranular materials followed by capsule filling or tablet 20 compression. Wet granulation entails blending intragranular materials. Wet granulate the blend with water, with or without a binder, (using high sheer, low sheer granulators) and dry (using temperatures up to 100° C). Material is milled and blended with extragranular materials followed by capsule filling or tablet compression. See, 25 Handbook of Pharmaceutical Granulation Technology, 1997, Dilip Parikh, Marcel Dekker, Inc. ISBN 0-8247-9882-1, pages 338-368.

2. Pharmaceutically Acceptable Compositions and Formulations:

In certain embodiments, pharmaceutically acceptable compositions of the present invention which comprise SKI-606 and one or more other excipients, such as, for example, one or more binders, carriers, viscosity modifying and suspending agents, wetting agents, wetting agents, sweeteners, pH modifying agents, flavoring agents, preservatives and combinations thereof. One skilled in the art will readily appreciate that the category under which a particular component is listed is not intended to be limiting; in some cases a particular component might appropriately fit it more than one category. Also, as will be appreciated, the same component can sometimes perform different functions, or can perform more than one function, in the context of a particular formulation, for example depending upon the amount of the ingredient and/or the presence of other ingredients and/or active compound(s).

In certain embodiments, the present invention provides a pharmaceutically acceptable solid composition comprising: 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, also referred to as SKI-606. SKI-606 is described in U.S. Pat No, 6,297,258, along with methods of preparing SKI-606, as described in U.S. Pat. No. 7, 297,795. SKI-606 has the following structure



SKI-606 Monohydrate

and is isolated as a monohydrate. The 3-cyanoquinoline compound, 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile, is a weak base with an intrinsic solubility of approximately 0.06 μg/mL at pH 8.0. Below pH 8, the solubility of the compound SKI-606 increases exponentially with decreasing pH due to ionization. However, degradation of SKI-606 was observed at low pH aqueous solution through hydrolysis, although the compound is relatively stable at pH higher than 5, when the 4 aminoquinoline group is not ionized.

In certain embodiments, the inventive SKI-606 formulation obviates one or more problems with solid formulations of 3-cyanoquinolines including variable dissolution, which appears to depend on particle size, accelerated dissolution on storage, and limited stability upon storage. The inventive croscarmellose SKI-606 formulations exhibit disintegration times (of 2-7 minutes) faster than comparable SKI-606 formulations employing a conventional disintegrating agent (e.g. crospovidone, disintegration times about 18-20 minutes).

In certain embodiments, the inventive SKI-606 formulation comprises a film coated SKI-606 formulation that is prepared by high shear wet granulation or pan coating. In other embodiments, the film coated SKI-606 tablet formulation is prepared by other conventional coating techniques.

Disintegration times were compared for SKI-606 formulation using a conventional disintegrating agent, crospovidone, and croscarmellose sodium and summarized in **Table** 2. The intragranular disintegrant in this case was kept constant at 3 % w/w. The two formulations have markedly different disintegration times, for instance tablet disintegration times (DT) with the 2% extragranular (EG) SKI-606/CCS formulation is

only 3.5 minutes as compared to the SKI-606/CPV formulation with a DT of 22 minutes. Additionally it is also observed that tablet DT is strongly dependent on tablet hardness for all the SKI-606/CPV formulations, whereas no such dependence is observed for the SKI-606/CCS formulations. For instance, even for the 3% IG and 2% EG SKI-606/CPV formulation, the DT times for the low and the high hardness tablets vary by 14 minutes (range), whereas the SKI-606/CCS formulations only vary by 3.5 minutes. This observation indicates that the SKI-606/CCS formulation was robust with respect to tablet hardness, a significant improvement with respect to tablet manufacturability characteristics of the inventive SKI-606 formulation.

Tablet dissolution of the inventive SKI-606 formulation (see **Figure** 1) was also carried out in 0.1 N HCl, which revealed that the tablet dissolution was faster for the SKI-606/CCS formulations at the 10 and 15 minutes at disintegrant concentrations lower than the ones used for SKI-606/CPV formulations. In addition the data also suggested that the lower binder concentrations enhanced dissolution especially at early time points.

In certain embodiments, amounts of croscarmellose sodium (CCS) in the inventive SKI-606 formulation that provide similar dissolution results are as follows:

1. 0- 2 % w/w intragranular concentration
2. 1-3% w/w extragranular concentration
3. Binder (Povidone concentrations) may also vary from 1-2% w/w.

In certain embodiments, the intragranular component to extragranular component ratio in the inventive SKI-606 formulation was changed from 3:1 to 2:2.

In certain embodiments, one intragranular (IG) component, a filler comprising microcrystalline cellulose (MCC), was transferred from the intragranular portion to the extragranular (EG) component to facilitate faster disintegration times during tabletting in the inventive SKI-606 formulation. The amount of extragranular filler component was increased to 15 weight % from 4 weight %, based on the weight of the SKI-606 formulation.

In certain embodiments, the grade of MCC in the EG component was changed from Avicel PH101™ to Avicel PH 102™ to facilitate tablet blend flow.

In certain embodiments, contrary to the common observation that reduction in particle size of the API generally causes an increase in rate of dissolution, it was observed that for SKI 606 formulation, decreasing the API particle size tends to lower the dissolution of the formulation when processed in a n identical fashion as the formulation with higher D90 API particle size. Thus it was observed that that the lower the API particle size, the slower the dissolution rate and higher the API particle size-faster the rate of dissolution, as summarized in **Figure** 6.

In order to maximize dissolution, one possible approach with the existing formulation is to increase the particle size of the drug like SKI-606. To slow down in dissolution an approach is to use API of lower particle size.

In certain embodiments, no change in the poloxamer concentration was made in the inventive SKI-606 formulation to retain in vivo effects when administered to a human or animal subject.

In certain embodiments, the formulation of the present invention can contain one or more non-rate-controlling layers, membranes or coatings. The location of the non-rate-controlling layer in the formulation is not critical. For example, the non-rate-controlling layer may be present between the at least one core and an enteric coating or a rate-controlling mechanism. Alternatively, the non-rate-controlling layer may surround or coat an enteric coating or a rate-controlling mechanism. The non-rate-controlling layer can be made of one or more polymers, as well as, other ingredients known in the art, such as, but not limited to, plasticizers, pigments/opacifiers, etc. Examples of polymers that can be used include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, ethylcellulose, polyvinyl alcohol, and polyethylene glycol. Examples of plasticizers that can be used include, but limited to, polyethylene glycol(s), glycerin, triacetin, triethyl citrate, diethyl phthalate and mineral oils. Examples of pigments/opacifiers that can be used include, but are not limited to, water soluble dyes, pigments, and natural products.

