(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 December 2015 (17.12.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/189807 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/17* (2006.01)
A61K 9/24 (2006.01) *A61K 31/495* (2006.01)
A61K 9/28 (2006.01) *A61K 31/66* (2006.01)
A61K 31/16 (2006.01)

(21) International Application Number:
PCT/IB2015/054447

(22) International Filing Date:
12 June 2015 (12.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1596/DEL/2014 12 June 2014 (12.06.2014) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: BI-LAYER TABLET FORMULATIONS OF CYCLOPHOSPHAMIDE AND CAPECITABINE AND HIGHLY FRACTIONATED METRONOMIC ADMINISTRATION THEREOF

(57) Abstract: The present invention relates to a convenient and stable bi-layer oral tablet formulation of cyclophosphamide and capecitabine. The methods of preparation of these formulations are described herein. Moreover, such formulations are useful for metronomic administration to treat cancer, e.g., breast cancer.

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BI-LAYER TABLET FORMULATIONS OF CYCLOPHOSPHAMIDE AND CAPECITABINE AND HIGHLY FRACTIONATED METRONOMIC ADMINISTRATION THEREOF

BACKGROUND OF THE INVENTION

The cervix, breast and oral cavities are the leading sites of cancers in women in developing countries. For example, the incidence rates have increased by 12% in developing countries like India from 1985 to 2005, and are on the upward trend. Although greater than twice the number of women in the United States are currently diagnosed with breast cancer than in those of a developing country like India, if no significant measures are taken such rates are expected to rise to U.S. levels by 2030.

Distinction of incidence rates in such developing countries may be even further highlighted between urban and rural areas. The urban areas show 4 to 5 times greater incidence of breast cancer, which is believed to be most predominantly due to lifestyle differences. However, while breast cancer incidence in developing countries is lower than in developed countries, the mortality rate is much higher (*e.g.*, 0.48 in India vs 0.25 in North America). This is, in major part, due to the inaccessibility of proper medication to those patients at the bottom of the healthcare system pyramid, including those patients from villages and rural areas with very little health insurance and coverage, and little access to oncology care and treatments.

The problems of this patient pool are further exacerbated by a high patient to doctor ratio that focuses doctor attention on symptomatic relief and cost control issues. Further, lower education standards (*e.g.*, including health information), increases the numbers of self healers who avoid seeking proper medical care. Proper medical care, including appropriate pharmaceutical agents, is often directly linked to access to doctors, without whom such patients cannot obtain these medicines. Moreover, patients who do seek medical care from a doctor often find that the required medications have poor stability under local storage conditions and can only be purchased in limited quantities, resulting in product availability issues.

As such, there is a need to develop safe and effective medication that addresses these issues for patients with cancer in developing countries.

SUMMARY OF THE INVENTION

Accordingly, the present invention relates to orally available formulations that provide a combination of two chemotherapeutic agents at doses that are: (1) convenient for the patient (*e.g.*, no need to see a doctor frequently); (2) safe (*e.g.*, minimal side effects vs. existing dosage forms; reduced need for re-hospitalizations for managing side effects); (3) effective (*e.g.*, efficacy similar to what is obtain with current standard of care); (4) simple in prescription for both patients and doctors (*e.g.*, no need for a complex training for doctors); and (5) stable at room temperature for a reasonable period of time. In particular, the present invention relates to a convenient and stable bi-layer oral tablet formulation of cyclophosphamide and capecitabine. The methods of preparation of these formulations are described herein. Moreover, such formulations are useful for metronomic administration to treat cancer, *e.g.*, breast cancer.

In developing countries, this metronomic administration is intended to reduce the common adverse effects very often associated with standard administration of these chemotherapeutic agents. Common adverse effects, such as nausea, diarrhea, neutropenia, hand-foot syndrome, mucositis, and cystitis, can often result in lowered compliance with standard therapeutic administration of cyclophosphamide or capecitabine, alone, or in combination. These non-compliance issues may further require strict doctor oversight, and in regions where doctor accessibility is lowered, result in management of adverse effects rather than reduction or prevention of disease.

One aspect of the invention provides a bi-layer oral tablet formulation comprising a fixed dose combination of cyclophosphamide, *e.g.*, cyclophosphamide-SG, and capecitabine, wherein the cyclophosphamide is in a first layer and the capecitabine is in a second layer.

Another aspect of the invention provides a method of treatment of cancer, *e.g.*, breast cancer, comprising metronomic administration of a formulation of the present invention to a subject. In a particular aspect, the metronomic administration is highly fractionated metronomic administration of the formulation. In a particular aspect, the administration is

not combined with any additional treatment or therapeutic agent. In a particular aspect, the method of treatment is the primary method of treatment, and the subject has not been pretreated with another method of treatment.

In another aspect, the invention provides a method of preparation of the bi-layer oral tablet formulations of the present invention, comprising compressing a first layer of cyclophosphamide with a second layer of capecitabine in a fixed dose combination.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a convenient and stable bi-layer oral tablet formulation of cyclophosphamide and capecitabine. The methods of preparation of these formulations are described herein. Moreover, such formulations are useful for metronomic administration to treat cancer, *e.g.*, breast cancer.

The present invention, including formulations, methods of preparation, and methods of use will be described with reference to the following definitions that, for convenience, are set forth below. Unless otherwise specified, the below terms used herein are defined as follows:

I. Definitions

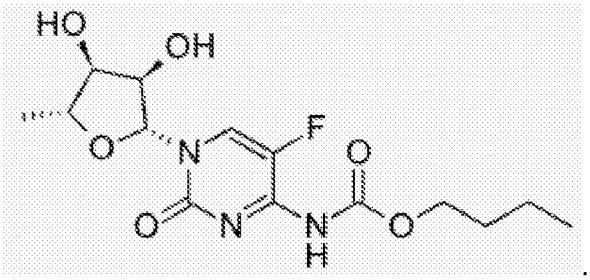
As used herein, the term “a,” "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

The term “about,” is used herein to indicate variability of ± 1% surrounding the designated value.

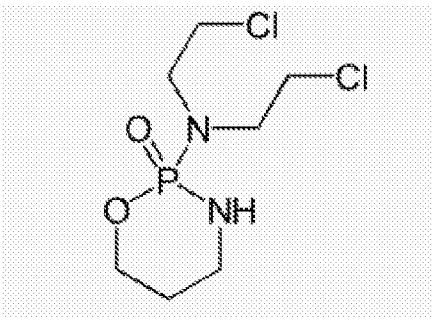
The terms “Acceptance Value” and “AV,” are used interchangeably herein, and each is art-recognized to define the uniformity value using a standard calculation performed for tablet dosage forms, *e.g.*, as defined in chapter 905 of United States Pharmacopeia entitled Uniformity of Dosage Units.

The language "advanced slugging protocol" is used herein to describe a novel formulation technique that utilizes a method of embedding a low melting API with suitable excipients that absorb the impact of milling, and that act as a protective coating to the API. In addition, the lower relative speeds and the elimination of the need for solvent by milling of the compressed slug affords a reduction of heat generation and an elimination of aqueous granulating materials associated with current granulation processes. In certain embodiments, the advanced slugging protocol is performed according to the methods described herein.

The term "capecitabine" is art-recognized, and is used herein to describe Capecitabine USP, or regulatory quality pentyl [1-(3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)-5-fluoro-2-oxo-1*H*-pyrimidin-4-yl]carbamates (*i.e.*, the active ingredient of Xeloda):



The term "cyclophosphamide" is art-recognized, and is used herein to describe Cyclophosphamide USP, or regulatory quality (*RS*)-*N*,*N*-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide (*i.e.*, the active ingredient of Endoxan, Cytoxan, Neosar, Procytox, and Revimmune):



The terms "cyclophosphamide-SG," and "cyclophosphamide-Second Generation," are used interchangeably herein to describe a cyclophosphamide formulation, wherein the cyclophosphamide contained therein possesses substantially improved stability, or

degradation resistance, over known cyclophosphamide formulations; improved uniformity over known cyclophosphamide formulations; and/or impurity profiles that are characterized by a substantial reduction in impurities generated during the formulation process as compared with known formulation processes. Accordingly, in certain embodiments, the cyclophosphamide-SG is degradation resistant. In certain embodiments, the cyclophosphamide-SG is uniformity enhanced. In certain embodiments, the cyclophosphamide-SG is purity enhanced.

An "excipient," as used herein, is any component of an oral dosage form that is not an active pharmaceutical ingredient (*i.e.*, not capecitabine or cyclophosphamide). Excipients include binders, lubricants, diluents, disintegrants, coatings, barrier layer components, glidants, and other components. Excipients are known in the art (see HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, FIFTH EDITION, 2005, edited by Rowe et al., McGraw Hill). Some excipients serve multiple functions or are so-called high functionality excipients. For example, talc may act as a lubricant, an anti-adherent, and a glidant. See Pifferi et al., 2005, "Quality and functionality of excipients" Farmaco. 54:1-14; and Zeleznik and Renak, Business Briefing: Pharmagenerics 2004.

The language "fixed dose combination" is art-recognized, and is used herein to describe a predetermined combination of drugs and respective dosages.

The term "metronomic" is art-recognized, and is used herein to describe a regimen of administration of an active pharmaceutical ingredient (API) that provides frequent, *e.g.*, once daily, low-dose chemotherapy over a longer period versus the standard administration of the same API, *e.g.*, to try to expose tumor cells to minimized concentrations of chemotherapy drugs for as long as possible. Highly fractionated metronomic administration, as compared with existing metronomic administration, further minimizes this concentration by providing dose amounts that are significantly less than the amounts used for accepted metronomic administration (*e.g.*, administered API amounts that are less than the accepted metronomic doses by greater than 30%, *e.g.*, greater than 40%, *e.g.*, greater than 50%). For example, such amounts are fractions of well-known metronomic dose amounts of the API used alone or in combination with other active pharmaceutical ingredients, and are intended to reduce further or even eliminate any known adverse effects of the API. This effective elimination of

adverse effects could reduce the amount of doctor oversight required while on these medications.

The term "metronomically effective amount," as used in the expression "metronomically effective amount of cyclophosphamide," is used herein to describe amounts of capecitabine or cyclophosphamide sufficient to attain a therapeutic benefit with minimized/reduced toxicity and/or side effects as compared with side effects produced at standard dosing levels.

The term "milling" is art-recognized, and is used herein to describe the act of grinding or crushing of material into smaller regulated particle sizes. The term "co-milling" is used when milling of two or more materials is performed at the same time.

The language "patient compliance" is used herein to describe a patient's consistent and rigorous conformity with a course of treatment prescribed. Such compliance is very often affected by side effects of drugs prescribed at standard dosing levels.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without contributing undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio.

The term "slugging" is art-recognized, and is used herein to describe a process of compressing a material into a compressed mass using punches, *e.g.*, a substantially round compressed mass using round punches. This compressed mass is known as a "slug."

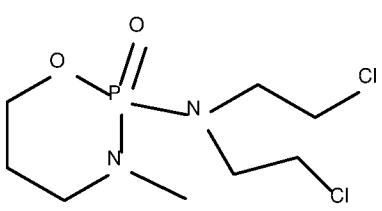
The term "therapeutically effective amount" is art-recognized, and is used herein to describe the amount of an agent, *e.g.*, cyclophosphamide and/or capecitabine, that is effective to result in a therapeutic effect, whether that therapeutic effect is seen via a single treatment or a cumulative course of treatment. In certain embodiments, a therapeutically effective amount includes metronomically effective amounts.

