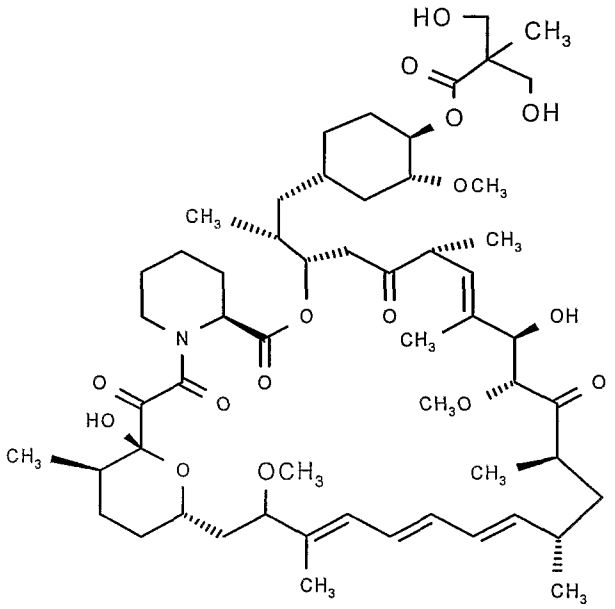
DIRECTLY COMPRESSIBLE PHARMACEUTICAL COMPOSITION FOR THE ORAL ADMINISTRATION OF CCI-779

BACKGROUND OF THE INVENTION

Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is an anticancer agent and is characterized by the following structure.



CCI-779

CCI-779 exhibits cytostatic, as opposed to cytotoxic properties, and may delay the progression of tumors or tumor recurrence. The mechanism of action of CCI-779 that results in the G1 to S phase block is novel for an anticancer drug. *In vitro*, CCI-779 has been shown to inhibit the growth of a number of histologically diverse tumor cells. Central nervous system (CNS) cancer, leukemia (T-cell), breast cancer, prostate cancer, and melanoma lines were among the most sensitive to CCI-779. The compound arrested cells in the G1 phase of the cell cycle.

CCI-779 has poor water solubility (less than 1 μg/ml) and high permeability (Log PC $\geq$ 4.1 in 1-octanol/water system and P_{eff} = 4-5 X 10^{-5} cm/sec obtained from *in situ* rat intestinal perfusion study using metoprolol tartrate as a marker) and is classified as class II compound according to BCS classification system. One obstacle towards the formulation of CCI-779 is its poor aqueous dissolution and low oral bioavailability.

Additionally, CCI-779 exhibits aqueous instability and has shown its potential to undergo oxidation.

A CCI-779 formulation was developed that employed a wet granulation manufacturing process. US Published Patent Application, Publication No. US- 2004-0077677-A1. This process involved preparation of a hydroalcoholic granulation solution of CCI-779. Further, although the resulting tablets were stable and bioavailable, the preparation of the hydroalcoholic solution was very tedious. Further, CCI-779 was thermodynamically unstable, precipitating within one day after its preparation, requiring it to be used immediately after its preparation.

In view of this, a simple manufacturing process is required that can produce stable and bioavailable tablets and can be used for commercial manufacturing.

SUMMARY OF THE INVENTION

The present invention provides a convenient and effective method to deliver therapeutic levels of CCI-779 to the patient. The invention provides pharmaceutical compositions containing a stable and bioavailable form of micronized CCI-779, and optionally, an antioxidant or a chelating agent, or mixtures thereof, in an immediate release dosage form for oral administration. The composition is in the form of a tablet or in filled capsules.

Other aspects and advantages of the invention will be readily apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides micronized CCI-779, that can be readable formulated into an oral dosage unit, and is particularly well suited for a directly compressible unit. The inventors have found that tablets prepared by direct compression of micronized CCI-779 formulations of the invention exhibited rapid and complete drug release, as compared to nonmicronized CCI-779, even when the nonmicronized CCI-779 was formulated with surfactants. See, *e.g.*, Example 4. Thus, the compositions of the invention provide fast drug release.

Briefly, CCI-779 is micronized under nitrogen and conventional micronizing techniques, for example with a Trost or jet mill, applied to non-micronized CCI-779. The preparation of non-micronized CCI-779 is described in U.S. Patent 5,362,718, which is hereby incorporated by reference. A regioselective preparation of non-micronized CCI-779 is described in US Patent 6,277,983, which is hereby incorporated by reference. However, the invention is not limited to the method by which the non-micronized CCI-779 is produced. Micronized CCI-779 typically has a particle size of about 0.2 to about 30 microns, about 0.5 to 25 microns, or about 0.5 to 20 microns, as described above.