In certain embodiments, the formulations of the present invention can also include at least one enteric coating. Any enteric coating can be used in the present invention, including, but not limited to, solutions or dispersions of methacrylic acid and methacrylic ester copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, ethyl acrylate/methacrylic acid copolymers, cellulose acetate trimellitate, shellac and combinations thereof. Additionally, the enteric coating used in the formulations of the present invention can be formed as a single or multiple layers. The thickness of the coating can be readily determined by those skilled in the art, but must be sufficient to protect the formulation in the acidic environment of the stomach.

In certain embodiments, solid pharmaceutically acceptable compositions of SKI-606 were invented, based on replacing one conventional disintegrating agent, crospovidone, with croscarmellose sodium, which unexpectedly resulted improved stability and uniform dissolution rate of the SKI-606 formulation (see **Table** 1 and **Figure**s 1-3).

Wetting agents are well known in the art and typically facilitate drug release and absorption. Exemplary wetting agents include poloxamer, polyoxyethylene ethers, polyoxyethylene sorbitan fatty acid esters polyoxyethylene fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether, polysorbates, cetyl alcohol, glycerol fatty acid esters (e.g., triacetin, glycerol monostearate, and the like), polyoxymethylene stearate, sodium lauryl sulfate, sorbitan fatty acid esters, sucrose fatty acid esters, benzalkonium chloride, polyethoxylated castor oil, and docusate sodium, and the like, and combinations thereof. In some embodiments, wetting agents include but are not limted to for example Polysorbate 80™, glycerin, Polysorbate 65™, polysorbate 60™ USP, Polysorbate 40™ USP, Polysorbate 20™ USP, Octoxynol-9, Nonoxynol-10™ USP, Poloxamer 235™, Poloxamer 188™ USP. In some embodiments, provided wetting agents comprise from about 0.1 weight % to about 5 weight %, about 1.0 weight % to about 4 weight %, or about 3.0 weight % based upon total weight of the formulation. In certain embodiments, the wetting agent is a poloxamer, including but not limited for example Poloxamer 188™ (Lutrol F-68).

Suitable binders (also referred to as "diluents" and/or "fillers") are known in the art. For example, suitable binders and fillers include but are not limited to starch, dextrin, sucrose, Sorbitol, Sodium Saccharin, Acesulfame potassium, Xylitol, Aspartame, Mannitol, starch, PVP (polyvinyl pyrrolidone), low molecular weight HPC (hydroxypropyl cellulose), microcrystalline cellulose (MCC), low molecular weight HPMC (hydroxypropyl methylcellulose), low molecular weight carboxymethyl cellulose, ethylcellulose, alginates, gelatin, polyethylene oxide, acacia, dextrin, sucrose, magnesium aluminum silicate, and polymethacrylates. Fillers include agents selected from the group consisting of microcrystalline cellulose, starch, lactitol, lactose, a suitable inorganic calcium salt, sucrose, glucose, mannitol, silicic acid, or a combination thereof. In some embodiments, binders and fillers comprise from about 1 weight % to about 25% or about 21.5 weight %, based upon total weight of the formulation. In some embodiments, the binder is one or more grades of MCC, including but not limited to Avicel PH101™ and Avicel PH 102™.

Incorporation of suitable disintegrant(s) into the inventive SKI-606 formulation facilitate dissolution. Suitable disintegrants are known in the art and include but are not limited to, agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, crospovidone (cross-linked PVP), sodium carboxymethyl starch (sodium starch glycolate), cross-linked sodium carboxymethyl cellulose (croscarmellose), pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum) or a combination thereof. In some embodiments, a disintegrant is crospovidone. In some embodiments, a disintegrant is croscarmellose sodium.

In some embodiments, a suitable lubricant is included in the inventive SKI-606 formulation. Suitable lubricants or glidants include for example stearates, sodium stearyl fumarate and magnesium salts, magnesium stearate. The amount of lubricants used is 0.2-5 weight percent of one or more lubricants, including about 0.5 weight %, based on the weight of the composition. In some embodiments, the lubricant is magnesium stearate.

Addition of one or more preservatives may be particularly useful in compositions that include SKI-606, and may provide protection from degradation and/or from

precipitation. Appropriate preservatives are known to those skilled in the art, and include any pharmaceutically acceptable preservative. Conventional preservatives include, but are not limited to sodium benzoate, Propyl parahydroxybenzoate, Sorbic acid, Propylparaben, Methylparaben, Butylated hydroxytoluene, Propionates, Potassium sorbate, Indinavir and combinations thereof. In some embodiments, provided preservatives comprise from about 0.05 weight %, to about 0.25 weight % or about 0.1 %, based upon total weight of the formulation.

Provided compositions may be formulated into a unit dosage form. Such formulations are well known to one of ordinary skill in the art. In certain embodiments, the present invention provides a formulation comprising a solid dosage form as a tablet. In other embodiments, the present invention provides a solution for oral administration. In some embodiments, a unit dosage form contains 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725 mg, 750 mg, 775 mg, 800 mg, 825 mg, 850 mg, 875 mg, 900 mg, 925 mg, 950 mg, 975 mg, 1000 mg, 1025 mg, 1050 mg, 1075 mg, 1100 mg, 1125 mg, 1150 mg, 1175 mg, 1200 mg, 1225 mg, 1250 mg, 1275 mg, 1300 mg, 1325 mg, 1350 mg, 1375 mg, 1400 mg, 1425 mg, 1450 mg, 1475 mg, 1500 mg of SKI-606. In some embodiments, a unit dosage form contains between 5 mg and 500 mg, inclusive, or between 10 mg and 450 mg, inclusive, of SKI-606. In some embodiments, a unit dosage form contains 50 mg, 75 mg, 100 mg, 150 mg, 250 mg, 300 mg, or 500 mg. In some embodiments, a unit dosage form contains more than 500 mg of SKI-606.

In some embodiments, the effective dosage of SKI-606 employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of body weight, optionally given in divided doses two to four times a day, or in sustained release form. The total daily dosage is projected to be from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For

example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

In some embodiments, pharmaceutical compositions of SKI-606 from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. In a preferred embodiment, Oral administration of SKI-606 is preferred.

For the treatment of cancer, the inventive SKI-606 formulations of this invention can be administered in combination with other anti-tumor substances or with radiation therapy. These other substances or radiation treatments can be given at the same or at different times as the compounds of this invention. These combined therapies may affect synergy and result in improved efficacy. For example, the compounds of this invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cisplatin or cyclophosamide, anti-metabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, and antiestrogens such as tamoxifen.