The term "layer" in the context of a unit dosage form is a physical region of a tablet or other dosage form. Two layers of a unit dosage form substantially distinct compartments if there exists a recognizable demarcation between the two components, even though they may be in direct physical contact with one another.

The term "stable," as used herein, refers to a composition in which the active pharmaceutical ingredients (i.e., capecitabine and cyclophosphamide) are present in an amount of at least 90%, *e.g.*, at least 95%, *e.g.*, at least 96%, *e.g.*, at least 97%, *e.g.*, at least 98%, *e.g.*, at least 99%, *e.g.*, or at least 99.5% of the originally label specified amount for each such ingredient after a specified period of time (*e.g.*, 3 months) and under specified conditions (*e.g.*, temperature and relative humidity). Such materials are considered to be "degradation resistant," as they resist degradation of the active agent. In certain embodiments, the term "stable" also refers to the presence of no more than (NMT) 3%, *e.g.*, no more than 2%, *e.g.*, no more than 1%, *e.g.*, no more than 0.9%, *e.g.*, no more than 0.8%, *e.g.*, no more than 0.7%, *e.g.*, no more than 0.6% of any one of the well-known/characterized impurities (Impurity A, B, C, or unspecified for Capecitabine; or Impurity A, B, C, D, or unspecified for Cyclophosphamide) after a specified period of time and under specified conditions. In a particular embodiment, the upper limits of these impurities for the formulations of the present invention are defined within the following table:

Impurities for Capecitabine	Stability Limits (% w/w)
Impurity-A	NMT 1.0
Impurity-B	NMT 1.0
Impurity-C	NMT 1.0
Individual unspecified impurity	NMT 0.20
Total Impurities	NMT 2.0
Impurities for Cyclophosphamide	Stability Limits (% w/w)
Impurity-A	NMT 1.5
Impurity-B	NMT 3.5
Impurity-C	NMT 1.5
Impurity-D	NMT 2.0
Individual unspecified impurity	NMT 1.0
Total Impurities	NMT 6.0

Such materials are considered "purity enhanced," as their impurity content is comparatively reduced. For example, in certain embodiments, Cyclophosphamide Impurity B:



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may be comparatively reduced.

The language "uniformity enhanced" is used herein to describe a uniform formulation that demonstrates an active pharmaceutical ingredient (API) is greater than 95%, *e.g.*, greater than 96%, *e.g.*, greater than 97% uniformly distributed in the formulation. Such uniformity may be determined and compared using Acceptance Value calculations, *e.g.*, as described herein.

The term "# mesh" and symbol "#" as used in the expressions "30# mesh" or "30#" indicate the presence of a mesh screen, wherein the number before the # symbol is used to indicate the size of the mesh used.

II. Tablet Formulations of the Invention

The present invention provides a fixed-dose combination drug comprising capecitabine and cyclophosphamide. In certain embodiments, the cyclophosphamide layer of the bi-layer tablet formulations of the present invention display significantly improved stability and/or impurity profiles over known formulations of cyclophosphamide. In particular, the pharmaceutical formulations in accordance with the present invention comprise Capecitabine and Cyclophosphamide in a single bi-layer unit dosage form.

Generally, a fixed-dose combination of drugs intended for immediate release is prepared by either making a powder mixture or a co-granulate of the two active ingredients with the necessary excipients, normally keeping the basic formulation of the corresponding mono-drug preparation and simply adding the second drug component.

With a combination of capecitabine and cyclophosphamide, this approach was not feasible due to the waxy solid nature, lack of stability at room temperature, and the low melting point of cyclophosphamide. Major challenges during the development of the formulations of the invention included:

<u>Uniformity of Cyclophosphamide</u>

There is a significant difference in the doses of the two active pharmaceutical ingredients (APIs) and thus achieving uniformity of cyclophosphamide was a challenge. Such uniformity, *e.g.*, of cyclophosphamide, is important for the product to match the target drug product specification, and is an important quality control parameter.

Sticking tendency during compression

Sticking is a significant problem during compression where small particles of the granules stick to the punches and produce improper surface. Cyclophosphamide tends to show sticking due it its low melting point and waxy nature. Achieving a process that sufficiently mitigated sticking was a significant challenge.

Uneven surface during coating

In certain embodiments, the dosage form is a film coated product. The film coating used is an aqueous based composition. Due to the affinity of the cyclophosphamide API for water, during the coating process the tablet surface would develop an uneven surface. Smooth surface on any film coated tablet indicates proper process and composition control of the coating dispersion and the film coating process. It also indicates that the film coating is evenly distributed on the tablet surface and is an important quality control parameter.

Stability of the formulation

Cyclophosphamide is prone to degradation via a ring opening process that is triggered by temperature, moisture and/or oxidation. The recommended storage condition of cyclophosphamide is 2-8°C. However, the developed formulation needed to tolerate temperatures of 21 to 25°C. Further, it had to tolerate film coated using an aqueous process, which causes it to expose to humidity and temperature.

Therefore, an orally available fixed dose combination drug which combines the features of pharmacologic efficacy, adequate drug stability and a reliable and robust method of manufacture has to overcome a number of technical problems. It is an object of the

present invention to provide such a fixed dose combination drug.

As such, in one embodiment, the invention features a bi-layer oral tablet formulation comprising a fixed dose combination of cyclophosphamide and capecitabine, wherein the cyclophosphamide is in a first layer and the capecitabine is in a second layer.

In another embodiment, the invention features a bi-layer oral tablet formulation comprising a first layer of cyclophosphamide-SG, and a second layer of capecitabine, wherein the first and second layer are compressed to form a single bi-layer oral tablet.

In certain embodiments of the invention, the first layer and the second layer are compressed to form a single bi-layer oral tablet.

In certain embodiments of the invention, the cyclophosphamide in the first layer is cyclophosphamide-SG.

In certain embodiments of the invention, the single bi-layer tablet is film coated, *e.g.*, wherein the film coating is applied by spray coating.

In certain embodiments of the invention, the tablet formulation comprises (i) a metronomically effective amount of cyclophosphamide and (ii) a metronomically effective amount of capecitabine.

In certain embodiments of the invention, the first layer and the second layer each is separately prepared and formed into a layer through compression prior to being compressed together to form a single, bi-layer oral tablet.

In certain embodiments of the invention, the two layers are compressed to produce a smooth surface suitable for coating.

In certain embodiments of the invention, there is no barrier layer interposed between the first layer and the second layer.

In certain embodiments of the invention, the amount of capecitabine is about 600 mg or less.

In certain embodiments of the invention, the amount of cyclophosphamide is about 40 mg or less.

In certain embodiments of the invention, the capecitabine is present in about 600 mg, and the cyclophosphamide is present in about 40 mg.

In certain embodiments of the invention, the capecitabine is present in about 300 mg, and the cyclophosphamide is present in about 20 mg.

A further object of the present invention is to obtain a formulation which gives rise to high patient compliance, by reducing the number of dosage unit forms of administration that need to be taken, such as tablets. In addition, greater patient compliance may be obtained by administering formulations in an amount and/or in a course of administration that reduces adverse events.

In certain embodiments oral dosage forms of the invention are formulated so that release of both active pharmaceutical ingredients (APIs) occurs (or begins to occur) at about the same time. "At about the same time" means that release of one API begins within 5 minutes of the beginning of release of the second API, *e.g.*, within 4 minutes, *e.g.*, within 3 minutes, *e.g.*, within 2 minutes, *e.g.*, essentially simultaneously. "At about the same time" can also mean that release of one API begins before release of the second API is completed.

In certain embodiments, in the unit dose forms of the invention, both the capecitabine and cyclophosphamide are formulated for immediate release, and not for release profiles commonly referred to as delayed release, sustained release, or controlled release.

In certain embodiments, the formulations of the present invention may be one component of a kit. In particular embodiments, said kit may comprise one or more unit doses of the bi-layer tablets of the present invention in combination with one or more unit doses of an agent useful for supportive care, *e.g.*, along with instructions/guidance on how to administer each of these unit doses (*e.g.*, for the treatment of breast cancer). In particular

embodiments, the instructions are integral to the packaging of the unit doses.

In certain embodiments, a formulation of the invention is to be provided as a package with supportive care agents.

A. Cyclophosphamide Layer

Pharmaceutical formulations in accordance with the present invention comprise a cyclophosphamide layer structured to be one layer of a bi-layer tablet, *e.g.*, comprising a therapeutically effective amount of cyclophosphamide. The layer comprises cyclophosphamide, and certain excipients selected to achieve degradation resistance, uniformity enhancement, and/or purity enhancement over known formulations of cyclophosphamide.

The waxy solid nature, lack of stability at room temperature, and low melting point (*i.e.*, about 49 - 53°C) of cyclophosphamide causes significant formulation challenges throughout the formulation process. In particular, the challenges of the cyclophosphamide described above were overcome by the formulations of the present invention:

Uniformity of Cyclophosphamide

The formulations of the present invention improve uniformity by utilizing separate granules for capecitabine and cyclophosphamide and compressing each in a separate layer of a bi-layer formulation. In addition, in certain embodiments, the cyclophosphamide layer is prepared using an advanced slugging protocol (described herein), which is a novel slugging process for the cyclophosphamide granules to achieve within layer uniformity. In addition, in particular embodiments, extended duration of blending of cyclophosphamide granules enhances uniformity and API dilution potential. Accordingly, in certain embodiments of the invention, the formulations of the present invention, *e.g.*, the cyclophosphamide layer, demonstrate uniformity enhancement.

Sticking tendency during compression

The problem of cyclophosphamide sticking during compression is addressed by co-milling the cyclophosphamide with suitable excipients at unconventionally low speed. In certain embodiments, about 99% of the granules were slugged using suitable punches at low hardness to ensure that the cyclophosphamide is suitably diluted yet uniformly distributed. Further, the advanced slugging protocol is a dry method of granulation which does not use water or any solvent.

The slugs were then milled using a mill. Without wishing to be bound by theory, it is believed that during slugging and milling the resultant granules embed the API in an excipient matrix which forms a protective coat to the API and enhances compressibility while mitigating/attenuating sticking of the granules to the punches.

Uneven surface during coating

The granules prepared by the advanced slugging protocol embed the cyclophosphamide in an excipient matrix which forms a protective coat to the cyclophosphamide. These granules are compressed as tablets and these tablets demonstrate surprisingly smooth surfaces.

Stability of the formulation

In certain embodiments, the tablets are film coated at slow spray speed and low temperature, thus avoiding exposure of the cyclophosphamide to higher temperature and higher humidity levels which may cause the degradation of the API. In particular embodiments, the film coated tablets may be packed in Alu Alu blisters (Aluminum forming foils and Aluminum lidding foils) and stored at 2 to 8°C to afford control of the impurity levels of cyclophosphamide. In other particular embodiments, storage may be at a temperature range of 2-8°C; yet the formulations remain stable with storage at, for example, room temperature for a period of one to three months. See Example 3.