The compositions of the invention contain micronized CCI-779 with a particle size range in which 10% are less than or equal to about 3 microns (μ), 50% are about 10 μ, and 90% are less than or equal to about 20 μ as determined by Malvern method. In one embodiment, the micronized CCI-779 has a particle size range of 10% are less than or equal to about 2 μ, 50% are about 5 μ, and 90% are less than or equal to about 16 μ as determined by Malvern method.

Suitably, the micronized CCI-779 is present in the composition of the invention in an amount from 0.1 % w/w to 50% w/w, based on the weight of an uncoated composition of the invention. This amount may be varied, depending upon the amount of micronized CCI-779 to be delivered to a patient. For example, an effective amount of micronized CCI-779 is generally in the range, *e.g.*, about 0.1 to about 50 mg, about 10 mg to about 30 mg, or about 0.5 to about 2 mg micronized CCI-779. The desired therapeutic regimen can be taken into consideration when formulating a composition of the invention. For example, micronized CCI-779 can be in the range of 0.1% w/w to 10% w/w for an uncoated composition of the invention. In another example, micronized CCI-779 can be in the range of 5% w/w to 25% w/w based upon the weight of an uncoated unit dose. In yet another example, micronized CCI-779 can be in the range of 6% w/w to 8% w/w, 15% w/w to 40% w/w, or 20% w/w to 30% w/w based on the weight of an uncoated unit dose.

In addition to containing micronized CCI-779, the composition of the present invention can contain pharmaceutically acceptable additives and/or excipients. Typically, these additives are biologically inert and useful for manufacture of a dosing

unit. The compositions of the invention may contain one or more filler/binder, disintegrant, a dissolution enhancer (including, *e.g.*, a surfactant), glidant, and lubricant. In certain embodiments, the compositions further contain one or more antioxidants, chelating agents, or pH modifiers. Optionally, the antioxidant, chelating agent, and/or pH modifier may be micronized. Micronized additives and excipients are prepared using conventional techniques, as described.

Examples of pharmaceutically acceptable binders, fillers, and disintegrants include sucrose, lactose, magnesium stearate, gum acacia, cholesterol, tragacanth, stearic acid, gelatin, casein, lecithin (phosphatides), carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, cetostearyl alcohol, cetyl alcohol, cetyl esters wax, dextrates, dextrin, lactose, dextrose, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyoxyethylene alkyl ethers, polyethylene glycols, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, and polyvinyl alcohol, and the like.

In one embodiment, the disintegrant is croscarmellose sodium. Suitably, a composition of the invention contains a total of about 3% w/w to 8% w/w disintegrant, *e.g.*, about 4% to about 6% w/w.

In one embodiment, the binders and fillers are selected from the group consisting of polyvinylpyrrolidone (povidone), lactose (including anhydrous lactose), and microcrystalline cellulose, and mixtures thereof. Suitably, a composition of the invention contains a total of about 75 % w/w to 88% w/w binder/filler, or about 80% w/w to 82% w/w binder/filler, based on the weight of an uncoated composition. For example, a composition of the invention may contain, in addition to the micronized CCI-779 and other components, about a low amount of povidone, *e.g.* about 5 to 7% w/w, and more desirably, about 6% w/w, with the remainder of the filler in the uncoated composition being supplied by other components. In another example, a composition of the invention may contain a high amount of povidone, e.g., about 25 to 35% w/w, and more desirably, about 30 to 32 % w/w povidone, with the remainder of the filler in the uncoated composition being supplied by other components. In yet another example, a composition

of the invention contains a combination of lactose, preferably anhydrous lactose, and microcrystalline cellulose, optionally with povidone or another filler/binder. In such a composition (based on uncoated weight), anhydrous lactose is generally present in an amount of about 30% w/w to about 60% w/w, and more desirably, about 30 % w/w, about 32% w/w, about 50% w/w, or about 55% w/w anhydrous lactose. Suitably, in such an uncoated composition, microcrystalline cellulose is present in an amount of about 15% w/w to about 30% w/w of the uncoated composition, and more desirably, about 16% w/w, about 23% w/w, about 25% w/w, about 28% w/w of the uncoated composition.

Dissolution enhancers may be included in the micronized CCI-779 composition (based on uncoated weight) of the invention. Preferably, one or more dissolution enhancers may optionally be present in the composition in an amount of from about 0.5 % w/w to about 10 % w/w, and preferably, from about 5% w/w to about 8% w/w, about 5.5%, about 6% w/w, or 6.5% w/w, based on the weight of an uncoated composition. Examples of dissolution enhancers include surfactants, chelating agents (*e.g.*, EDTA), disintegrants, or combinations thereof.