Based on the results disclosed for SKI-606 and other 3-cyanoquinoline compounds in U.S. Pat. No. 6,297,258, the inventive SKI-606 formulations are useful antineoplastic agents of significant efficacy, which are useful in treating, inhibiting the growth of, or eradicating neoplasms. In particular, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms that express EGFR such as those of the breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, or lung. In addition, the compounds of this invention are useful in treating, inhibiting the growth of, or eradicating neoplasms of the breast that express the receptor protein produced by the erbB2 (Her2) oncogene. Based on the results obtained, the compounds of this invention are also useful in the treatment of polycystic kidney disease.

3. Combination Products and Combined Administration:

In certain embodiments, inventive compositions, and formulations thereof, may be administered alone to treat one or more disorders as described herein, or alternatively may be administered in combination with (whether simultaneously or sequentially) one or more other active agents useful to treat one or more disorders as described herein. Thus, an inventive composition, or formulation thereof, can be administered concurrently with, prior to, or subsequent to, one or more active agents.

In certain embodiments, inventive compositions include one or more other active agents in addition to SKI-606 that is not SKI-606. In some embodiments, inventive formulations comprise both another anticancer compound and SKI-606.

The amount of additional active agent(s) present in combination compositions of this invention will typically be no more than the amount that would normally be administered in a composition comprising that active agent as the only therapeutic agent. In certain embodiments of the present invention, the amount of additional active agent will range from about 50% to 100% of the amount normally present in a composition comprising that compound as the only therapeutic agent.

In certain embodiments, inventive formulations may also be used in conjunction with and/or in combination with conventional therapies for gastrointestinal dysfunction to aid in the amelioration of constipation and bowel dysfunction. For example, conventional therapies include, but may not be limited to functional stimulation of the intestinal tract, stool softening agents, laxatives (e.g., diphelymethane laxatives, cathartic laxatives, osmotic laxatives, saline laxatives, etc), bulk forming agents and laxatives, lubricants, intravenous hydration, and nasogastric decompression.

4. Uses and Kits of Inventive Compositions:

Provided compositions, and formulations thereof, are also useful in treatment of conditions including cancers involving angiogenesis, immune suppression, sickle cell anemia, vascular wounds, and retinopathy, treatment of inflammation associated disorders (e.g., irritable bowel syndrome), immune suppression, chronic inflammation.

In still further embodiments, veterinary applications (e.g., treatment of domestic animals, e.g. horse, dogs, cats, etc.) of use of inventive compositions, and formulations thereof, are provided. Thus, use of provided formulations in veterinary applications analogous to those discussed above for human subjects is contemplated.

It will also be appreciated that inventive compositions, and formulations thereof, can be employed in combination therapies, that is, an inventive composition, or formulation thereof, can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. Particular combination therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that therapies employed may achieve a desired effect for the same disorder (for example, a formulation may be administered concurrently with another compound used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic compounds which are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated”.

In other embodiments, inventive compositions, and formulations thereof, and unit dose forms are useful in preparation of medicaments, including, but not limited to medicaments useful in the treatment of cancer.

Still further encompassed by the invention are pharmaceutical packs and/or kits comprising inventive compositions, and formulations thereof, and a container (e.g., a foil or plastic package, or other suitable container). Optionally instructions for use are additionally provided in such kits.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

Examples 1 and 2: Preparation of Pharmaceutically Acceptable Compositions of SKI-606

SKI-606 is prepared according to the methods described in detail in one or more of U.S. Pat Nos. 6,297,258 and 7,297,795. An exemplary inventive formulation of SKI-606 and a comparative SKI-606 formulation are summarized in **Table** 1.

Table 1. SKI-606 Formulations

Intragranular Components	**SKI-606 Formulation 1 (% w/w)**	**Comparative SKI-606 formulation (% w/w)**
SKI-606 monohydrate (equivalent to SKI-606 free base)	69	69
Microcrystalline Cellulose (MCC, Avicel PH101™)	6.5	17.5
Crospovidone (CPV)	NA	3
Croscarmellose Sodium (CCS)	2	NA
Poloxamer 188™ (Lutrol F-68)	3	3
Povidone (Kollidon 25™)	2	2
Weight % Intragranular Components	**82.5**	**94.5**
Extragranular Components		
Microcrystalline Cellulose (MCC, Avicel 101™)	NA	4
Microcrystalline Cellulose (MCC, Avicel 102™)	15	NA
Crospovidone	NA	1
Croscarmellose Sodium	2	NA
Magnesium stearate	0.5	0.5
Weight % Extragranular Components	**17.5**	**5.5**
Coating (Opadry II systems)	**3**	**4**

NA-not applicable or not available

Tablets of the 500 mg strength were compressed using the appropriate tooling equipment and the tablets were compressed at low (11-13kp), target (14-16 kp) and

high (17-19 kp) hardnesses. These tablets were then evaluated for disintegration time in 0.1 N HCl.

The comparative SKI-606 formulation was prepared by the process of high shear wet granulation, wet milling, fluidized bed drying, dry milling, blending and compression to tablets that are subsequently film coated. This formulation has been associated with high percentage of gastric irritation in fasted individuals.

Disintegration times were compared for SKI-606 formulation using a conventional disintegrating agent, crospovidone, and croscarmellose sodium and summarized in **Table** 2. The intragranular disintegrant in this case was kept constant at 3% w/w. The two formulations have markedly different disintegration times, for instance tablet disintegration times (DT) with the 2% extragranular (EG) CCS formulation is only 3.5 minutes as compared to the CPV formulation with DT of 22 minutes. Additionally it is also observed that tablet DT is strongly dependent on tablet hardness for all the CPV formulations, whereas no such dependence is observed for the CCS formulations. For instance, even for the 2% CPV formulation, the DT times for the low and the high hardness tablets vary by 14 minutes, whereas the CCS formulations only vary by 3.5 minutes. This observation points to the fact that the CCS formulation was robust with respect to tablet hardness. This is a significant improvement with respect to tablet manufacturability characteristics, especially since the tablets are meant to be immediate release tablets.