As used herein, a stable composition is one which retains the pharmaceutically active ingredients in an amount greater than about 92.5% for cyclophosphamide relative to the amount noted on the label as present in the particular composition, after a specified period of

time (*e.g.*, 3 months) and under specified conditions (*e.g.*, temperature and relative humidity). Stability may also be determined by the presence and quantity of impurities. A principal degradant produced through the chemical interaction of cyclophosphamide in compositions of the present invention is cyclophosphamide Impurity B; and a quantitative determination of the presence of this degradant in a unit dose form of the present invention held under forced degradation conditions for a period of time yields valuable information about the long-term stability of the composition under given (*e.g.*, room temperature) storage conditions. Assays for evaluating the stability of a pharmaceutical composition, such as those described in the present invention, are known in the pharmaceutical arts. For example, one can determine the percentage of active pharmaceutical ingredients present in a given composition, as well as the presence and percentage of impurities, through the use of standard analytical techniques.

Accordingly, in certain embodiments of the invention, the formulations of the present invention, *e.g.*, the cyclophosphamide layer, surprisingly demonstrate stability over extended periods of time, *e.g.*, 3 months, without the requirement of storage at conditions previously established for known formulations of cyclophosphamide; such formulations, surprisingly, are considered to possess degradation resistance, and/or purity enhancement under these more flexible/convenient storage conditions in this specified time period.

In certain embodiments of the invention, the first layer comprises components selected from the group consisting of cyclophosphamide, a gliding agent, a diluent, a disintegrant, a lubricant, and any combination thereof. In particular embodiments, the cyclophosphamide layer comprises the following composition:

Cyclophosphamide USP	Active
Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	Gliding Agent
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent
Croscarmellose Sodium Ph Eur / USP	Disintegrant
Magnesium Stearate Ph Eur / USP	Lubricant.

In certain specific embodiments, the cyclophosphamide layer comprises the following composition:

Cyclophosphamide USP	4.07 % w/w of tablet;
Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	0.37 % w/w of tablet;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	10.81% w/w of tablet;
Croscarmellose Sodium Ph Eur / USP	0.51% w/w of tablet; and
Magnesium Stearate Ph Eur / USP	0.50% w/w of tablet.

In certain embodiments of the invention, the cyclophosphamide layer is prepared by an advanced slugging protocol. This novel protocol may be used to develop other formulations that have arrived at one or more of the same formulation challenges as the present invention, and such uses are intended to be part of this invention. In particular embodiments, the advanced slugging protocol comprises the following steps:

co-milling the cyclophosphamide with a gliding agent and a diluent at low speed, *e.g.*, about 50 to 80 rpm (*e.g.*, through a 30 mesh screen, *e.g.*, using oscillating granulation) to produce a co-milled mixture;

blending (*e.g.*, at about 12 rpm for about 60 minutes, *e.g.*, in a double cone blender) the co-milled mixture with a combination of a sifted disintegrant and a lubricant, *e.g.*, Croscarmellose Sodium Ph Eur / USP and Magnesium Stearate Ph Eur / USP, *e.g.*, sifted through a 30 mesh screen, *e.g.*, using a vibratory sifter;

slugging the blended mixture on a tablet compression machine, *e.g.*, using 11 mm round plain punches with a target weight of 500 mg and target hardness of about 50 newton;

milling the slugs at low speed, *e.g.*, about 50 to 80 rpm (*e.g.*, through a 30 mesh screen, *e.g.*, using oscillating granulation);

lubricating the milled slugs with a sifted lubricant, *e.g.*, Magnesium Stearate, *e.g.*, sifted through 60 mesh screen, *e.g.*, in Double Cone Blender, *e.g.*, at about 12 rpm for about 5 minutes; and

compressing the lubricated milled slug into a tablet layer comprising cyclophosphamide, such that cyclophosphamide-SG is formed.

In certain embodiments of the invention, the cyclophosphamide-SG is degradation resistant.

In certain embodiments of the invention, the cyclophosphamide-SG is uniformity enhanced.

In certain embodiments of the invention, the cyclophosphamide-SG is purity enhanced. In particular embodiments, any individual impurity related to an active agent (*e.g.*, any one of the well-known/characterized impurities: Impurity A, B, C, or unspecified for Capecitabine; or Impurity A, B, C, D, or unspecified for Cyclophosphamide) is present in amounts less than about 3.0 percent of the label content of the active agent, and the total impurities related to active agents are present in amounts less than about 6.0 percent of the label content of the active agents. In specific embodiments, no more than about 3.5% of Impurity B of Cyclophosphamide is present when the composition is stored at room temperature for a period of one to three months. In a particular embodiment, the upper limits of these impurities for the formulations of the present invention are defined within the following table:

Impurities for Capecitabine	Stability Limits (% w/w)
Impurity-A	NMT 1.0
Impurity-B	NMT 1.0
Impurity-C	NMT 1.0
Individual unspecified impurity	NMT 0.20
Total Impurities	NMT 2.0
Impurities for Cyclophosphamide	Stability Limits (% w/w)
Impurity-A	NMT 1.5
Impurity-B	NMT 3.5
Impurity-C	NMT 1.5
Impurity-D	NMT 2.0
Individual unspecified impurity	NMT 1.0
Total Impurities	NMT 6.0

B. Capecitabine Layer

Pharmaceutical formulations in accordance with the present invention comprise a capecitabine layer structured to be one layer of a bi-layer tablet, *e.g.*, comprising a therapeutically effective amount of capecitabine. The layer comprises capecitabine and, optionally, one or more pharmaceutically acceptable excipients.

In certain embodiments of the invention, the second layer comprises components selected from the group consisting of capecitabine, a diluent, a disintegrant, a binder, a lubricant, and any combination thereof. In a particular embodiment, the second layer comprises the following composition:

Capecitabine USP	Active;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent;
Croscarmellose Sodium Ph Eur / USP	Disintegrant ;
Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	Binder; and
Magnesium Stearate Ph Eur / USP	Lubricant.

In certain specific embodiments, the second layer comprises the following composition:

Capecitabine USP	60.98% w/w of tablet;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	12.50% w/w of tablet;
Croscarmellose Sodium Ph Eur / USP	4.68% w/w of tablet;
Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	1.52% w/w of tablet; and
Magnesium Stearate Ph Eur / USP	1.63% w/w of tablet.

In certain embodiments, the second layer is prepared by high shear wet granulation. In particular embodiments, the high shear wet granulation comprises the following steps:

sifting capecitabine together with a disintegrant, *e.g.*, Croscarmellose Sodium Ph Eur / USP, and a diluent, *e.g.*, Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP, through a mesh screen, *e.g.*, 20 mesh screen;

dry mixing the sifted mixture in a high shear mixer, *e.g.*, for a duration of about 15 minutes, *e.g.*, using impeller speed at slow speed (*e.g.*, about 100 rpm) and chopper off.

dissolving a binder, *e.g.*, Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP in a solvent, *e.g.*, purified water, with continuous stirring to create a granulating solution;

granulating the dry mixed mixture using the granulating solution in a high shear mixer and slow impeller speed (*e.g.*, over duration of about 4 to 5 minutes using impeller slow speed (about 100 rpm) and chopper off during solution addition), followed by kneading the wet mass at fast impeller speed, *e.g.*, for about 2 minutes at impeller fast speed (about 125 rpm) and chopper slow speed (about 1000 rpm), to form wet granules ;

drying the wet granules in a fluid bed drier(*e.g.*, Rapid Drier), *e.g.*, with an inlet temperature of 50±10°C and blower speed of about 20 to 30 rpm, until LOD of not more than 1.0% w/w at 60°C is achieved. In certain embodiments, the drying is continued until the desired LOD is achieved, *e.g.*, for about 120 to 180 minutes;

milling the dried granules, *e.g.*, using 1.5 mm screen fitted, *e.g.*, in a Cone mill;

sifting a disintegrant, *e.g.*, Croscarmellose Sodium Ph Eur / USP, and a diluent, *e.g.*, Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP (*e.g.*, through a vibratory sifter, *e.g.*, through a 30 mesh screen), and blending the sifted mixture with the milled dried granules, *e.g.*, in a Double Cone Blender at about 12 rpm, *e.g.*, for about 15 minutes;

lubricating the mixture of dried granules by blending with a sifted lubricant, *e.g.*, Magnesium Stearate, *e.g.*, which has been sifted through a 60 mesh screen, *e.g.*, in a Double Cone Blender, *e.g.*, at about 12 rpm, *e.g.*, for about 5 minutes; and

compressing the lubricated mixture into a tablet layer comprising capecitabine.

Certain minor variations may be tolerable in the capecitabine formulation layer (*e.g.*, even in these particular embodiments of the capecitabine layer) within the spirit of the present invention. The excipients can include any one or more of the excipients identified in Example 1 herein, or other excipients known to those of skill in the art that are suitable for the specific objectives of the present invention.

A variety of excipients may be combined with capecitabine in the capecitabine layer of the formulations of the present invention. The provision of various excipients may be useful to impart particular qualities to the capecitabine component of the pharmaceutical composition, or to provide a beneficial characteristic that may be desirable for processing to prepare the bi-layer tablet formulation. Pharmaceutically acceptable excipients useful in compositions of the present invention can include binders, lubricants, diluents, disintegrants, and glidants, or the like, as known in the art. See *e.g.*, HANDBOOK OF PHARMACEUTICAL MANUFACTURING FORMULATIONS, 2004, Ed. Sarfaraz K Niazi, CRC Press; HANDBOOK OF PHARMACEUTICAL ADDITIVES, SECOND EDITION, 2002, compiled by Michael and Irene Ash, Synapse Books; and REMINGTON SCIENCE AND PRACTICE OF PHARMACY, 2005, David B. Troy (Editor), Lippincott Williams & Wilkins.

Binders useful in compositions of the present invention are those excipients that impart cohesive qualities to components of a pharmaceutical composition. Commonly used binders include, for example, starch; sugars, such as, sucrose, glucose, dextrose, and lactose; cellulose derivatives such as powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose (SMCC), hydroxypropylcellulose, low-substituted hydroxypropylcellulose, hypromellose (hydroxypropylmethylcellulose); and mixtures of these and similar ingredients.

Lubricants may be added to the present formulations to reduce sticking by a solid formulation to the equipment used for production of a unit does form, such as, for example, the punches of a tablet press. Examples of lubricants include magnesium stearate and calcium stearate. Other lubricants include, but are not limited to, aluminum-stearate, talc, sodium benzoate, glyceryl mono fatty acid (*e.g.*, glyceryl monostearate from Danisco, UK), glyceryl dibehenate (*e.g.*, CompritolATO888™ Gattefosse France), glyceryl palmito-stearic

ester (*e.g.*, Precirol™, Gattefosse France), polyoxyethylene glycol (PEG, BASF) such as PEG 4000-8000, hydrogenated cotton seed oil or castor seed oil (Cutina H R, Henkel) and others.

Diluents can be added to the formulations of the invention to increase bulk weight of the material to be formulated, *e.g.*, tabletted, in order to achieve the desired weight.