In one embodiment, the surfactant is about 0.25 % w/w to about 10 % w/w of an uncoated composition, and preferably, about 5% w/w to about 6.5% w/w. In one embodiment, the surfactant is selected from sodium lauryl sulfate (also known as sodium dodecyl sulfate). Other suitable surfactants are well known to those of skill in the art and can be selected including, without limitation, polysorbates including, *e.g.*, polysorbate 80, Polaxamer 188™ surfactant, sodium lauryl sulfate (sodium dodecyl sulfate), salts of bile acids (taurocholate, glycocholate, cholate, deoxycholate, *etc.*) which may be combined with lecithin. Alternatively, ethoxylated vegetable oils, such as Cremophor EL, vitamin E tocopherol propylene glycol succinate (Vitamin E TGPS), polyoxyethylene-polyoxypropylene block copolymers, and poloxamers.

Acceptable antioxidants include, but are not limited to, citric acid, d,l-α-tocopherol, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof. It is expected that the total amount of antioxidants in the formulations of this invention will be in concentrations ranging from 0.001% to 3% w/w, and preferably, about 0.01 w/w to about

1% w/w, and more preferably, about 0.02 % w/w to 0.1% w/w, based on the weight of an uncoated composition. In one embodiment, the antioxidant is a combination of BHA and BHT, which may be in nonmicronized form or preferably, in micronized form.

Chelating agents and other materials capable of binding metal ions, such as ethylene diamine tetra acetic acid (EDTA) and its salts and hydrates (e.g., EDTA calcium disodium hydrous) are useful in the compositions of the invention. Typically, where present, a chelating agent is present in an amount less than 1 % w/w, e.g., about 0.001 % w/w to about 0.01 % w/w, based on the weight of an uncoated composition. In one embodiment, the chelating agent is present in micronized form.

Acceptable pH modifying agents include, but are not limited to citric acid and salts thereof (e.g., sodium citrate), dilute HCl, and other mild acids or bases capable of buffering a solution containing CCI-779 to a pH of 4 to 6. Where present in a composition of the invention, such pH modifiers are present in an amount up to about 1% w/w, *e.g.*, about 0.001% w/w to about 0.1% w/w, based on the weight of an uncoated composition. Optionally, the pH modifier, can be present in micronized form.

Other suitable components include lubricants and/or glidants. In one embodiment, the lubricant and the glidants can each be present in the composition of the invention in an amount of 0.01 wt% to about 1 wt%, about 0.1 wt% to about 2 wt%, or about 0.2 to about 0.5%, of an uncoated composition. In some embodiments, the lubricant and glidants are present in the composition in amounts of less than 1 wt% of an uncoated composition. An example of a suitable lubricant is magnesium stearate and an example of a suitable glidants is silicone dioxide.

Other suitable inert components of the formulation will be readily apparent to one of skill in the art.

The compositions of the invention are formed into a suitable dosing unit for delivery to a patient. Suitable dosing units include oral dosing units, such as a directly compressible tablet, a capsule, a powder and a suspension. The compositions of the invention can also be formulated for delivery by other suitable routes. These dosing units are readily prepared using the methods described herein and those known to those of skill in the art.

In one embodiment, a composition of the invention is prepared by dry mixing micronized CCI-779 with the other additives in a suitable mixer. The powder mix is then directly compressed into unit dose tablets.

Without limitation as to the method of preparation of a composition of the invention, an example of a suitable micronized CCI-779 formulation includes a low amount of povidone. The following weight percentages are based upon an uncoated composition of the invention.

CCI-779, Micronized	6% w/w;
Sodium Lauryl Sulfate	6% w/w;
Povidone	6% w/w;
Lactose Anhydrous	50 % w/w;
Microcrystalline Cellulose	25% w/w;
Croscarmellose Sodium	6% w/w;
Glidant	0.25% w/w; and
Magnesium Stearate	0.25% w/w.

Still a further example of a suitable micronized CCI-779 composition contains a high amount of povidone, with weight percentages based upon an uncoated composition of the invention:

Micronized CCI-779	6 % w/w;
Sodium Lauryl Sulfate	6% w/w;
Povidone	31% w/w;
Lactose Anhydrous	34% w/w;
Microcrystalline Cellulose	16% w/w;
Croscarmellose Sodium	6% w/w ;
Glidant	0.25% w/w; and
Magnesium Stearate	0.5% w/w.