Table 2. Disntegration times for SKI-606 500mg dose formulations employing Crospovidone versus Croscarmellose sodium as disintegrating agent. (For reference to formulations, refer to **Table** 2A)

Binder 1%, EG CPV-1%			**Binder 1%, EG CPV-5%**			**Binder 2%, EG CPV-2%**		
Run 1			**Run 2**			**Run 3**		
Low	Target	Hard	Low	Target	Hard	Low	Target	Hard
9 min 56 sec	18 min 20sec	27 min 20 sec	6 min 37 sec	10 min 45 sec	12 min	15 min 25 sec	22 min 10 sec	29 min 20 sec

Binder 2%, EG CPV-5%			**Binder 2%, EG CCS-1%**			**Binder 2%, EG CCS-2 %**			**Binder 2%, EG CPV-1%**		
Run 4			**Run 5**			**Run 6**			**Run 7**		
Low	Target	Hard	Low	Target	Hard	Low	Target	Hard	Low	Target	Hard
10 min 11 sec	13 min 30 sec	18 min 41 sec	2 min 20 sec	4 min 10 sec	5 min	2 min 25 sec	3 min 30 sec	6 min	16 min 35 sec	30 min 20 sec	40 min

Where Hard tablets ->16 kp tablet hardness, target tablets- 14-16 kp and Low hardness-11-13 kp (kp- Kilo Pascals)

Table 2A: Percent composition of Formulations referred to in **Table** 2

	Run 1	**Run 2**	**Run 3**	**Run 4**	**Run 5**	**Run 6**	**Run 7**
Intragranular Portion							
SKI-606 monohydrate equivalent to anhydrous base	69	69	69	69	69	69	69
Microcrystalline Cellulose (Avicel 101™)	6.5	6.5	5.5	5.5	5.5	5.5	5.5
Crospovidone (CPV)	3	3	3	3	NA	NA	3
Croscarmellose Sodium (CCS)	NA	NA	NA	NA	3	3	NA
Poloxamer 188 (Lutrol F-68™)	3	3	3	3	3	3	3
Povidone (Kollidon 25™)	1	1	2	2	2	2	2
Intragranular Totals (%)	**82.5**	**82.5**	**82.5**	**82.5**	**82.5**	**82.5**	**82.5**
Extragranular Portion							
Microcrystalline Cellulose (Avicel	16	12	15	12	16	15	16

	Run 1	**Run 2**	**Run 3**	**Run 4**	**Run 5**	**Run 6**	**Run 7**
101™)**							
Crospovidone (CPV)	1	5	2	5	NA	NA	1
Croscarmellose Sodium (CCS)	NA	NA	NA	NA	1	2	NA
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Exragranular Totals (%)	**17.5**	**17.5**	**17.5**	**17.5**	**17.5**	**17.5**	**17.5**

Tablet dissolution of the inventive SKI-606 formulation (see **Figure** 1) was also carried out in 0.1 N HCl, which revealed that the tablet dissolution was faster for the CCS formulations at the 10 and 15 minutes at concentrations lower than the ones used for CPV. In addition the data also suggested that the lower binder concentrations enhanced dissolution especially at early time points.

These trials demonstrate that CCS formulation was better from processability point in that granulation endpoint was not reached suddenly unlike CPV formulations- where endpoint was very susceptible to water input, and CCS formulation disintegration time (DT) was less susceptible to tablet hardness. Lowering of binder may correlate to adequate dissolution with CPV.

It is also evident that for the inventive SKI-606 formulation, which included croscarmellose sodium as a disintegrant, the dissolution is not sensitive to API particle size at 15 minutes, as summarized in **Table** 3. In addition for all IG/EG ranges studied, the only ratio that gave slower dissolution for CCS formulation at 15 minutes is 1%/0 % intra/extragranular disintegrant. For all other levels, release is more than 90%.

Table 3 : Effect of Disintegrant and API D_{90} on 500 mg Core Tablet Disintegration and Dissolution

Disintegrant type	CPV	CPV	CPV	CCS	CCS	CCS	CCS	CCS
API D_{90} (microns)	38	20	20	20	20	38	38	38
Binder (% w/w)	2	2	1	2	2	2	2	2
IG Disintegrant (% w/w)	3	3	3	3	3	2	1	1
EG disintegrant (%	3	3	1	1	0	0	1	0

w/w)								
Disintegration time (min) [for 14-16 kp Tablets]	18.32	15.73	25.48	4.18	4.75	14.3	7.4	23.4
% released at 15 min in 0.1 N HCl	67.68	50.21	23.41	94.21	92	97	97.2	67.6
% released at 30 min in 0.1 N HCl	94	89	47	98	97	101	99	96

These studies show that the croscarmellose sodium formulations were superior from a manufacturability perspective in that the granulation endpoints were easier to identify (reduced risk of over-granulation); the disintegration times for the croscarmellose sodium formulations were impacted less by tablet hardness; and lowering binder (povidone) concentration results in higher rates of dissolution of CPV formulations as expected due to its influence on rate of tablet disintegration. The change in binder was not deemed necessary for the CCS formulation that shows excellent tablet disintegration times and dissolution regardless of the binder concentration.

The results of extensive experimentation demonstrated that croscarmellose sodium formulations were more robust with respect to variability in drug substance particle size and consistency of dissolution profile for product on stability. Some advantages were seen bychanging the intra to extragranular ratio of microcrystalline cellulose to improve both tablet disintegration times as well as blend flow, and keeping the poloxamer and the binder same as the reference composition.

It is also evident that for the inventive SKI-606 formulation which included croscarmellose sodium as a disintegrant, the dissolution is slower for smaller particle size, as summarized in Tables 2 and 3.

In addition, it was observed that no incompatibilities or degradation were seen at 2 and 4 weeks with either disintegrant at 40° C (dry and wet). Batches on stability studies at 40° C and 40° C /75% RH conditions showed that dissolution shifts observed with CPV, but not with CCS, as summarized in **Figure**s 2 and 3.

Based on the measured data and results, the croscarmellose formulation is seen to provide superior SKI-606 tablet formulations, as API variability effect on dissolution and dissolution shift on stability areboth addressed, while making minimal changes to the formulation (It was thus decided to keep the binder povidone and poloxamer constant at 2% and 3% respectively.) Disintegrant type and the IG/EG disintegrant ratio was changed from 3:1 in clinical to 2:2 (% w/w). **Figure**s 4 and 5 describe the effect on disoolution by changing the intra and extragranular disintegrant ratios for both croscarmellose and Crospovidone respectively.

Example 3: Preparation of Fast Dissolving Pharmaceutically Acceptable Compositions of SKI-606

SKI-606 is prepared according to the methods described in detail in one or more of U.S. Pat Nos. 6,297,258 and 7,297,795. An exemplary inventive fast dissolving formulation of SKI-606 and a comparative SKI-606 formulation are summarized in **Table** 4.