Disintegrants useful in the present compositions are those excipients included in the formulations of the invention in order to ensure that the composition has an acceptable disintegration rate in an environment of use. Examples of disintegrants include starch derivatives (*e.g.*, sodium carboxymethyl starch and pregelatinized corn starch such as starch 1500 from Colorcon) and salts of carboxymethylcellulose (*e.g.*, sodium carboxymethylcellulose), crospovidone (cross-linked PVP polyvinylpyrrolidinone (PVP), *e.g.*, Polyplasdone™ from ISP or Kollidon™ from BASF).

Glidants refer to excipients included in the formulations of the invention to keep the component powder flowing as a tablet is being made, preventing formation of lumps. Nonlimiting examples of glidants are colloidal silicon dioxides such as CAB-O-SIL™ (Cabot Corp.), SYLOID™, (W.R. Grace & Co.), AEROSIL™ (Degussa), talc, and corn starch.

C. Coating

In certain embodiments of the invention, the tablet formulation of the present invention is film coated.

In certain embodiments of the invention, the film coating is applied by spray coating.

In certain embodiments of the invention, the applied film coating comprises components selected from the group consisting of a film former, a plasticizer, an anti tacking agent, an opacifier, a solvent, and any combination thereof. In particular embodiments, the applied film coating comprises the following composition:

Eudragit NE 30 D	Film Former;

Poly Ethylene Glycol 4000 Ph Eur / USP	Plasticizer;
Polysorbate 80 Ph Eur / USP	Plasticizer;
Talc Ph Eur / USP	Anti Tacking Agent;
Titanium Dioxide Ph Eur / USP	Opacifier; and
Purified Water	Solvent.

In certain embodiments of the invention, film coatings of the present invention are designed to be applied at slow spray speed and low temperature, thus avoiding exposure of the cyclophosphamide higher temperature and higher humidity levels that may cause the degradation of the cyclophosphamide.

In addition, it should be noted that the film coatings of the tablet formulations of the present invention further demonstrate the increased stability of the present formulations, which may be compared to the commercially available reference standards prepared individually and require the use of a much more protective sugar coating.

III. Methods of Preparation of the Bi-layer Tablet Compositions of the Invention

The first layer, comprising capecitabine, and the second layer, comprising cyclophosphamide, *e.g.*, cyclophosphamide-SG, may be produced as described herein below. However, it is within the ability of one of ordinary skill in the art, guided by the present disclosure and with reference to the pharmaceutical literature, to prepare and manufacture unit dosage forms of the invention in accordance with the methods of the invention.

Another embodiment of the present invention provides a method of preparation of any tablet formulation of the present invention, comprising compressing a first layer of cyclophosphamide, *e.g.*, cyclophosphamide-SG, with a second layer of capecitabine in a fixed dose combination. In certain embodiments, the first layer and the second layer each is separately prepared and formed into a layer through compression prior to being compressed together to form a single, bi-layer oral tablet. In specific embodiments, the two layers are compressed to produce a smooth surface suitable for coating.

In certain embodiments of the invention, the second layer is prepared by high shear wet granulation. In particular embodiments, the high shear wet granulation comprises the following steps:

sifting capecitabine together with a disintegrant and a diluent;

dry mixing the sifted mixture in a high shear mixer;

dissolving a binder in a solvent with continuous stirring to create a granulating solution;

granulating the dry mixed mixture using the granulating solution in a high shear mixer and slow impeller speed, followed by kneading the wet mass at fast impeller speed;

drying the wet granules in a fluid bed drier;

milling the dried granules;

sifting a disintegrant and a diluent, and blending the sifted mixture with the milled dried granules;

lubricating the mixture of dried granules by blending with a sifted lubricant; and

compressing the lubricated mixture into a tablet layer comprising capecitabine. In certain embodiments the capecitabine is sifted together with a disintegrant, *e.g.*, Croscarmellose Sodium Ph Eur / USP, and a diluent, *e.g.*, Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP, through a mesh screen, *e.g.*, 20 mesh screen. In certain embodiments, the sifted mixture is dry mixed in a high shear mixer, *e.g.*, for a duration of about 15 minutes, *e.g.*, using impeller speed at slow speed (*e.g.*, about 100 rpm) and chopper off. In certain embodiments, the binder, *e.g.*, Hydroxy Propyl Methyl Cellulose 5 centipoise (cps) Ph Eur / USP, is dissolved in a solvent, *e.g.*, purified water, with continuous stirring to create a granulating solution. In certain embodiments, the dry mixed mixture is granulated using the granulating solution in a high shear mixer and slow impeller speed (*e.g.*, over duration of about 4 to 5 minutes using impeller slow speed (about 100 rpm) and chopper off

during solution addition), followed by kneading the wet mass at fast impeller speed, *e.g.*, for about 2 minutes at impeller fast speed (about 125 rpm) and chopper slow speed (about 1000 rpm), to form wet granules. In certain embodiments, the wet granules are dried in a fluid bed drier (*e.g.*, Rapid Drier), *e.g.*, with an inlet temperature of 50±10°C and blower speed of about 20 to 30 rpm, until LOD (Loss on Drying) of not more than 1.0% w/w at 60°C is achieved. In particular embodiments, the drying is continued until the desired LOD is achieved, *e.g.*, for about 120 to 180 minutes. In certain embodiments, the dried granules are milled, *e.g.*, using 1.5 mm screen fitted, *e.g.*, in a Cone mill. In certain embodiments, the disintegrant, *e.g.*, Croscarmellose Sodium Ph Eur / USP, is sifted with a diluent, *e.g.*, Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP (*e.g.*, through a vibratory sifter, *e.g.*, through a 30 mesh screen), and the sifted mixture is blended with the milled/dried granules, *e.g.*, in a Double Cone Blender at about 12 rpm, *e.g.*, for about 15 minutes. In certain embodiments, the mixture of dried granules is lubricated by blending with a sifted lubricant, *e.g.*, Magnesium Stearate, *e.g.*, which has been sifted through a 60 mesh screen, *e.g.*, in a Double Cone Blender, *e.g.*, at about 12 rpm, *e.g.*, for about 5 minutes.

In certain embodiments of the invention, the first layer is prepared by an advanced slugging protocol or by direct compression. In certain embodiments of the invention, the first layer is prepared by direct compression. In certain embodiments of the invention, the first layer is prepared by an advanced slugging protocol. In particular embodiments, the advanced slugging protocol comprises the following steps:

co-milling the cyclophosphamide with a gliding agent and a diluent at low speed to produce a co-milled mixture;

blending the co-milled mixture with a combination of a sifted disintegrant and a lubricant;

slugging the blended mixture on a tablet compression machine;

milling the slugs at low speed;

lubricating the milled slugs with a sifted lubricant; and

compressing the lubricated milled slug into a tablet layer comprising cyclophosphamide, such that cyclophosphamide-SG is formed. In certain embodiments, the cyclophosphamide is co-milled with a gliding agent and a diluent at low speed, *e.g.*, about 50 to 80 rpm (*e.g.*, through a 30 mesh screen, *e.g.*, using oscillating granulation) to produce a co-milled mixture. In certain embodiments, the co-milled mixture is blended (*e.g.*, at about 12 rpm for 60 minutes, *e.g.*, in a double cone blender) with a combination of a sifted disintegrant and a lubricant, *e.g.*, Croscarmellose Sodium Ph Eur / USP and Magnesium Stearate Ph Eur / USP, *e.g.*, sifted through a 30 mesh screen, *e.g.*, using a vibratory sifter. In certain embodiments, the blended mixture is slugged on a tablet compression machine, *e.g.*, using 11 mm round plain punches with a target weight of 500 mg and target hardness of about 50 newton. In certain embodiments, the slugs are milled at unconventionally low speed, *e.g.*, about 50 to 80 rpm (*e.g.*, through a 30 mesh screen, *e.g.*, using oscillating granulation). In certain embodiments, the milled slugs are lubricated with a sifted lubricant, *e.g.*, Magnesium Stearate, *e.g.*, sifted through 60 mesh screen, *e.g.*, in Double Cone Blender, *e.g.*, at about 12 rpm for about 5 minutes.

As noted above, in some embodiments, the tablets are coated for oral administration to improve stability, reduce degradation, reduce hygroscopicity, to make the tablet easier to swallow, to mask taste, for cosmetic reasons, or for other reasons. Coating of tablets and caplets is well known in the art. In particular, film coatings of the present invention are film coated at slow spray speed and low temperature, thus avoiding exposure of the cyclophosphamide higher temperature and higher humidity levels that may cause the degradation of the cyclophosphamide.

Coating systems are typically mixtures of polymers, plasticisers, coloring agents and other excipients, which can be stirred into water or an organic solvent to produce a dispersion for the film coating of solid oral dosage tablets. Materials that can be used for readily soluble films include cellulose derivatives (such as hydroxypropylmethyl cellulose) or amino-alkylmethacrylate copolymers (*e.g.* Eudragit™E). Suitable coat layers, for illustration and not limitation, include the following composition:

Eudragit NE 30 D	Film Former;
Poly Ethylene Glycol 4000 Ph Eur / USP	Plasticizer;

Polysorbate 80 Ph Eur / USP	Plasticizer;
Talc Ph Eur / USP	Anti Tacking Agent;
Titanium Dioxide Ph Eur / USP	Opacifier; and
Purified Water	Solvent.

In certain embodiments of the invention, the method further comprises film coating the single bi-layer tablet, *e.g.*, the film coating is applied by spray coating, *e.g.*, using an auto coater. In particular embodiments, the film coating is prepared by

homogenizing an anti-tacking agent, *e.g.*, Talc Ph Eur / USP, with an opacifier, *e.g.*, Titanium Dioxide Ph Eur / USP, in a solvent, *e.g.*, purified water, to form a homogenized mixture;

dispersing one or more plasticizers, *e.g.*, Polysorbate 80 Ph Eur / USP and Poly Ethylene Glycol 4000 Ph Eur / USP, in a film former, *e.g.*, in Eudragit NE 30D, with continuous stirring to form a dispersed mixture; and

mixing the homogenized mixture with the dispersed mixture by stirring, *e.g.*, for about 45 minutes, *e.g.*, at rates suitable to achieve a vortex in the coating dispersion. In certain embodiments, the parameters for coating are: spray rate of about 10 to 15 grams / minute / gun, nozzle diameter of about 1.0 mm, inlet air temperature of 50±10°C, bed temperature of 40±10°C, exhaust temperature of 40±10°C, Pan RPM is 4 to 6 (*i.e.*, wherein the Pan indicates the coating pan which is standard equipment of all coating machines), and Atomization Air Pressure of about 0.5 to 1.0 bar.

In certain embodiments of the invention, the film coated tablets are packed in Alu Alu blisters (Aluminum forming foils and Aluminum lidding foils) and stored at about 2 to 8°C to ensure adequate control of the impurity levels of cyclophosphamide.

Furthermore, the cyclophosphamide-SG described in the present invention is an advancement in technology for cyclophosphamide formulation, which affords a stabilized cyclophosphamide that is degradation resistant, purity enhanced, and/or uniformity enhanced. As such, in certain embodiments, the method of preparation of the cyclophosphamide, and

the resulting compressed material may be independently prepared and used (*e.g.*, and coated) for treatment of a subject.

IV. Methods of Treatment Using Formulations of the Invention

In another embodiment, the present invention provides a method of treatment of cancer, *e.g.*, breast cancer, comprising metronomic administration of a formulation of the present invention to a subject. In certain embodiments, the metronomic administration is highly fractionated metronomic administration of the formulation.