Yet a further example of a suitable micronized CCI-779 dosing unit, with weight percentages based on total uncoated composition, is:

Micronized CCI-779	6% w/w;
Butylated Hydroxyanisol	0.022% w/w;
Butylated Hydroxytoluene	0.05% w/w;
EDTA	0.011% w/w;
Citric acid	0.08% w/w
Poloxamer 188	6% w/w
Lactose Anhydrous	55% w/w
Microcrystalline Cellulose	28 w/w
Croscarmellose Sodium	4% w/w
Glidant	0.25% w/w; and
Magnesium Stearate	0.5% w/w.

Yet another example of a suitable dosing unit, with weight percentages based on total uncoated composition, is:

CCI-779 (Micronized)	6% w/w;
Butylated Hydroxyanisole (Micronized)	0.022% w/w;
Butylated Hydroxytoluene (Micronized)	0.05% w/w;
EDTA Calcium Disodium, Hydrous (Micronized)	0.011% w/w;
Citric Acid Anhydrous (Micronized)	1 % w/w;
Sodium Lauryl Sulfate	6% w/w;
Povidone K-25	65% w/w;
Microcrystalline Cellulose	23% w/w;
Anhydrous Lactose	50% w/w;
Croscarmellose Sodium	6 % w/w;
Colloidal Silicone Dioxide	0.25% w/w; and
Magnesium Stearate	0.50% w/w.

Optionally, the tablets are film-coated. Suitable film-coatings are known to those of skill in the art. For example, the film-coating can be selected from among suitable polymers such as hydroxypropylmethylcellulose, ethyl cellulose, polyvinyl alcohol, and combinations thereof. Such coatings may also contain placticizers and other desirable components. In one embodiment, the coatings are inert. Other suitable film-coatings can be readily selected by one of skill in the art. Where applied, the weight percent of the film coat is generally in the range of 1 % w/w to 6 % w/w, about 2 % w/w, about 3% w/w, about 4% w/w or about 5% w/w, and more desirably, about 2% w/w, based on the total weight of the coated composition.

The invention further provides a method of delivering CCI-779 to a patient, said method comprising the step of administering a micronized CCI-779 dosing unit according to the invention.

It is contemplated that when the formulations of this invention are used as an immunosuppressive or anti-inflammatory agent, they can be administered in conjunction with one or more other immunoregulatory agents. Such other antirejection chemotherapeutic agents include, but are not limited to azathioprine, corticosteroids, such as prednisone and methylprednisolone, cyclophosphamide, cyclosporin A, FK-506, OKT-3, and ATG. By combining one or more of the formulations of the present invention with such other drugs or agents for inducing immunosuppression or treating inflammatory conditions, lesser amounts of each of the agents may be required to achieve the desired effect. See, e.g., *Transplantation Proc.* **23**: 507 (1991).

The dosage requirements may vary the severity of the symptoms presented and the particular subject being treated. Daily oral dosages of micronized CCI-779 can be 0.05 to 30 mg, about 1 mg to 25 mg, about 5 mg to about 10 mg. In one example, when micronized CCI-779 is used in combination therapy at daily doses in the range of 0.5 to 10 mg. In another example, micronized CCI-779 is used in monotherapy at daily doses in the range of 1 mg to 30 mg. In other embodiments, daily doses are 2 to 5 mg when micronized CCI-779 is used in combination therapy, and 5 to 15 mg when micronized CCI-779 is used as monotherapy.

Treatment can be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages will be determined by the administering physician based on experience with the individual subject treated. In general, the formulations of this invention are most desirably administered at a concentration that will generally afford effective results without causing any unacceptable harmful or deleterious side effects.

The following examples of illustrative of specific embodiments of the invention and are not a limitation on the present invention. The following provide representative examples of the formulations of this invention. These examples are illustrative only, and do not limit the invention.

EXAMPLE 1: Directly Compressible Tablet Formulations Prepared By Employing Non-Micronized CCI-779

The compositions included in this example employed non-micronized CCI-779 and were prepared with or without a surfactant. The tabletting was carried out by dry blending and direct compression method.