Table 4. Exemplary Fast Dissolving SKI-606 Formulation with Croscarmellose sodium .

Intragranular	**Fast dissolving SKI-606 formulation (% w/w)**	**Comparative SKI-606 Formulation (% w/w)**
SKI-606 Monohydrate (equivalent to anhydrous SKI-606 free base)	69	69
Microcrystalline Cellulose (101™)	6.5	17.5
Crospovidone (CPV)	NA	3
Croscarmellose Sodium (CCS)	2	NA
Poloxamer 188 (Lutrol F-68™)	3	3
Povidone (Kollidon 25™)	2	2
% Intragranular portion	**82.5**	**94.5**
Extragranular		
Microcrystalline Cellulose (101™)	--	4
Microcrystalline Cellulose (102™)	15	--
Crospovidone	NA	1
Croscarmellose Sodium	2	NA
Magnesium stearate	0.5	0.5
% Extragranular portion	**17.5**	**5.5**
Coating	**3**	**4**

NA-not applicable or not available

The gastric irritation effect of the formulation may be a result of prolonged residence time in the stomach and upper GI tract. The inventive SKI-606 formulation also provides a relatively fast dissolving salt of the drug that solubilizes faster in the GI tract. The fast dissolving salts of the drug includes the citrate, succinate, fumarate, Di-HCl, Di- mesylate, acetate, maleate, tartarate and HCl salts to name a few, providing a SKI-606 formulation useful for dissolving or disintegrating faster within the GI tract to cause rapid drug dissolution.

A faster disintegrating formulation was prepared by making a few changes to the current formulation. This was done by incorporating the following changes in the formulation: eplacing the disintegrant crospovidone with croscarmellose sodium. This disintegrant acts by a “swelling” action promoting early disintegration times as compared to the “wicking” action promoted disintegration with the crospovidone. It is found to exert a faster disintegrant action at comparable concentrations as the crospovidone.In addition to replacing the disintegrant, an additional change done was the change in the ratio of the microcrystalline cellulose. Microcrystalline cellulose, Avicel PH 101 was reduced intragranularly and increased extragranularly to help improve the disintegrant efficacy. The grade was also changed from Avicel 101 to a larger particle sized 102 to improve blend flow and compressibility. This approach was found to yield faster disintegrating and dissolving tablets, both of which are expected to improve the gastric outcome in the stomach. The inventive SKI-606 formulation is based on this approach.

Example 4: Preparation of Pharmaceutically Acceptable Compositions of SKI-606 as Coated Tablet

SKI-606 is prepared according to the methods described in detail in one or more of U.S. Pat Nos. 6,297,258 and 7,297,795. An exemplary coated tablet from inventive formulation of SKI-606 at two different unit dosages is summarized in **Table** 5.

Table 5. Coated Tablets of SKI-606 formulation at Different Unit Dosage strengths

Claim: 69.0% Batch Size: 25 Kg									
Ingredient	Function	Based on tablet core % wt/wt	Based on Intragranular solids portion	Input/ Dosage Unit (For 500 mg dose strength)		Input/ Dosage Unit (For 100 mg dose strength)		Representative Batch Formula	
		% wt/wt	% wt/wt	Input	Unit	Input	Unit	Input	Unit
SKI-606 monohydrate equivalent to anhydrous base	Active	68.96	83.6	500	mg	100.0	mg	17.241	Kg
Microcrystalline cellulose (PH 101) [a]	Filler	6.50	7.9	47.1	mg	9.420	mg	1.624	Kg
Croscarmellose Sodium	Disintegrant	2.0	2.4	14.49	mg	2.898	mg	0.500	Kg
Poloxamer 188	Wetting agent	3.0	3.6	21.74	mg	4.348	mg	0.750	Kg
Povidone, K-25	Binder	2.0	2.4	14.49	mg	2.898	mg	0.500	Kg
Purified Water [b]	Granulating Solution	QS	QS	241.86	mg	48.37	mg	8.340	Kg
Totals		82.46	100	597.820	mg	119.564	mg	20.615	Kg

Dry blend and Coating portion:

Table 6. Dry blends and coated SKI-606 formulations.

Ingredient	Function	Based on tablet core % wt/wt	Input/ Dosage Unit Input (500 mg)	Input/ Dosage Unit Input (100 mg)	Unit	Representative Batch Formula Input	Unit
Dried SKI-606 granulation portion	NA	82.46	597.820	119.564	mg	20.615	Kg
Microcrystalline cellulose (PH 102)	Filler	15.042	109.055	21.811	mg	3.761	Kg
Croscarmellose Sodium	Disintegrant	2.0	14.5	2.900	mg	0.500	Kg
Magnesium Stearate	Lubricant	0.5	3.625	0.725	mg	0.125	Kg

Ingredient	Function	Based on tablet core % wt/wt	Input/ Dosage Unit Input (500 mg)	Input/ Dosage Unit Input (100 mg)	Unit	Representative Batch Formula Input	Unit
Totals		100.0	725.00	145.000	mg	25.0	Kg
COATING							
Opadry-II yellow, 85F12390	Coating agent	3.0	NA	4.350	mg	0.975	Kg
Opadry-II red, 85F15642			21.75	NA			
Purified Water	Coating carrier	QS	123.25	24.650	mg	5.525	Kg
Totals		103.0	746.75	149.350	mg	6.5	Kg

The SKI-606 formulation and coated tablets of the SKI-606 formulation were prepared as follows:

MANUFACTURING PROCEDURE

The SKI-606 formulation and coated tablets of the SKI-606 formulation were prepared as follows:

Weighed the following ingredients for a batch size of 25 Kg:

SKI-606 monohydrate

17.241Kg

Microcrystalline cellulose (Avicel PH 101) 1.624 Kg

Croscarmellose sodium 0.5 Kg

Povidone K-25 0.5 Kg

Poloxamer 0.75 Kg

1. Dissolved the Povidone and the poloxamer into the purified water.
2. Added the SKI-606, microcrystalline cellulose (PH 101), and croscarmellose sodium of the intra-granular portion to the high shear granulator and mix for a minimum of 4 minutes, or until uniform. The dry ingredients may be passed through a screen, if necessary, to de-lump prior to pre-blending.
3. While mixing, added the Step 1 solution to the high shear granulator and mix until a suitable granulation is achieved. The water quantity may be adjusted to achieve a satisfactory granulation endpoint if required.