In one embodiment, the present invention is directed to methods of treating subjects in need of treatment. Subjects in need of capecitabine and cyclophosphamide treatment include those individuals who have been diagnosed with cancer, *e.g.*, breast cancer. More generally, subjects in need of capecitabine and cyclophosphamide treatment are those individuals who receive a therapeutic benefit from administration of capecitabine and cyclophosphamide.

In certain embodiments of the invention, the subject is human.

In certain embodiments of the invention, the subject is not pretreated, and the formulation is the primary therapeutic course of treatment.

In certain embodiments, dosage forms of the present invention are designed for administration once per day (OPD) administration of capecitabine and cyclophosphamide to a patient in need thereof.

In certain embodiments, dosage forms of the present invention are designed for administration twice per day (TPD) administration of capecitabine and cyclophosphamide to a patient in need thereof.

In certain embodiments, the formulations provided herein may be used as a primary therapeutic, as compared to a combination or secondary therapy.

EXEMPLIFICATION

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

Example 1

Bi-layer Tablet Compositions of the Present Invention

A bi-layer tablet composition of capecitabine and cyclophosphamide according to the present invention can be prepared by separately preparing a capecitabine layer, which is then compressed with a cyclophosphamide layer and an optional over-coating.

A summary of the materials used in the bi-layer tablet composition described are provided in Table 1 below.

Table 1: Capecitabine/Cyclophosphamide (600/40 mg and 300/20 mg) Tablets

Sr. No.	Ingredients	Function	% w/w	mg / tab
Intra-granular for Cyclophosphamide Layer				
9	Cyclophosphamide USP	Active	4.07	40.00
10	Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	Gliding Agent	0.37	3.60
11	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent	10.81	106.40
12	Croscarmellose Sodium Ph Eur / USP	Disintegrant	0.51	5.00
13	Magnesium Stearate Ph Eur / USP	Lubricant	0.30	3.00
Extra-granular for Cyclophosphamide Layer				
14	Magnesium Stearate Ph Eur / USP	Lubricant	0.20	2.00
		Cyclophosphamide Layer Weight	16.26	160.00
Intra-granular for Capecitabine Layer				
1	Capecitabine USP	Active	60.98	600.00
2	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent	8.43	83.00
3	Croscarmellose Sodium Ph Eur / USP	Disintegrant	2.85	28.00

Granulating Solution for Capecitabine Layer				
4	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	Binder	1.52	15.00
5	Purified Water	Granulation Solvent	--	q.s.
Extra-granular for Capecitabine Layer				
6	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent	4.07	40.00
7	Croscarmellose Sodium Ph Eur / USP	Disintegrant	1.83	18.00
8	Magnesium Stearate Ph Eur / USP	Lubricant	1.63	16.00
		Capecitabine Layer Weight	81.30	800.00
		Total Combined Bi-layer Tablet Weight	97.56	960.00
Coating Composition				
15	Eudragit NE 30 D	Film Former	0.61	6.050
16	Poly Ethylene Glycol 4000 Ph Eur / USP	Plasticizer	0.41	4.030
17	Polysorbate 80 Ph Eur / USP	Plasticizer	0.08	0.820
18	Talc Ph Eur / USP	Anti Tacking Agent	0.67	6.550
19	Titanium Dioxide Ph Eur / USP	Opacifier	0.67	6.550
20	Purified Water	Solvent	--	q.s.
	Final Film Coated Tablet Weight		**100.00**	**984.00**

Ph Eur: European Pharmacopeia
USP: United States Pharmacopeia
q.s: quality sufficient
Sr No.: Serial Number

Synthetic Preparation of Capecitabine Layer :

The *Capecitabine USP*, Croscarmellose Sodium Ph Eur / USP and Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP were sifted together using a vibratory sifter through a 20 mesh screen. This mixture was then dry mixed in a high shear mixer for a duration of 15 minutes, using impeller speed at slow speed (about 100 rpm) and chopper off.

This mixture was then granulated using solution of Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP prepared by dissolving the HPMC in purified water with continuous stirring. The granulation was performed in a high shear mixer over duration of about 4 to 5 minutes using impeller slow speed (about 100 rpm) and chopper off during solution addition. The wet mass was then kneaded for about 2 minutes at impeller fast speed (about 125 rpm) and chopper slow speed (about 1000 rpm) .

The wet granules were then dried in a Fluid bed drier (Rapid Drier) with an inlet temperature of 50±10°C and blower speed of 20 to 30 rpm, until LOD (Loss on Drying) of not more than 1.0% w/w at 60°C is achieved. The drying was continued until the desired LOD was achieved, *i.e.*, about 120 to 180 minutes.

The dried granules were then milled using a 1.5 mm screen fitted in a Cone mill and then blended with a mixture prepared by sifting together Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP through a 30 mesh screen using a vibratory sifter. The blending was performed in a Double Cone Blender at 12 rpm for 15 minutes.

The blended mixture was then lubricated with Magnesium Stearate sifted through a 60 mesh screen. The lubrication was performed in a Double Cone Blender at 12 rpm for 5 minutes.

Synthetic Preparation of Cyclophosphamide Layer:

Cyclophosphamide USP, Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP and Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP were co-milled through a 30 mesh screen using an oscillating granulator at slow speed (50 to 80 rpm). This milled mixture was blended with a combination of Croscarmellose Sodium Ph Eur / USP and Magnesium Stearate Ph Eur / USP that had been sifted through a 30 mesh screen using a vibratory sifter. The blending was performed in a Double Cone Blender at 12 rpm for 60 minutes.

This blended mixture was slugged on a tablet compression machine using 11 mm round plain punches with a target weight of 500 mg and target hardness of about 50 newton.

The slugs were then milled through a 30 mesh screen using an oscillating granulator at slow speed (50 to 80 rpm).

The milled slugs were then lubricated with Magnesium Stearate sifted through a 60 mesh screen. The lubrication was performed in a Double Cone Blender at 12 rpm for 5 minutes.

Bi-layer Compression: Capecitabine 600 mg and Cyclophosphamide 40 mg:

The capecitabine layer, with an average weight of 800 mg, and which contains 600 mg of capecitabine was compressed.

The cyclophosphamide layer, with an average weight of 160 mg, and which contains 40 mg of cyclophosphamide was compressed.

The parameters of this compression process are shown below:

Parameters	Values for tablets of strength 600/40 mg
Tooling	20 mm x 10.5 mm, oval shaped, plain, standard concave, D tooling
Description	White to off white colored biconvex capsule shaped bi-layered uncoated tablets plain on both sides.
Average Weight	960 mg ± 3% (931.2 mg to 988.8 mg)
Thickness	6.0 mm ± 0.3 mm
Hardness	80 to 130 Newton
Length and Width	20 mm ± 0.2 mm and 10.5 ± 0.2 mm
Friability	0.7% w/w
Disintegration Time	5 to 9 minutes

Bi-layer Compression: Capecitabine 300 mg and Cyclophosphamide 20 mg:

Capecitabine and cyclophosphamide 300/20 mg bi-layer tablets may be similarly prepared by using the same % w/w, but half of each starting reagent.

The capecitabine layer, with an average weight of 400 mg, and which contains 300 mg of capecitabine was compressed.

The cyclophosphamide layer, with an average weight of 80 mg, and which contains 20 mg of cyclophosphamide was compressed.

The parameters of this compression process are shown below:

Parameters	Values for tablets of strength 300/20 mg
Tooling	18 mm x 6 mm, oval shaped, plain, standard concave, D tooling
Description	White to off white colored biconvex capsule shaped bi-layered uncoated tablets plain on both sides.
Average Weight	480 mg ± 3% (465.6 mg to 494.4 mg)
Thickness	4.6 mm ± 0.3 mm
Hardness	80 to 130 Newton
Length and Width	18 mm ± 0.2 mm and 6.0 ± 0.2 mm
Friability	0.6% w/w
Disintegration Time	5 to 9 minutes

Synthetic Preparation of Coating:

Talc Ph Eur / USP and Titanium Dioxide Ph Eur / USP were homogenized in purified water. This mixture was mixed with a dispersion of Polysorbate 80 Ph Eur / USP and Poly Ethylene Glycol 4000 Ph Eur / USP in Eudragit NE 30D (dispersed with continuous stirring); wherein the mixing was performed using continued stirring for about 45 minutes, creating a secondary dispersion.

The secondary dispersion was then sprayed onto the compressed bi-layer tablets using an Auto coater, to obtain film coated tablets. The parameters for coating were: spray rate of 10 to 15 grams / minute / gun, nozzle diameter of 1.0 mm, inlet air temperature of 50±10°C,

bed temperature of 40±10°C and exhaust temperature of 40±10°C, Pan RPM was 4 to 6, and Atomization Air Pressure of 0.5 to 1.0 bar.

The target weight gain for higher strength was 24 mg and the uncoated bi-layered tablet weight was 960 mg; resulting in a final weight of the film coated tablet of 984 mg.

The target weight gain for lower strength was 12 mg and the uncoated bi-layered tablet weight was 480 mg; resulting in a final weight of the film coated tablet of 492 mg.

Example 2

Manufacturing Process Development

Before arriving at the formulations described herein, and exemplified in Example 1, several approaches were attempted to overcome the formulation issues described herein above, for example, related to stability, purity, sticking, uneven surface for coating, uniformity, and/or process simplification.

Approach I: Capecitabine Granules by Top Spray Granulation and Cyclophosphamide granules using Direct Compression

The first approach attempted to use direct compression for cyclophosphamide and top spray granulation for capecitabine

Sr. No	Ingredients	
Capecitabine Layer		mg/tab
1	Capecitabine USP	600.00
2	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	118.00
3	Croscarmellose Sodium Ph Eur / USP	28.00
4	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	30.00
5	Purified Water	q.s.
6	Croscarmellose Sodium Ph Eur / USP	8.00
7	Magnesium Stearate Ph Eur / USP	16.00
	Weight of the Capecitabine Layer	800.00

Cyclophosphamide Layer		
1	Cyclophosphamide USP	43.60
2	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	262.80
3	Povidone K 90 Ph Eur / USP	6.80
4	Croscarmellose Sodium Ph Eur / USP	20.00
5	Magnesium Stearate Ph Eur / USP	6.80
	Weight of cyclophosphamide Layer	340.00
	Bi-layer Tablet Weight	1140.00

Capecitabine Procedure	
Step 1	Capecitabine USP, Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP was sifted through a 20 mesh sieve.
Step 2	The mixture of Step 1 was dry mixed in a Fluid Bed Processor with a flap opening of 45% inlet temperature of 50±10°C for 5 minutes.
Step 3	Hydroxy propyl methyl cellulose 5 cps was dissolved in purified water under stirring until a clear solution was obtained.
Step 4	The mixture of Step 2 was granulated by spraying the solution of Step 3 using a top spray procedure in a Fluid Bed Processor with a flap opening of 35% to 65% and inlet temperature of 50±10°C, bed temperature of 40±10°C. This was performed for 120 to 180 minutes. Top Spray includes a process where the solution is sprayed from the top of a fluidized bed.
Step 5	The wet mass was dried in Fluid Bed Processor at inlet temperature of 50±10°C until Loss on Drying (LOD) at 60°C of not more than 1.5%. LOD is measured in a Halogen Moisture Analyzer until a constant weight of the sample was achieved at a given temperature of drying.
Step 6	The dried granules were through 30 mesh sieve using a vibratory sifter.
Step 7	Croscarmellose Sodium was sifted through 30# mesh sieve using a vibratory sifter.
Step 8	Step 6 with Step 7 were pre lubricated in Double Cone Blender for 15 min at 12 rpm.
Step 9	Magnesium Stearate was sifted through 60# sieve using a vibratory sifter
Step 10	Step 8 was then lubricated with Step 9 in Double Cone Blender for 5 min at 12 rpm.
Cyclophosphamide Procedure	
Step 1	Cyclophosphamide USP, Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP

	and Croscarmellose Sodium Ph Eur / USP was sifted through a 40 mesh sieve using a vibratory sifter.
Step 2	Povidone K-90 was sifted through a 30 mesh screen using a vibratory sifter.
Step 3	Step 1 and step 2 were blended in a Double Cone Blender for 15 min at 12 rpm.
Step 4	Magnesium Stearate was sifted through a 60 mesh screen using a vibratory sifter.
Step 5	Step 3 was lubricated with Step 4 in a Double Cone Blender for 5 min at 12 rpm.
Step 6	The samples were submitted to check the uniform distribution of cyclophosphamide within the lubricated blend and then carried forward the blend to the compression stage.