Table 1: Quantitative Composition of CCI-779 Tablets, 5mg Containing Non-Micronized CCI-779 without Surfactant

Ingredients	Percent Wt/Wt	Mg/tablet	Function
CCI-779, non-micronized	1.44	5.00	Active
Butylated Hydroxyanisol, NF	0.1	0.35	Antioxidant
Butylated Hydroxytoluene, NF	0.05	0.18	Antioxidant
EDTA, USP	0.01	0.04	Chelating agent
Sodium Citrate Anhydrous	0.75	2.62	pH modifier
Citric acid, Anhydrous USP	0.25	0.87	pH modifier
Povidone, K17, USP	7.14	24.99	Filler/ Binder
Lactose Anhydrous, NF	34.30	120.05	Filler

Microcrystalline Cellulose,NF (Avicel PH 112)	51.46	180.11	Filler/ Binder
Croscarmellose Sodium, NF	4.00	14.0	Disintegrant
Magnesium Stearate, NF	0.50	1.75	Lubricant
Total	0.05	350	

Table 2: Quantitative Composition of CCI-779 Tablets, 25 mg Containing Non-Micronized CCI-779 and Surfactant

Ingredients	Percent Wt/Wt	mg/tablet	Function
CCI-779, non-micronized	6.25	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, K17, USP	31.25	125.00	Filler/ Binder
Lactose Anhydrous, NF	33.75	135.00	Filler
Microcrystalline Cellulose,NF (Avicel PH 112)	16.375	65.50	Filler/ Binder
Croscarmellose Sodium, NF	6.0	24.00	Disintegrant
Silicone dioxide (Aerosil 200)	0.25	1.00	Glidant
Magnesium Stearate, NF	0.50	2.00	Lubricant
Total	100	400	

CCI-779 tablets prepared by direct compression of nonmicronized CCI-779 with standard excipients and fillers, in the presence or absence of surfactants yielded tablets that did not exhibit rapid and complete drug release, and thereby resulted in an unsuitable formulation for CCI-779.

EXAMPLE 2: Directly Compressible Tablet Formulations Prepared By Employing Micronized CCI-779, Sodium Lauryl Sulphate And Povidone

The tablet formulations for this example are manufactured using the following protocol.

Microcrystalline cellulose (Avicel PH-112) and povidone K-25 are passed through a screen and transferred to a V-blender of suitable size. Micronized CCI-779 is preblended with a portion of lactose anhydrous separately, then passed through a screen and added to the V-blender. Sodium lauryl sulfate, croscarmellose sodium, silicone dioxide and a portion of lactose anhydrous are passed through a screen and transferred to the V blender. The remaining lactose anhydrous is passed through a screen and transferred it to V-blender and the lids are closed. The material is blended without activation of intensifier bar. Magnesium stearate is passed through a screen, premixed with a weight equivalent portion of powder, blended from V-blender, transferred to the lubricant premix to V-blender and blended without activation of intensifier bar. The final blend is compressed using a tablet press with suitable tooling.

Table 3: Quantitative Composition of CCI-779 Tablets, 25 mg Containing Low level of Povidone

Ingredients	**Percent Wt/Wt**	**Mg / tablet**	**Function**
CCI-779, Micronized	6.250	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, USP K25	6.250	25.00	Filler/ Binder
Lactose Anhydrous, NF	50.583	202.33	Filler
Microcrystalline Cellulose,NF (Avicel PH 112)	24.543	98.172	Filler/ Binder
Croscarmellose Sodium, NF	6.000	24.00	Disintegrant
Aerosil 200, NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant

Total	100	400	

Table 4: Quantitative Composition of CCI-779 Tablets, 25 mg Containing High Level of Povidone

Ingredients:	Percent Wt/Wt	Mg / tablet	Function
CCI-779, Micronized	6.250	25.00	Active
Sodium Lauryl Sulfate, NF	5.625	22.50	Surfactant
Povidone, USP K-25	31.250	125.00	Filler/ Binder
Lactose Anhydrous, NF	33.750	135.00	Filler
Microcrystalline Cellulose, NF (Avicel PH 112)	16.375	65.50	Filler/ Binder
Croscarmellose Sodium, NF	6.000	24.00	Disintegrant
Silicone dioxide (Aerosil 200), NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant
Total	100	400	

EXAMPLE 3: Directly Compressible Tablet Formulations Prepared By Employing Micronized CCI-779 And Poloxamer As Surfactant

The table formulations for this example are manufactured according to the following protocol.

Pass the poloxamer 188, microcrystalline cellulose (Avicel PH-112) and a portion of anhydrous lactose through a screen and blend. Mill the blend containing poloxamer with the help of a Fitz mill and transfer it to a V-blender of suitable size.

Preblend a portion of anhydrous lactose with micronized butylated hydroxyanisole, butylated hydroxytoluene, EDTA calcium disodium, hydrous, and citric acid anhydrous. Then add CCI-779 to this preblend, mix and add to the V-blender.