4. The granulation may be passed through a mill or screen, if necessary, to facilitate a uniform granulation before drying.
5. Dried the granulation in a fluid bed dryer until a satisfactory endpoint is reached. The LOD at this point should be below 3% w/w with a target between 1-1.5 % w/w under test temperature conditions.
6. Passed the dried granulation through a mill equipped with an appropriate sieve or screen to facilitate a satisfactory particle size distribution for blending. Retain a portion of this for Step 10.
7. Added the granulation to a suitable blender. If required, mix the dry sized granulation for a minimum of 5 minutes, or until uniform.
8. Calculate the amounts of extragranular ingredients based on yields obtained of the dried granulation.
9. The dry blend ingredients may be passed through a screen, prior to blending. Retain a sample of microcrystalline cellulose if required for blending in Step 10. Add the microcrystalline cellulose and croscarmellose sodium to the mixer and blend for 10 minutes, or until uniform.
10. Added either a portion of granulation from Step 6 or microcrystalline cellulose (PH 102) from Step 9 to the magnesium stearate and mix to form a lubricant pre-blend. Add the lubricant pre-blend to the Step 9 blender and mix for a minimum of 2 minutes, or until uniform.
11. Compress the granulation using appropriate tooling, at adequate hardness

Preparation and Application of Coating Suspension

1. Prior to mixing, the dry color was passed through a screen, if necessary. Using a suitable mixer and tank, to the color coat was added to the purified water and mixed until a satisfactory suspension was formed. The suspension may be sieved through an appropriate screen.

2. 5 Kg of the coating suspension was applied to the bed for a total 3% wt/wt weight gain. This may if required be verified by tablet weight gain.

Table 7: Examples of Coated Tablets of SKI-606 formulation with Crospovidone disintegrant at Different Unit Dosages

Ingredients	**Qty (%w/w) of tablet core weight**	**Qty/tablet (mg) for 100 mg dose tablet**	**Qty/tablet (mg) for 500 mg dose tablet**
SKI 606 monohydrate (Based on 96% assay)	69	104.17	520.83
Avicel pH 101	7.5	6.7	33.52
Crospovidone	1.0	1.45	7.25
Poloxamer-188™	3.0	4.35	21.74
Povidone	2.0	2.9	14.49
Water	QS		
Extragranular ingredients			
Crospovidone	3.0	4.35	21.74
Avicel pH 101™	14.0	20.29	101.45
Magnesium stearate	0.5	0.724	3.62
Total Uncoated tablet weight (mg)		**145.0**	**725.0**
Opadry II Yellow 85F12390 at 4% w/w		6.04	--
Opadry II **Red** 85F15642 85F12390 at 4% w/w		--	30.19
Total tablet weight of coated tablet (mg)		**151.04**	**755.19**

The SKI-606 formulation and coated tablets of the SKI-606 formulation were prepared as follows for a batch size of 1 Kg core tablets:

Weighed the following ingredients:

SKI-606 monohydrate

718.4g

Microcrystalline cellulose (Avicel PH 101) 46.23 g

Crospovidone 10.0 g

Povidone K-25 20.00g

Poloxamer 188 30.00 g

1.Passed SKI-606, Microcrystalline Cellulose and Crospovidone from step 1 through a 20 mesh screen and ingredients were added to a high shear mixer.

2. Mixed the ingredients in step 2 in a high shear granulator for 2 minutes at low plow speed (Impeller only).

3. Dissolved Poloxamer 188 and Povidone K-25 in Purified water in another mixer. Used low mixer speed to avoid the generation of foam

4. Set the impeller and chopper speed to low setting. Added the solution from step 4 using a pump to granulate the mix in Step 3. If necessary, when the granulation solution was exhausted, continued mixing for an additional 2- 5 minutes with the chopper and impeller at low speed. Added additional Purified Water if necessary while mixing until the granulation end point is reached. Checked for the desired granulation end point. Record the total amount of water used to granulate and the total mixing time as well as power or torque reading if available.

5. Dried the granulation in a Fluid bed dryer with inlet suggested set value temperature of 70°C ±5°C to a suggested L.O.D. range of 1 .5% to 2.5 %. Weighed and recorded yield.

6. Passed the dried granulation through a Comil at low speed (suggested mill speed 700 rpm or below and suggested screen: 20 mesh,). Weighed and recorded yield.

FINAL BLEND:

7. Based on the yield in step 7, calculated the amount of ingredients required for (extra granular) dry addition.
8. Transferred the milled granulation from Step 9 into a suitable size V-blender.

9. Weighed the Microcrystalline cellulose (PH 101), Crospovidone and passed through a 20-mesh screen and add to the V-blender in step 11. Blend for 10 minutes without the intensifier bar activation.

10. Passed Magnesium stearate through a 30-mesh screen and bag blend with an equal portion of granulation of step 12 and added to the V-blender. Blend for 2 minutes without intensifier bar.

11. Weighed and recorded yield.

Compress tablets at known weights and hardnesses and film coated compressed tablets.

In certain embodiments, the inventive SKI-606 formulation obviates one or more problems with solid formulations of 3-cyanoquinolines, namely, variable dissolution and a tendency for certain SKI-606 formulations (see comparative Example) to undergo small yet significant shifts on in dissolution on aging at both room temperature and under accelerated conditions when tested in buffer solution or under acidic conditions, as summarized in **Figure**s 10 and 12. **Figure** 11 shows the lack of dissolution shift for the croscarmellose formulation. **Figure** 12 shows the dissolution shifts in existing formulation. The poloxamer 188 in the SKI-606 comparative formulation was responsible for the shift in dissolution observed. Poloxamer though a solid at room temperature tends to undergo liquefaction at and around temperatures near its melting point of 48-52° C. Studies summarized in **Figure**s 13 and 14 revealed that the poloxamer in the Crospovidone based formulation was indeed the reason that the tablets were shifting in dissolution.

In certain embodiments, SKI-606 tablet formulations were prepared with varying amounts of poloxamer, ranging from 0, 1.5, 3, 4.5 and 6% w/w, based on the weight of the SKI-606 formulation. Unexpectedly. it was observed that there existed a clear dependency of tablet dissolution on the percent poloxamer content of the formulation, when tested in 0.1 N HCl. **Figure** 13 summarizes the effects of varying poloxamer content on tablet dissolution at similar water and binder addition rates in 0.1 N HCl. It is observed that the poloxamer actually appears to retard the release especially at early time points for the tablets tested. Poloxamer appeared to retard initial tablet dissolution at 15 and 30 minutes in a concentration dependent manner. See **Table 8**.