Observations/Conclusions:

The cyclophosphamide granules were submitted for blend uniformity analysis using solvents to suitably extract the formulation to analyze the API content in accordance with standard protocols for uniformity analysis. This blend uniformity test ensures that cyclophosphamide is uniformly distributed in the lubricated blend prior to compression step. The samples were collected from three different locations within the same blend and the results were as follows: Sample 1 result 82.1%, Sample 2 result 138.6%, Sample 3 result 109%, and Pooled Sample of all the three locations showed a result of 110.7%. In this way, it was demonstrated that the direct compression approach for cyclophosphamide may not yield uniformity

The feasibility for bi-layer compression was also evaluated, by compressing the Capecitabine layer and cyclophosphamide layer. The resulted tablets showed sticking on the cyclophosphamide granules side during compression

Thus based on above observations, this composition/strategy was not pursued further.

Approach II: Capecitabine Granules by Top Spray Granulation and Cyclophosphamide Granules using Non-aqueous Granulation

The second approach attempted to use non aqueous based granulation for cyclophosphamide and top spray granulation for capecitabine

Sr. No	Ingredients	mg/tab
Capecitabine Layer		
1	Capecitabine USP	600.00
2	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	118.00
3	Croscarmellose Sodium Ph Eur / USP	28.00
4	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	30.00
5	Purified Water	q.s.
6	Croscarmellose Sodium Ph Eur / USP	8.00
7	Magnesium Stearate Ph Eur / USP	16.00
	Weight of the Capecitabine Layer	800.00
Cyclophosphamide Layer		
1	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	227.50
2	Croscarmellose Sodium Ph Eur / USP	20.00
3	Povidone K 90 Ph Eur / USP	3.40
4	Iso Propyl Alcohol	q.s.
5	Povidone K 90 Ph Eur / USP	3.40
6	Cyclophosphamide USP	43.60
7	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	35.30
8	Magnesium Stearate Ph Eur / USP	6.80
	Weight of cyclophosphamide Layer	340.00
	Bi-layer Tablet Weight	1140.00

Capecitabine Procedure	
Step 1	Capecitabine USP, Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP was sifted through a 20 mesh sieve.
Step 2	The mixture of Step 1 was dry mixed in a Fluid Bed Processor with a flap opening of 45% inlet temperature of 50±10°C for 5 minutes.
Step 3	Hydroxy propyl methyl cellulose 5 cps was dissolved in purified water under stirring until a clear solution was obtained.
Step 4	The mixture of Step 2 was granulated by spraying the solution of Step 3 using a top

	spray procedure in a Fluid Bed Processor with a flap opening of 35% to 65% and inlet temperature of 50±10°C, bed temperature of 40±10°C. This was performed for 120 to 180 minutes. Top Spray includes a process where the solution is sprayed from the top of a fluidized bed.
Step 5	The wet mass was dried in Fluid Bed Processor at inlet temperature of 50±10°C until Loss on Drying (LOD) at 60°C of not more than 1.5%. LOD is measured in a Halogen Moisture Analyzer until a constant weight of the sample was achieved at a given temperature of drying.
Step 6	The dried granules were through 30 mesh sieve using a vibratory sifter.
Step 7	Croscarmellose Sodium was sifted through 30# mesh sieve using a vibratory sifter.
Step 8	Step 6 with Step 7 were pre-lubricated in Double Cone Blender for 15 min at 12 rpm.
Step 9	Magnesium Stearate was sifted through 60# sieve using a vibratory sifter
Step 10	Step 8 was then lubricated with Step 9 in Double Cone Blender for 5 min at 12 rpm.
Cyclophosphamide Procedure	
Step 1	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP (227.5 g), Povidone K 90 Ph Eur / USP (3.4 g) and Croscarmellose Sodium Ph Eur / USP were sifted through 30 mesh screen sieve using a vibratory sifter.
Step 2	The mixture of step 1 was dry mixed in a rapid mixer granulator for 15 min at impeller slow speed (approx. 100 rpm) and chopper off.
Step 3	Povidone K 90 Ph Eur / USP (3.4 g) was dissolved in Iso-Propyl Alcohol, and the cyclophosphamide USP was dispersed in this solution with stirring.
Step 4	The dry mixed mixture of Step 2 was granulated using the dispersion of step 3 at impeller slow speed (approx. 100 rpm) and chopper off.
Step 5	The wet mass was then dried in a Fluid Bed Processor at inlet temperature of 30±5°C until LOD of not more than 2.0% is achieved at 40°C when detected in a Halogen Moisture Analyser.
Step 6	The dried mass of step 4 was then sifted through a 20 mesh screen sieve using a vibratory sifter.
Step 7	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP (35.3 g) was then sifted through a 30 mesh screen sieve using a vibratory sifter.
Step 8	Step 6 was pre-lubricated with step 7 by blending in Double Cone Blender for 15 min at 12 rpm.

Step 9	Magnesium Stearate was sifted through a 60 mesh screen using a vibratory sifter.
Step 10	Step 8 was lubricated with Step 9 in Double Cone Blender for 5 min at 12 rpm.
Step 11	The final blended product was carried forward to the compression stage.

Observations and conclusions:

The feasibility for bi-layer compression was evaluated by compressing the capecitabine layer and cyclophosphamide layer. The resulting bi-layered tablets showed no sticking during compression

Although there was no sticking observation during compression, there was a significant increase in the impurity levels. The samples were submitted for impurity analysis using solvents to suitably extract the formulation to analyze the API content in accordance with standard protocols for measuring impurity levels, where it was observed that there is a high level of cyclophosphamide Impurity B, with a value of 2.006%.

Thus this strategy was not to be carried forward.

Approach III: Capecitabine Granules by Top Spray Granulation and Cyclophosphamide Granules using Slugging

The third approach attempted to use a slugging approach for cyclophosphamide and high shear granulation for capecitabine.

Sr. No	Ingredients	mg/tab
Capecitabine Layer		
1	Capecitabine USP	600.00
2	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	118.00
3	Croscarmellose Sodium Ph Eur / USP	28.00
4	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	30.00
5	Purified Water	q.s.
6	Croscarmellose Sodium Ph Eur / USP	8.00
7	Magnesium Stearate Ph Eur / USP	16.00

	Weight of the Capecitabine Layer	800.00
Cyclophosphamide Layer		
1	Cyclophosphamide USP	43.60
2	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	165.00
3	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP	97.80
4	Povidone K 90 Ph Eur / USP	6.80
5	Croscarmellose Sodium Ph Eur / USP	20.00
6	Magnesium Stearate Ph Eur / USP	6.80
	Weight of cyclophosphamide Layer	340.00
	Bi-layer Tablet Weight	1140.00

Capecitabine Procedure	
Step 1	Capecitabine USP, Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP was sifted through a 20 mesh sieve.
Step 2	The mixture of Step 1 was dry mixed in a Fluid Bed Processor with a flap opening of 45% inlet temperature of 50±10°C for 5 minutes.
Step 3	Hydroxy propyl methyl cellulose 5 cps was dissolved in purified water under stirring until a clear solution was obtained.
Step 4	The mixture of Step 2 was granulated by spraying the solution of Step 3 using a top spray procedure in a Fluid Bed Processor with a flap opening of 35% to 65% and inlet temperature of 50±10°C, bed temperature of 40±10°C. This was performed for 120 to 180 minutes. Top Spray includes a process where the solution is sprayed from the top of a fluidized bed.
Step 5	The wet mass was dried in Fluid Bed Processor at inlet temperature of 50±10°C until Loss on Drying (LOD) at 60°C of not more than 1.5%. LOD is measured in a Halogen Moisture Analyzer until a constant weight of the sample was achieved at a given temperature of drying.
Step 6	The dried granules were through 30 mesh sieve using a vibratory sifter.
Step 7	Croscarmellose Sodium was sifted through 30# mesh sieve using a vibratory sifter.
Step 8	Step 6 with Step 7 were pre lubricated in Double Cone Blender for 15 min at 12 rpm.
Step 9	Magnesium Stearate was sifted through 60# sieve using a vibratory sifter
Step 10	Step 8 was then lubricated with Step 9 in Double Cone Blender for 5 min at 12 rpm.

Cyclophosphamide Procedure	
Step 1	Cyclophosphamide USP and Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP (165 g) were mixed in a Double Cone Blender for 15 min at 12 rpm.
Step 2	The blend of Step 1 was slugged using 11 mm round punches with approx. weight of 500 mg per slug and approx. hardness of 40 – 60 Newton.
Step 3	The slugs of step 2 were milled through a 30 mess screen using an oscillating granulator at slow speed (50 to 80 rpm).
Step 4	The milled slugs, Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP (97.8 g), Povidone K 90 Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP were co-milled through a 30 mesh screen sieve using a vibratory sifter.
Step 5	The product of Step 4 was pre-lubricated by blending in Double Cone Blender for 15 min at 12 rpm.
Step 6	Magnesium Stearate was sifted through 60 screen mesh using a vibratory sifter.
Step 7	Step 5 was lubricated with Step 6 in Double Cone Blender for 5 min at 12 rpm.
Step 8	The samples were submitted to check the uniform distribution of cyclophosphamide within the lubricated blend, and the blend was carried forward to the compression stage.

Observations and conclusions:

The cyclophosphamide granules were submitted for blend uniformity analysis. This blend uniformity test ensures that cyclophosphamide is uniformly distributed in the lubricated blend prior to compression step. The samples were collected from three different locations within the same blend and the results were as follows, Sample 1 result 99.0%, Sample 2 result 93.20%, Sample 3 result 100.40%, and Pooled Sample of all the three locations showed a result of 97.30%.

The feasibility for bi-layer compression was also evaluated by compressing the capecitabine layer and cyclophosphamide layer. The resulted tablets showed sticking during compression.