Take a portion of anhydrous lactose, croscarmellose sodium, and colloidal silicon dioxide (Aerosil 200) and pass through a screen, blend and transfer it to V-blender. Pass the remaining anhydrous lactose through a screen and transfer it to V-blender. Close the lids and blend the material without activation of the intensifier bar. Pass magnesium stearate through a screen, premix with a weight equivalent portion of powder blend and transfer the lubricant premix to V-blender and blend without the activation of the intensifier bar. Compress the final blend using a tablet press equipped with suitable tooling.

Table 5: Quantitative Composition of CCI-779 Tablets, 25 mg Containing Poloxamer

Ingredients:	**Percent Wt/Wt**	**Mg / tablet**	**Function**
CCI-779, Micronized	6.250	25.00	Active
Butylated Hydroxyanisol, NF	0.022	0.088	Antioxidant
Butylated Hydroxytoluene, NF	0.050	0.20	Antioxidant
EDTA, calcium disodium hydrous, USP	0.011	0.044	Chelating agent
Citric acid, Anhydrous USP	0.080	0.32	pH modifier
Poloxamer 188, NF	6.250	25.00	Surfactant
Lactose Anhydrous, NF	55.060	220.24	Filler
Microcrystalline Cellulose,NF (Avicel PH 112)	27.527	108.58	Filler/ Binder
Croscarmellose Sodium, NF	4.000	16.00	Disintegrant
Aerosil 200, NF	0.250	1.00	Glidant
Magnesium Stearate, NF	0.500	2.00	Lubricant
Total	100	400	

EXAMPLE 4 - Dissolution of CCI-779 Tablets

All the CCI-779 tablet formulations were evaluated by dissolution test. Dissolution test was performed using USP method II in 500 ml of 0.4% sodium lauryl sulfate at 75 RPM paddle speed. Table 6 summarizes the dissolution characteristics of the neat CCI-779 API and various tablet formulations of CCI-779.

Table 6: Dissolution Data of CCI-779 Tablet Formulations

	Percent CCI-779 Dissolved					
Time (min)	**CCI-779 (API) L21296-119***	**Batch Table 1**	**Batch Table 2**	**Batch Table 4**	**Batch Table 3**	**Batch Table 5**
10	4	31	30	56	87	90
20	9	42	58	87	96	94
30	14	50	74	95	98	95
45	21	56	86	97	99	97
60	----	----	93	98	100	97

* Pure CCI-779 was filled in hard gelatin capsules to test its dissolution.

Dissolution results in Table 6 show that the tablets prepared by direct compression method (Table 1) did not exhibit rapid and complete drug release. Even the addition of a surfactant (Table 2) did not enhance dissolution of CCI-779 from these tablets. However, the directly compressible compositions of the invention containing micronized CCI-779 (Tables 3, 4, 5) exhibited fast and complete drug release.

EXAMPLE 5: Bioavailability of CCI-779 in Human - Evaluation of Oral Dosage Forms

The three prototype tablet formulations containing micronized CCI-779 (Tables 3, 4 and 5) were further evaluated for absorption in human volunteers. A

previously used clinical formulation prepared by wet granulation process was used as a control. The results of this biostudy are shown in Table 7 below.

The following chart relates the treatments of the bio-study to the compositions in this document and respective batch numbers of clinical batches:

Treatment	**Composition in**
High Povidone	Table 3
Low Povidone	Table 4
Poloxamer	Table 5
Control	--

Table 7: Pharmacokinetic Parameters (± S.D) Following Oral Administration of CCI-779 Tablet, 25 mg to Human Volunteers

Treatment	**$t_{1/2}$ (hr)**	**C_{max} (ng/ml)**	**T_{max} (hr)**	**$AUC_{0-\infty}$ (ng.hr/ml)**
Low Povidone	79.5 (17.0)	17.06 (8.07)	2.16 (0.9)	554.6 (187.7)
High Povidone	81.8 (23.7)	18.7 (9.6)	2.86 (2.1)	575.4 (190)
Poloxamer	77.9 (18.7)	11.36 (7.0)	4.08 (2.12)	544.0 (150.4)
Control	81.8 (17.2)	27.458 (12.4)	1.39 (0.637)	664.1 (217.5)

EXAMPLE 6: CCI-779 10 mg Film Coated Tablet Formulation Prepared By Employing Micronized CCI-779