Table 8: Disintegration times in 0.1N HCl of SKI-606 500 mg Tablet Cores with Varying Poloxamer content

Poloxamer concentration (% w/w)	**DoE-1/Run Number**	**Tablet DT range [N=6) (min)**
0	2	6.2-6.6
1.5	1	10.6-12.9
3.0	3	11.5-13.1
4.5	7	14.1-15.6
6.0	5	14.3-14.9

Although the poloxamer in tablets tends to retard dissolution initially, it was found to speed up dissolution on accelerated stability at later timepoints in 0.1 N HCl media as seen in the data summarized in **Table** 9.

Table 9: Increase in Percent dissolved for the DoE batches in 0.1N HCl and pH 4 Buffer (Stability Studies)

Water (G)	**Binder addition rate (g/min)**	**Poloxamer (% w/w)**	**Release at 15 min (%) in 0.1 N HCl (+ -Increase in % dissolution from initial)**	
147	58.5	0	***Initial***	***66***
			1M@40 Deg C	+3
			1M@40 Deg C/75% RH	+6
162	58.5	1.5	***Initial***	***50***
			1M@40 Deg C	+19
			1M@40 Deg C/75% RH	+22
147	58.5	3.0	***Initial***	***43***
			1M@40 Deg C	+11
			1M@40 Deg C/75% RH	+31
158	66	4.5	***Initial***	***38***
			1M@40 Deg C	+13
			1M@40 Deg C/75% RH	+8
147	58.5	6.0	***Initial***	***38***
			1M@40 Deg C	+6
			1M@40 Deg C/75% RH	+14

On accelerated stability, poloxamer causes a dissolution shift in a concentration dependent manner from 0 to 3% w/w. The dissolution shift beyond 3% poloxamer concentration plateaus off with no evident trends. These results verify that the poloxamer can cause dissolution shifts to happen on stability. The poloxamer chains on aging and at accelerated temperatures are believed to become more mobile, and thus instead of holding the granules together in the tablet the mobile polymer chains tends to "soften" the tablets. This could be as a result of granule softening over time as well as

increased tendency to disintegrate. Also seen are lowered disintegration times on stability. Once the tablet has disintegrated the granules in the tablet actually show behavior very similar to all known surfactants. Increase in surfactant tends to increase granule dissolution as seen in **Figure** 14.

This dissolution shift problem was obviated by the inventive SKI-606 formulation, by replacing the wetting agent poloxamer, which also functions as a surfactant, in the formulation. The use of a lower melting point surfactant (one that was liquid at room temperature) could help to address this issue. Polyoxyethylene (20) sorbitan monooleate (Tween™ or polysorbate 80™ i) is one of the commonly used surfactants in use. The concentration of Polyoxyethylene (20) sorbitan monooleate (Polyoxyethylene sorbitan monooleate (Tween-80)™) tested was 1% in place of the 3% poloxamer in the formulation. This was used in the CPV formulation with 3% IG and 1% EG CPV as the disintegrant. This was deemed acceptable as the dissolution and other manufacturability characteristics tested at this concentration were acceptable. In addition, Polyoxyethylene sorbitan monooleate (Tween-80)™ is a commonly used pharmaceutically acceptable wetting agent and also functions as a surfactant.

In addition to addressing dissolution shift, testing of the robustness of these formulations with respect to active pharmaceutical ingredient API particle size is desirable. The comparative SKI-606 formulation the API particle size appeared to influence the dissolution i.e. smaller the API particle size, slower the dissolution. With the SKI/Tween-80 formulation, this effect was minimized or negligible (**Figure** 17) and the SKI-606 formulations comprising the alternative wetting agent Polyoxyethylene sorbitan monooleate (Tween-80)™ were superior in aging (**Figures** 15 and 16) to the comparative SKI-606 formulation

Examples 11 and 12: Preparation of Pharmaceutically Acceptable Compositions of SKI-606

SKI-606 is prepared according to the methods described in detail in one or more of U.S. Pat Nos. 6,297,258 and 7,297,795. An exemplary inventive formulation of SKI-606 and a comparative SKI-606 formulation are summarized in **Table** 10.

Table 10. SKI-606 Formulations

Intragranular Components	**SKI-606 Formulation 1 (% w/w)**	**Comparative SKI-606 formulation (% w/w)**	**SKI-606 Alternate Surfactant Formulation (% w/w)**
SKI-606 monohydrate equivalent to SKI-606 base	69	69	69
Microcrystalline Cellulose (MCC, Avicel PH101)	6.5	17.5	19.5
Crospovidone (CPV)	NA	3	3
Croscarmellose Sodium (CCS)	2	NA	NA
Poloxamer 188™ (Lutrol F-68™™)	3	3	NA
Polyoxyethylene sorbitan monooleate (Tween -80)			1
Povidone (Kollidon 25)	2	2	2
Weight % Intragranular Components	**82.5**	**94.5**	**94.5**
Extragranular Ingredients			
Microcrystalline Cellulose (MCC, Avicel 101™)	NA	4	4
Microcrystalline Cellulose (MCC, Avicel 102™)	15	NA	NA
Crospovidone	NA	1	1
Croscarmellose Sodium	2	NA	NA
Magnesium stearate	0.5	0.5	0.5
Weight % Extragranular Components	**17.5**	**5.5**	**5.5**
Coating (Opadry II systems)	**3**	**4**	**4**

NA-not applicable or not available

Alternative SKI-606 Formulation comprising Polyoxyethylene sorbitan monooleate (Tween-80) as a wetting are summarized in Tables 11-13.

Table 11. Alternate SKI-606 Formulations Comprising Polyoxyethylene sorbitan monooleate (Tween-80) and varying Crospovidone.

Ingredients	**Alternate Tween formulation (% w/w)**	**Alternate Tween formulation (% w/w)**	**Alternate Tween formulation (% w/w)**
SKI-606 Monohydrate equivalent to SKI-606 base	69	69	69
Microcrystalline Cellulose (MCC, Avicel PH101)	21.5	20.5	18.5
Crospovidone (CPV)	1	2	4
Croscarmellose Sodium (CCS)	NA	NA	NA
Tween-80™	1	1	1
Povidone (Kollidon 25™)	2	2	2
Weight % Intragranular Components	**94.5**	**94.5**	**94.5**
Microcrystalline Cellulose (MCC, Avicel 101)	2	3	5
Crospovidone	3	2	0
Magnesium stearate	0.5	0.5	0.5
Weight % Extragranular Components	**5.5**	**5.5**	**5.5**

Table 12. Alternate SKI-606 Formulations Comprising Varying Polyoxyethylene sorbitan monooleate (Tween-80).