The uniformity results of cyclophosphamide were better than the direct compression approach, however, sticking was observed during compression. This strategy was further optimized with certain modifications as described below.

Optimized Approach III : Capecitabine Granules by Rapid Mixer Granulator and Cyclophosphamide Granules Using Slugging Approach

Approach III was further optimized to simultaneously resolve the sticking and non-uniformity concerns. In particular, the capecitabine layer was prepared using Rapid mixer granulator and the cyclophosphamide layer was prepared using slugging.

Sr. No.	Ingredients	mg / tab
Intra-granular for Cyclophosphamide Layer		
9	Cyclophosphamide USP	40.00
10	Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	3.60
11	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	106.40
12	Croscarmellose Sodium Ph Eur / USP	5.00
13	Magnesium Stearate Ph Eur / USP	3.00
Extra-granular for Cyclophosphamide Layer 2		
14	Magnesium Stearate Ph Eur / USP	2.00
	Cyclophosphamide Layer 2 Weight	160.00
Intra-granular for Capecitabine Layer		
1	Capecitabine USP	600.00
2	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	83.00
3	Croscarmellose Sodium Ph Eur / USP	28.00
Granulating Solution for Capecitabine Layer 1		
4	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	15.00
5	Purified Water	q.s.
Extra-granular for Capecitabine Layer		
6	Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	40.00
7	Croscarmellose Sodium Ph Eur / USP	18.00
8	Magnesium Stearate Ph Eur / USP	16.00
	Capecitabine Layer 1 weight	800.00
	Layer 1 + Layer 2 = Bi-layer Weight	960.00
Coating Composition		
15	Eudragit NE 30 D	6.050

16	Poly Ethylene Glycol 4000 Ph Eur / USP	4.030
17	Polysorbate 80 Ph Eur / USP	0.820
18	Talc Ph Eur / USP	6.550
19	Titanium Dioxide Ph Eur / USP	6.550
20	Purified Water	q.s.
	Final Film Coated Tablet Weight	984.00

Capecitabine Procedure	
Step 1	Capecitabine USP, Croscarmellose Sodium Ph Eur / USP and Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP were sifted together through a 20 mesh screen using a vibratory sifter.
Step 2	The product of step 1 was dry mixed in a high shear mixer for a duration of 15 minutes, using impeller speed at slow speed (about 100 rpm) and chopper off.
Step 3	Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP was dissolved in purified water with continuous stirring
Step 4	The mixture of Step 2 was granulated using the solution of step 3 in a high shear mixer over duration of about 4 to 5 minutes using impeller slow speed (about 100 rpm) and chopper off during solution addition. The wet mass was then kneaded for about 2 minutes at impeller fast speed (about 125 rpm) and chopper slow speed (about 1000 rpm).
Step 5	The wet granules of Step 4 were dried in Fluid bed drier (Rapid Drier) with an inlet temperature of 50±10°C and blower speed of 20 to 30 rpm, until Loss on Drying (LOD) of not more than 1.0% w/w at 60°C was achieved . The drying is continued until the desired LOD was achieved at a duration of about 120 to 180 minutes. The LOD was measured in a Halogen Moisture Analyzer until a constant weight of the sample was achieved at a given temperature of drying.
Step 6	The dried granules of Step 4 were milled using 1.5 mm screen fitted in a Cone mill.
Step 7	Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP and Croscarmellose Sodium Ph Eur / USP were sifted through a 30 mesh screen using a vibratory sifter.
Step 8	Products of Step 6 and Step 7 were blended in a Double Cone Blender at 12 rpm for 15 minutes.

Step 9	Magnesium Stearate was sifted through 60 mesh screen.
Step 10	Step 8 was lubricated with Step 9 in a Double Cone Blender at 12 rpm for 5 minutes.
Cyclophosphamide Procedure	
Step 1	Cyclophosphamide USP, Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP and Microcrystalline Cellulose (Avicel PH 112) Ph Eur / USP were co-milled through a 30 mesh screen using an oscillating granulator at slow speed (50 to 80 rpm).
Step 2	Croscarmellose Sodium Ph Eur / USP and Magnesium Stearate Ph Eur / USP were sifted through a 30 mesh screen using a vibratory sifter.
Step 3	The products of Step 2 and Step 3 were blended in a Double Cone Blender at 12 rpm for 60 minutes.
Step 4	The blend of Step 3 was slugged on a tablet compression machine using 11 mm round plain punches with a target weight of 500 mg and target hardness of about 50 newton.
Step 5	The slugs were milled through a 30 mesh screen using an oscillating granulator at slow speed (50 to 80 rpm).
Step 6	Magnesium Stearate was sifted through a 60 mesh screen
Step 7	Step 5 was lubricated with Step 6 in Double Cone. Blender at 12 rpm for 5 minutes.

The capecitabine layer with an average weight of 800 mg was compressed, which contains capecitabine 600 mg

The cyclophosphamide layer with an average weight of 160 mg was compressed, which contains cyclophosphamide 40 mg

Observations and conclusions:

The cyclophosphamide layer was submitted for blend uniformity analysis. This blend uniformity test ensures that cyclophosphamide is uniformly distributed in the lubricated blend prior to compression step. The samples were collected from six different locations within the same blend and the results were as follows, Sample 1 result 98.5%, Sample 2 result 102.6%,

Sample 3 result 99.2%, Sample 4 result 100.1%, Sample 5 result 98.9%, Sample 6 result 99.7% and Pooled Sample of all the six locations showed a result of 102.8%.

The feasibility for bi-layer compression was also evaluated by compressing the capecitabine layer and cyclophosphamide layer. The resulted tablets showed no sticking during compression.

As such, the tablets showed a smooth appearance during coating and better control in the impurity levels of cyclophosphamide.

This strategy was selected as the finalized composition and process; however, the capecitabine granulation process was converted to high shear granulation which was simpler and time saving.

It was further identified that this cyclophosphamide layer composition was also capable of use in a direct compression protocol.

Example 3

Stability Analysis

Suitable stability measurements known as standard in the art for API or impurity analysis have been made on certain formulations described herein at time points: 1 month, 2 months, 3 months, and 6 months.

I. API Stability of Formulations of the Present Invention

Stability Profile for strength 300/20 mg

Assay	Strength 300/20 mg Pack Alu Alu Blisters													
	Stability Limits		30°C / 75% RH				25°C / 60% RH				2 – 8 °C			
		Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Capecitabine	90.0% - 110.0%	99.2	98.3	102.2	99.1	100.8	100.0	101.3	100.1	100.8	98.6	100.3	98.8	99.8
Assay	Stability	Initial	1 M	2 M	3 M	6 M	1	2	3	6	1	2	3	6

	Limits						M	M	M	M	M	M	M	M
Cyclophosphamide	92.5% - 107.5%	103.0	100.1	100.1	94.4	80.5	104.6	100.8	98.2	99.4	100.3	104.9	103.2	102.4

Stability Profile for strength 600/40 mg

Assay	Strength 600/40 mg Pack Alu Alu Blisters													
	Stability Limits		30°C / 75% RH				25°C / 60% RH				2 – 8 °C			
		Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Capecitabine	90.0% - 110.0%	100.3	99.0	98.0	98.2	101.6	102.2	98.9	101.5	102.0	101.7	99.5	99.8	101.6
Assay	Stability Limits	Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Cyclophosphamide	92.5% - 107.5%	103.4	98.3	99.3	97.8	70.7	99.8	103.8	103.2	99.3	103.5	101.6	104.1	102.7

As is evident from the tables above, in certain embodiments of the bi-layer formulation, storage at a temperature range of 2-8°C, or at temperatures 25°C with (60% relative humidity) may be suitable for up to and beyond 6 months. However, at a temperature of 30°C with 75% relative humidity the stability of the API are within the tolerated limits up to 3 months.

II. Impurity Profiles of Formulations of the Present Invention

Impurity Profile for strength 300/20 mg

Related Substances	Strength 300/20 mg Pack Alu Alu Blisters													
	Stability		30°C / 75% RH				25°C / 60% RH				2 – 8 °C			
Capecitabine	Limits	Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Impurity-A	NMT 1.0	0.103	0.125	0.173	0.194	0.239	0.126	0.206	0.149	0.173	0.100	0.167	0.113	0.122
Impurity-B	NMT 1.0	0.123	0.139	0.182	0.203	0.301	0.142	0.140	0.156	0.212	0.127	0.120	0.127	0.166
Impurity-C	NMT 1.0	0.022	0.042	0.030	0.032	0.033	0.039	0.031	0.045	0.052	0.031	0.025	0.027	0.042
Individual unspecified impurity	NMT 0.20	0.025	0.036	0.036	0.035	0.029	0.038	0.029	0.033	0.031	0.035	0.033	0.036	0.028
Total Impurities	NMT 2.0	0.310	0.37	0.458	0.491	0.651	0.37	0.449	0.409	0.547	0.32	0.380	0.340	0.457
Cyclophosphamide	Stability	Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M

	Limits													
Impurity-A	NMT 1.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Impurity-B	NMT 3.5	0.511	1.565	2.021	3.839	1.667	1.053	1.780	1.693	1.600	0.743	0.764	0.793	0.815
Impurity-C	NMT 1.5	ND	ND	0.214	0.333	1.355	ND	0.110	0.077	0.084	ND	ND	ND	ND
Impurity-D	NMT 2.0	ND	0.081	0.092	0.047	1.628	0.052	0.075	0.041	0.017	ND	0.053	ND	ND
Individual unspecified impurity	NMT 1.0	0.060	0.152	0.542	0.497	1.441	0.095	0.097	0.127	0.138	0.079	0.098	0.086	0.137
Total Impurities	NMT 6.0	0.617	2.458	3.747	5.077	8.305	1.326	2.136	2.458	2.634	0.931	0.986	1.155	1.050

ND: Not Detected

Impurity Profile for strength 600/40 mg

Related Substances	Strength 600/40 mg Pack Alu Alu Blisters													
	Stability		30°C / 75% RH				25°C / 60% RH				2 – 8 °C			
Capecitabine	Limits	Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Impurity-A	NMT 1.0	0.107	0.135	0.175	0.194	0.257	0.117	0.214	0.143	0.186	0.099	0.204	0.109	0.116
Impurity-B	NMT 1.0	0.128	0.156	0.181	0.200	0.353	0.143	0.149	0.153	0.225	0.133	0.131	0.135	0.110
Impurity-C	NMT 1.0	0.024	0.044	0.023	0.030	0.029	0.034	0.027	0.029	0.028	0.037	0.036	0.026	0.029
Individual unspecified impurity	NMT 0.20	0.032	0.038	0.026	0.031	0.030	0.038	0.034	0.034	0.037	0.035	0.034	0.034	0.032
Total Impurities	NMT 2.0	0.330	0.40	0.459	0.485	0.702	0.36	0.461	0.384	0.591	0.33	0.443	0.335	0.337
Cyclophosphamide	Stability		30°C / 75% RH				25°C / 60% RH				2 – 8 °C			
	Limits	Initial	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M	1 M	2 M	3 M	6 M
Impurity-A	NMT 1.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Impurity-B	NMT 3.5	0.419	1.503	1.762	2.273	2.137	0.756	1.081	1.020	0.999	0.594	0.692	0.695	0.777
Impurity-C	NMT 1.5	0.128	0.122	0.385	0.509	1.655	0.102	0.100	0.070	0.092	0.098	0.114	0.064	ND
Impurity-D	NMT 2.0	0.010	0.031	0.056	0.045	1.321	0.025	0.047	0.009	0.059	0.003	0.002	ND	ND
Individual unspecified impurity	NMT 1.0	0.026	0.337	0.284	0.321	0.983	0.102	0.086	0.131	0.130	0.061	0.102	0.08	0.110
Total Impurities	NMT 6.0	0.637	2.683	2.786	3.658	7.705	1.084	1.383	1.618	1.767	0.880	1.002	0.926	0.946

ND: Not Detected

As is evident from the tables above, the impurity profiles demonstrate that each impurity is within the stability limit prescribed through the all the time points at temperatures

of 2-8 °C and 25°C with 60% relative humidity. However, at a temperature of 30°C with 75% relative humidity the impurity profiles are within the tolerated limits up to 3 months.