Table 8: Quantitative Composition of CCI-779 Tablets, 10 mg

Ingredients:	**Percent Wt/Wt**	**mg / tablet**	**Function**
CCI-779, Micronized	6.25	10.00	Active
Butylated Hydroxyanisol, Micronized	0.022	0.035	Antioxidant
Butylated Hydroxytoluene, Micronized	0.050	0.080	Antioxidant
EDTA, Calcium Disodium, Hydrous, Micronized	0.011	0.044	Chelating agent
Citric acid, Anhydrous, Micronized	1.038	1.661	pH modifier
Sodium Lauryl Sulfate	5.625	9.00	Surfactant
Povidone K-25	6.25	10.00	Filler/Binder
Microcrystalline Cellulose (Avicel PH 112)	23.483	37.573	Filler/ Binder
Anhydrous Lactose	50.521	80.833	Filler
Croscarmellose Sodium	6.00	9.60	Disintegrant
Colloidal Silicon Dioxide (Aerosil 200)	0.25	0.40	Glidant
Magnesium Stearate (Vegetable Extract)	0.50	0.80	Lubricant
Total (Core Tablet Weight)	100	160.00	
Opadry II® White 85F18422, HPMC and other inert components	3.00	4.95	

EXAMPLE 7: CCI-779 30 mg Film Coated Tablet Formulation Prepared By Employing Micronized CCI-779

Table 9: Quantitative Composition of CCI-779 Tablets, 30 mg

Ingredients:	**Percent Wt/Wt**	**mg / tablet**	**Function**
CCI-779, Micronized	6.25	30.000	Active
Butylated Hydroxyanisol, Micronized	0.022	0.105	Antioxidant
Butylated Hydroxytoluene, Micronized	0.050	0.240	Antioxidant
EDTA, Calcium Disodium, Hydrous, Micronized	0.011	0.054	Chelating agent
Citric acid, Anhydrous, Micronized	1.038	4.983	pH modifier
Sodium Lauryl Sulfate	5.625	27.00	Surfactant
Povidone K-25	6.25	30.000	Filler/Binder
Microcrystalline Cellulose (Avicel PH 112)	23.483	112.718	Filler/ Binder
Anhydrous Lactose	50.521	242.501	Filler
Croscarmellose Sodium	6.00	28.800	Disintegrant
Colloidal Silicon Dioxide (Aerosil 200)	0.25	1.200	Glidant
Magnesium Stearate (Vegetable Extract)	0.50	2.400	Lubricant
Total (Core Tablet Weight)	100	480.00	
Opadry II® White 85F18422, HPMC and other inert components	2.00	9.796	

The documents cited throughout this specification are hereby incorporated by reference. Minor variations and modifications to the methods and materials set forth in the foregoing detailed description and illustrative examples will be readily apparent to those of skill in the art and are encompassed within the scope of the invention.

CLAIMS:

1. A pharmaceutical composition comprising micronized CCI-779.

2. A pharmaceutical composition according to claim 1, wherein the micronized CCI-779 has a particle size range of 10% are less than or equal to about 3 μ, 50% are about 10 μ, and 90% are less than or equal to about 20 μ as determined by Malvern method.

3. A pharmaceutical composition according to claim 1, wherein the micronized CCI has a particle size range of 10% are less than or equal to about 2 μ, 50% are about 5 μ, and 90% are less than or equal to about 16 μ as determined by Malvern method.

4. A pharmaceutical composition according to any one of claims 1 to 3 which is an immediate release solid dosage form.

5. A composition according to any one of claims 1 to 3 selected from the group consisting of a directly compressible tablet, a capsule, a powder and a suspension.

6. A pharmaceutical composition according to any one of claims 1 to 5, wherein the micronized CCI-779 is present in an amount from 5 % w/w to 10% w/w of the composition.

7. A pharmaceutical composition according to any one of claims 1 to 6, further comprising:

about 5% w/w to about 6.5% w/w surfactant;
about 75 % w/w to about 85% w/w filler/binder;
about 4% w/w to about 6% w/w disintegrant.

8. A pharmaceutical composition according to claim 7, wherein the surfactant is sodium lauryl sulfate.

9. A pharmaceutical composition according to claim 7 or claim 8, wherein the filler/binder is selected from the group consisting of povidone, lactose, and microcrystalline cellulose, and mixtures thereof.

10. A pharmaceutical composition according to any one of claims 7 to 9, wherein the disintegrant is croscarmellose sodium.

11. A pharmaceutical composition according to any one of claims 1 to 11, further comprising one or more antioxidants, a chelating agent, and/or a pH modifier.

12. A pharmaceutical composition according to claim 11, wherein any one of the one or more antioxidants, a chelating agent and/or pH modifier is micronized.