Ingredients	**Alternate Tween formulation (% w/w)**	**Alternate Tween formulation (% w/w)**	**Alternate Tween formulation (% w/w)**
SKI-606 Monohydrate equivalent to SKI-606 base	69	69	69
Microcrystalline Cellulose (MCC, Avicel PH101)	20	20.25	19.75
Crospovidone (CPV)	3	3	3
Croscarmellose Sodium (CCS)	NA	NA	NA
Tween-80™	0.5	0.25	0.75
Povidone (Kollidon 25)	2	2	2
Weight % Intragranular Components	**94.5**	**94.5**	**94.5**
Microcrystalline Cellulose (MCC, Avicel 101)	4	4	4
Crospovidone	1	1	1
Magnesium stearate	0.5	0.5	0.5
Weight % Extragranular Components	**5.5**	**5.5**	**5.5**

Table 13. Alternate SKI-606 Formulations Comprising Polyoxyethylene sorbitann monooleate (Tween-80) with varying binder concentrations.

Ingredients	Alternate Tween formulation (% w/w)	Alternate Tween formulation (% w/w)	Alternate Tween formulation (% w/w)
SKI-606 Monohydrate equivalent to SKI-606 base	69	69	69
Microcrystalline Cellulose (MCC, Avicel PH101)	20.5	19.5	18.5
Crospovidone (CPV)	3	3	3
Croscarmellose Sodium (CCS)	NA	NA	NA
Tween-80™	1	1	1
Povidone (Kollidon 25)	1	2	3
Weight % Intragranular Components	**94.5**	**94.5**	**94.5**
Microcrystalline Cellulose (MCC, Avicel 101)	4	4	4
Crospovidone	1	1	1
Magnesium stearate	0.5	0.5	0.5
Weight % Extragranular Components	**5.5**	**5.5**	**5.5**

The comparative SKI-606 formulation was prepared by the process of high shear wet granulation, wet milling, fluidized bed drying, dry milling, blending and compression to tablets that are subsequently film coated.

In certain embodiments, the inventive SKI-606 formulation comprises a film coated SKI-606 formulation that is prepared by high shear wet granulation or pan coating. In other embodiments, the film coated SKI-606 tablet formulation is prepared by other conventional coating techniques.

CLAIMS

We claim:

1. A pharmaceutically acceptable composition comprising: intragranular components (a) 20-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile based on the weight of the composition; (b) povidone; (c) microcrystalline cellulose; (d) 0.25-5 weight percent of croscarmellose sodium based on the weight of the composition, (e) poloxamer; and extragranular components (f) microcrystalline cellulose; and (g) magnesium stearate.

2. A pharmaceutically acceptable composition comprising: intragranular components (a) 25-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile based on the weight of the composition; (b) povidone; (c) microcrystalline cellulose; (d) 0.25-5 weight percent of croscarmellose sodium based on the weight of the composition, (e) poloxamer; and extragranular components (f) microcrystalline cellulose; and (g) magnesium stearate.

3. The composition according to claim 1, wherein the amount of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile is about 69 weight %, based on the weight of the composition.

4. The composition according to any one of claims 1-3, wherein the amount of croscarmellose sodium is about 1-3 weight %, in the intragranular portion, based on the weight of the composition.

5. The composition according to any one of claims 1-3, wherein the amount of croscarmellose sodium is about 1-3 weight %, in the extragranular portion, based on the weight of the composition.

6. The composition according to claim 1, wherein the amount of povidone is about 2 weight %, based on the weight of the composition.

7. The composition according to claim 1, wherein the amount of microcrystalline cellulose is about 21.5 weight %, based on the weight of the composition.

8. The composition according to claim 7, wherein the amount of microcrystalline cellulose as an intragranular component is about 6.5 weight %, based on the weight of the composition; or the amount of microcrystalline cellulose as an extragranular component is about 15 weight %, based on the weight of the composition; or both.

9. The composition according to claim 1, wherein the amount of poloxamer is about 3 weight %, based on the weight of the composition.

10. The composition according to claim 1, wherein the amount of magnesium stearate is about 0.5 weight %, based on the weight of the composition.

11. A pharmaceutically acceptable composition for oral administration, comprising: intragranular components (a) 25-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile; (b) 0.5-5.0 weight percent of povidone; (c) 1–25 weight percent of microcrystalline cellulose; (d) 0.5-5 weight percent of croscarmellose sodium; (e) 0.2-5 weight percent of poloxamer, based on the weight of the composition; and extragranular components (f) 1–25 weight percent of microcrystalline cellulose; (g) 0.5-5 weight percent of croscarmellose sodium; and (h) 0.5-5 weight percent of magnesium stearate, based on the weight of the composition of the uncoated/core tablet.

12. The composition according to claim 8, wherein the amount of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile is about 69 weight %, based on the weight of the composition.

13. The composition according to claim 11 or 12, wherein the amount of croscarmellose sodium is about 1-3 weight %, in the intragranular portion, based on the weight of the composition.

14. The composition according to claim 11 or 12, wherein the amount of croscarmellose sodium is about 1-3 weight %, in the extragranular portion, based on the weight of the composition.

15. The composition according to claim 11, wherein the amount of povidone is about 2 weight %, based on the weight of the composition; the amount of microcrystalline cellulose is about 21.5 weight %, based on the weight of the composition; the amount of poloxamer is about 3 weight %, based on the weight of the composition; or the amount of magnesium stearate is about 0.5 weight %, based on the weight of the composition.

16. The composition according to claim 15, wherein the amount of microcrystalline cellulose as an intragranular component is about 6.5 weight %, based on the weight of the composition; the amount of microcrystalline cellulose as an extragranular component is about 15 weight %, based on the weight of the composition; or both.

17. A pharmaceutically acceptable composition comprising: intragranular components 25-80 weight percent of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile based on the weight of the composition; and 0.25-5 weight percent of croscarmellose sodium based on the weight of the composition; and extragranular components optionally comprising microcrystalline cellulose; and magnesium stearate.

18. The composition according to claim 1 or 11, in the form of an oral suspension of 4-(2,4-dichloro-5-methoxy-phenylamino)-6-methoxy-7-[3-(4-methyl-piperazin-1-yl)-propoxy]-quinoline-3-carbonitrile.

19. The composition according to claim 1 or claim 11, in the form of a wet granulated, film coated tablet, or in the form of a pan coated tablet.

20. A method for treating cancer comprising administering an effective amount of a composition according to claim 1 or claim 11.