As such, it may be concluded that in certain developing countries, wherein greater temperature and humidity must be tolerated, *e.g.*, which may approach a temperature of 30°C with 75% relative humidity, the formulations of the present invention remain stable with storage at, for example, room temperature for a period of up to three months.

Incorporation By Reference

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents were considered to be within the scope of this invention and are covered by the following claims. Moreover, any numerical or alphabetical ranges provided herein are intended to include both the upper and lower value of those ranges. In addition, any listing or grouping is intended, at least in one embodiment, to represent a shorthand or convenient manner of listing independent embodiments; as such, each member of the list should be considered a separate embodiment.

CLAIMS

1. A bi-layer oral tablet formulation comprising a fixed dose combination of cyclophosphamide and capecitabine, wherein the cyclophosphamide is in a first layer and the capecitabine is in a second layer.

2. The tablet formulation of claim 1, wherein the first layer and the second layer are compressed to form a single bi-layer oral tablet.

3. The tablet formulation of claim 2 or 3, wherein the cyclophosphamide in the first layer is cyclophosphamide-SG.

4. The tablet formulation of any one of claims 1 to 3, wherein the single bi-layer tablet is film coated.

5. The tablet formulation of claim 4, wherein the film coating is applied by spray coating.

6. The tablet formulation of claim 4 or 5, wherein the applied film coating comprises components selected from the group consisting of a film former, a plasticizer, an anti tacking agent, an opacifier, a solvent, and any combination thereof.

7. The tablet formulation of claim 6, wherein the applied film coating comprises the following composition:

Eudragit NE 30 D	Film Former;
Poly Ethylene Glycol 4000 Ph Eur / USP	Plasticizer;
Polysorbate 80 Ph Eur / USP	Plasticizer;
Talc Ph Eur / USP	Anti Tacking Agent;
Titanium Dioxide Ph Eur / USP	Opacifier; and
Purified Water	Solvent.

8. The tablet formulation of any one of claims 1 to 7, comprising (i) a metronomically effective amount of cyclophosphamide and (ii) a metronomically effective amount of capecitabine.

9. The tablet formulation of any one of claims 1 to 8, wherein capecitabine is present in about 600 mg, and the cyclophosphamide is present in about 40 mg.

10. The tablet formulation of any one of claims 1 to 8, wherein capecitabine is present in about 300 mg, and the cyclophosphamide is present in about 20 mg.

11. The tablet formulation of any one of claims 1 to 10, wherein the first layer and the second layer are each separately prepared and formed into said layer through compression prior to being compressed together to form a single, bi-layer oral tablet.

12. The tablet formulation of any one of claims 1 to 11, wherein the two layers are compressed to produce a smooth surface suitable for coating.

13. The tablet formulation of any one of claims 1 to 12, wherein the second layer comprises components selected from the group consisting of capecitabine, a diluent, a disintegrant, a binder, a lubricant, and any combination thereof.

14. The tablet formulation of any one of claims 1 to 13, wherein the second layer comprises the following composition:

Capecitabine USP	Active;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent;
Croscarmellose Sodium Ph Eur / USP	Disintegrant ;
Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	Binder; and
Magnesium Stearate Ph Eur / USP	Lubricant.

15. The tablet formulation of any one of claims 4 to 14, wherein the second layer comprises the following composition:

Capecitabine USP	60.98% w/w of tablet;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	12.50% w/w of tablet;

Croscarmellose Sodium Ph Eur / USP	4.68% w/w of tablet;
Hydroxy Propyl Methyl Cellulose 5 cps Ph Eur / USP	1.52% w/w of tablet; and
Magnesium Stearate Ph Eur / USP	1.63% w/w of tablet.

16. The tablet formulation of any one of claims 4 to 15, wherein there is no barrier layer interposed between the first layer and the second layer.

17. The tablet formulation of any one of claims 1 to 16, wherein the second layer is prepared by high shear wet granulation.

18. The tablet formulation of any one of claims 1 to 17, wherein the first layer comprises components selected from the group consisting of cyclophosphamide, a gliding agent, a diluent, a disintegrant, a lubricant, and any combination thereof.

19. The tablet formulation of any one of claims 1 to 18, wherein the first layer comprises the following composition:

Cyclophosphamide USP	Active
Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	Gliding Agent
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	Diluent
Croscarmellose Sodium Ph Eur / USP	Disintegrant
Magnesium Stearate Ph Eur / USP	Lubricant

20. The tablet formulation of any one of claims 4 to 19, wherein the first layer comprises the following composition:

Cyclophosphamide USP	4.07 % w/w of tablet;
Colloidal Silicon Dioxide (Aerosil 200) Ph Eur / USP	0.37 % w/w of tablet;
Micro Crystalline Cellulose (Avicel PH 112) Ph Eur / USP	10.81% w/w of tablet;
Croscarmellose Sodium Ph Eur / USP	0.51% w/w of tablet; and

Magnesium Stearate Ph Eur / USP	0.50% w/w of tablet.

21. The tablet formulation of any one of claims 1 to 20, wherein the first layer is prepared by an advanced slugging protocol or by direct compression.

22. The tablet formulation of claim 21, wherein the advanced slugging protocol comprises the following steps:

co-milling the cyclophosphamide with a gliding agent and a diluent at low speed to produce a co-milled mixture;

blending the co-milled mixture with a combination of a sifted disintegrant and a lubricant;

slugging the blended mixture on a tablet compression machine;

milling the slugs at low speed;

lubricating the milled slugs with a sifted lubricant; and

compressing the lubricated milled slug into a tablet layer comprising cyclophosphamide, such that cyclophosphamide-SG is formed.

23. The tablet formulation of any one of claims 1 to 22, wherein the cyclophosphamide-SG is degradation resistant.

24. The tablet formulation of any one of claims 1 to 23, wherein the cyclophosphamide-SG is uniformity enhanced.

25. The tablet formulation of any one of claims 1 to 24, wherein the cyclophosphamide-SG is purity enhanced.

26. The tablet formulation claim 25, wherein any individual impurity related to an active agent is present in amounts less than about 3 percent of the label content of the active agent, and the total impurities related to active agents are present in amounts less than about 6 percent of the label content of the active agents.

27. The tablet formulation claim 25, wherein no more than about 3.5% of a Impurity B of Cyclophosphamide is present when the composition is stored at room temperature for a period of one to three months.

28. A method of treatment of cancer comprising metronomic administration of a formulation of any one of claims 1 to 27 to a subject.

29. The method of claim 28, wherein the metronomic administration is highly fractionated metronomic administration of the formulation.

30. The method of claim 28 or 29, wherein the subject is human.

31. The method of any one of claims 28 to 30, wherein the subject is not pretreated, and the formulation is the primary therapeutic course of treatment.

32. The method of any one of claims 28 to 30, wherein the amount of capecitabine is about 600mg or less.

33. The method of any one of claims 28 to 31, wherein the amount of cyclophosphamide is about 40 mg or less.

34. A method of preparation of any one the bi-layer oral tablet formulations of claims 1 to 27, comprising compressing a first layer of cyclophosphamide with a second layer of capecitabine in a fixed dose combination.

35. The method of claim 34, wherein the cyclophosphamide in the first layer is cyclophosphamide-SG.

36. The method of claim 34 or 35, further comprising film coating the single bi-layer tablet.

37. The method of claim 36, wherein the film coating is applied by spray coating.

38. The method of claim 36 or 37, wherein the film coating is prepared by

homogenizing an anti-tacking agent in a solvent to form a homogenized mixture;

dispersing one or more plasticizers in a film former with continuous stirring to form a dispersed mixture; and

mixing the homogenized mixture with the dispersed mixture by stirring.

39. The method of any one of claims 34 to 38, wherein the first layer is prepared by an advanced slugging protocol or by direct compression.

40. The method of claim 39, wherein the advanced slugging protocol comprises the following steps:

co-milling the cyclophosphamide with a gliding agent and a diluent at low speed to produce a co-milled mixture;

blending the co-milled mixture with a combination of a sifted disintegrant and a lubricant;

slugging the blended mixture on a tablet compression machine;

milling the slugs at low speed;

lubricating the milled slugs with a sifted lubricant; and

compressing the lubricated milled slug into a tablet layer comprising cyclophosphamide, such that cyclophosphamide-SG is formed.

41. The method of any one of claims of 34 to 40, wherein the second layer is prepared by high shear wet granulation.

42. The method of claim 39, wherein the high shear wet granulation comprises the following steps:

sifting capecitabine together with a disintegrant and a diluent;

dry mixing the sifted mixture in a high shear mixer;

dissolving a binder in a solvent with continuous stirring to create a granulating solution;

granulating the dry mixed mixture using the granulating solution in a high shear mixer and slow impeller speed, followed by kneading the wet mass at fast impeller speed;

drying the wet granules in a fluid bed drier;

milling the dried granules;

sifting a disintegrant and a diluent, and blending the sifted mixture with the milled dried granules;

lubricating the mixture of dried granules by blending with a sifted lubricant; and

compressing the lubricated mixture into a tablet layer comprising capecitabine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054447

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/24 A61K9/28 A61K31/16 A61K31/17
A61K31/495 A61K31/66
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2015/044961 A2 (INTAS PHARMACEUTICALS LTD [IN]) 2 April 2015 (2015-04-02) pages 1, 4 - page 6	1,2,4,6, 8-10,13, 14, 17-19, 21,28,34
A	WO 2013/028186 A1 (OXFORD ONCOLOGY INC [US]; KERR DAVID [GB]) 28 February 2013 (2013-02-28) page 12, paragraph 2; claims 17,28 page 26	1-42
A	WO 2007/143212 A1 (ARIAD GENE THERAPEUTICS INC [US]; GIANNI LUCA [IT]; BEDROSIAN CAMILLE) 13 December 2007 (2007-12-13) paragraphs [0096], [0168]; example 1	1-42

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2015	07/10/2015

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054447

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	"Clinical Efficacy of Capecitabine and Cyclophosphamide (XC) in Patients with Metastatic Breast Cancer ＊", , 1 August 2011 (2011-08-01), XP55215684, Retrieved from the Internet: URL:http://ousar.lib.okayama-u.ac.jp/file/46848/65_4_231.pdf [retrieved on 2015-09-23] the whole document -----	1-42

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/054447

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