13. An oral CCI-779 dosing unit comprising micronized CCI-779, a surfactant, a filler/binder, a distintegrant, a glidant, and a lubricant.

14. An oral CCI-779 dosing unit according to claim 13, wherein the micronized CCI-779 has a particle size range of 10% are less than or equal to about 2 μ, 50% are about 5 μ, and 90% are less than or equal to about16 μ as determined by Malvern method.

15. An oral CCI-779 dosing unit according to claim 13 or claim 14, wherein the micronized CCI-779 is present in an amount from 0.1 % w/w to 10% w/w of the dosing unit, based on total uncoated weight.

16. An oral CCI-779 dosing unit according to any one of claims 13 to 15, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate and Polaxamer 188 surfactant.

17. An oral CCI-779 dosing unit according to any one of claims 13 to 16, wherein the filler is selected from the group consisting of microcrystalline cellulose, anhydrous lactose, povidone, and mixtures thereof.

18. An oral CCI-779 dosing unit according to any one of claims 13 to 17, wherein the disintegrant is croscarmellose sodium.

19. An oral CCI-779 dosing unit according to any one of claims 13 to 18, wherein the lubricant is magnesium stearate.

20. An oral CCI-779 dosing unit according to claim 15, comprising:

6 to 7 % w/w	micronized CCI-779;
5 to 7% w/w	surfactant;
50 to 90% w/w	filler;
3 to 8% w/w	disintegrant;
less than 1% w/w	glidant; and
less than 1% w/w	lubricant.

21. An oral CCI-779 dosing unit according to claim 20 comprising:

CCI-779, Micronized	6.25% w/w;
Sodium Lauryl Sulfate	5.6% w/w;
Povidone	6.25% w/w;
Lactose Anhydrous	50 % w/w;
Microcrystalline Cellulose	25% w/w;
Croscarmellose Sodium	6% w/w;
Glidant	0.25% w/w; and
Magnesium Stearate	0.25% w/w.

22. An oral CCI-779 dosing unit according to claim 20 comprising:

Micronized CCI-779	6 % w/w;
Sodium Lauryl Sulfate	6% w/w;

Povidone	31% w/w;
Lactose Anhydrous	34% w/w;
Microcrystalline Cellulose	16% w/w;
Croscarmellose Sodium	6% w/w ;
Glidant	0.25% w/w; and
Magnesium Stearate	0.5% w/w.

23. An oral CCI-779 dosing unit according to claim 20 comprising:

Micronized CCI-779	6% w/w;
Butylated Hydroxyanisol	0.022% w/w;
Butylated Hydroxytoluene	0.05% w/w;
EDTA	0.011% w/w;
Citric acid	0.08% w/w
Poloxamer 188	6% w/w
Lactose Anhydrous	55% w/w
Microcrystalline Cellulose	28 w/w
Croscarmellose Sodium	4% w/w
Glidant	0.25% w/w; and
Magnesium Stearate	0.5% w/w.

24. An oral CCI-779 dosing unit according to claim 20 comprising:

CCI-779 (Micronized)	6% w/w;
Butylated Hydroxyanisole (Micronized)	0.022% w/w;
Butylated Hydroxytoluene (Micronized)	0.050% w/w;
EDTA Calcium Disodium, Hydrous (Micronized)	0.011% w/w;
Citric Acid Anhydrous (Micronized)	1% w/w;
Sodium Lauryl Sulfate	6% w/w;
Povidone	6% w/w;
Microcrystalline Cellulose	24% w/w;

Anhydrous Lactose	51% w/w;
Croscarmellose Sodium	6% w/w;
Colloidal Silicone Dioxide	0.25% w/w; and
Magnesium Stearate	0.5% w/w.

25. An oral CCI-779 dosing unit according to any of claims 13 to 24, wherein said dosing unit further comprises a seal coat.

26. An oral CCI-779 dosing unit according to claim 25, wherein said seal comprises about 2% w/w hydroxypropylmethylcellulose of the coated composition.

27. An oral CCI-779 dosing unit according to any of claims 13 to 26, wherein said dosing unit is selected from the group consisting of a tablet and a capsule.

28. A method of delivering CCI-779 to a patient, said method comprising the step of administering an oral CCI-779 dosing unit according to any of claims 13 to 27.

29. Use of micronized CCI-779 in preparing a medicament.

30. Use according to claim 29, wherein said micronized CCI-779 is directly compressed to form the medicament.

31. Use of micronized CCI-779 in preparing an oral dosing unit according to any of claims 13 to 27.