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(54) Benævnelse: **FARMACEUTISK SAMMENSÆTNING, SOM OMFATTER ET AMIDDERIVAT, DER HÆMMER VÆKSTEN AF CANCERCELLER, OG ET SMØREMIDDEL UDEN METALSALT**

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Anonymous: "Handbook of Pharmaceutical Excipients", 2006, Pharmaceutical Press, XP002736604, * page 767 *
Anonymous: "The Merck Index", 2001, Merck&Co., Inc., XP002736605, * item 5675; page 5682 *

Fortsættes ...

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition comprising an amide derivative or its pharmaceutically acceptable salt inhibiting the growth of cancer cells and a non-metallic salt lubricant.

BACKGROUND OF THE INVENTION

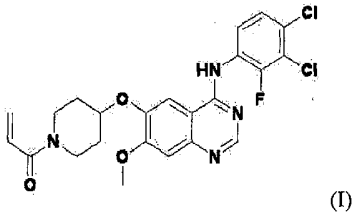
[0002] The epidermal growth factor receptor (EGFR) is known to have four receptor subtypes, *i.e.,* EGFR/ErbB1, Her-2/ErbB2, Her-3/ErbB3, and Her-4/ErbB4. They are abnormally overexpressed in most solid tumor cells. Also, activation of the receptor by ligands leads to activation of the cellular signaling pathway, which gives rise to growth, differentiation, angiogenesis, metastasis, and resistance of tumor cells (A. Wells, Int. J. Biochem. Cell Biol., 1999, 31, 637-643). Therefore, it is expected that blocking of the tumor cell signaling pathway mediated by the epidermal growth factor receptor would produce antitumor effects. Hence, there have been many research efforts for developing anticancer drugs targeting the epidermal growth factor receptor.

[0003] Such anticancer drugs targeting the epidermal growth factor receptor are categorized into two groups: monoclonal antibodies targeting an extracellular domain and small molecule drugs targeting an intracellular tyrosine kinase. The monoclonal antibodies have an advantage of a good pharmaceutical efficacy with a less extent of side effects due to its selective binding on the epidermal growth factor receptors. However, the monoclonal antibodies have drawbacks that they are quite expensive and must be administered by injection. Meanwhile, the small molecule drugs targeting a tyrosine kinase are relatively inexpensive and orally administrable, and they also have a good pharmaceutical efficacy through reacting with the receptor subtypes (*e.g.*, EGFR, Her-2, Her-3 and Her-4) selectively or simultaneously.

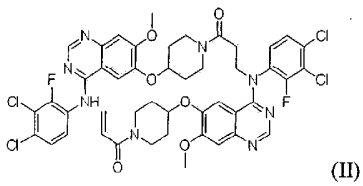
[0004] Examples of the small molecule drugs include selective inhibitors of EGFR such as Iressa® (Gefitinib, AstraZenaca) and Tarceva® (Erlotinib, Roche), and dual inhibitors simultaneously blocking EGFR and Her-2 such as Tykerb® (Lapatinib, GlaxoSmithKline). These drugs are currently being used for treating lung cancer and advanced Her-2 positive breast cancer, respectively. Clinical trials therefor are also being conducted to increase the efficacy against other solid tumors.

[0005] A recent study has reported that a second mutation--*i.e.*, a threonine-to-methionine substitution at the amino acid position 790 in adenosine triphosphate (ATP)-binding sites to the EGFR tyrosin kinase domain--can reduce the binding ability of the drug, which results in a drastic decrease in the drug response rate (C.H. Gow, et al., PLoS Med., 2005, 2(9), e269). Thus, it is required to develop a drug having enhanced inhibitory activities against EGFR resistant cancer cells.

[0006] Korean Patent Laid-open Publication No. 2008-0107294 discloses a compound of formula (I), which selectively and effectively inhibits the growth of cancer cells and the development of drug resistance induced by the EGFR and its mutants without side effects. However, it has been found that the pharmaceutical formulation comprising the compound of formula (I) as an active ingredient and its pharmaceutically acceptable additives facilitates the formation of a compound of formula (II) (hereinafter, referred to as the related compound IV) under certain storage conditions, thereby reducing the amount of the compound of formula (I).



(I)



(II)

[0007] The purity of an active ingredient is an important factor for preparing a safe and effective pharmaceutical composition because certain impurities contained in a drug substance may produce side effects during treatment. Some of the impurities can be removed during the preparation of the drug. But certain materials produced by degradation of the drug due to the changes in such various conditions as temperature, humidity and light may remain as impurities.

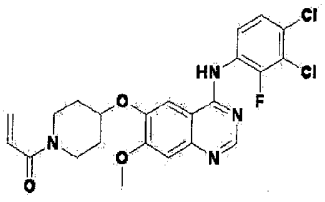
[0008] The present inventors have endeavored to study the factors that promote the formation of the related compound IV during storage of a pharmaceutical formulation comprising a compound of formula (I) and have found that pharmaceutically acceptable additives, particularly metallic salts contained in lubricants, cause expedition of the formation of the related compound IV. Hence, the present inventors have developed a pharmaceutical composition having an enhanced stability by employing a non-metallic salt lubricant, which is free of a metallic salt component.

SUMMARY OF THE INVENTION

[0009] It is an object of the present invention to provide a pharmaceutical composition with an improved stability, comprising an amide derivative or a pharmaceutically acceptable salt thereof, which effectively inhibits the growth of cancer cells.

[0010] In accordance with one aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a non-metallic salt lubricant:

, wherein said non-metallic salt lubricant is selected from the group consisting of fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc, and a mixture thereof.



(I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, which respectively show:

Fig. 1: the stability test results showing the amount of the related compound IV produced after heating the pharmaceutical compositions of Examples 1 to 8 and Comparative Example 1 at 60 °C ;

Fig. 2: the stability test results showing the amount of the related compound IV produced after heating the pharmaceutical compositions of Comparative Examples 1 to 4 and Example 1 at 60 °C ;

Fig. 3: the accelerated stability test results showing the amount of the related compound IV produced after exposure of the pharmaceutical compositions of Examples 1 and 2 and Comparative Examples 1 and 3 under the accelerated conditions (40 °C and 75% RH); and

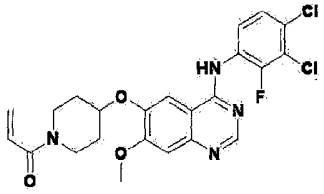
Fig. 4: the accelerated stability test results in a HDPE bottle showing the amount of the related compound IV produced after exposure of the pharmaceutical compositions of Examples 1 and 2 and Comparative Examples 1 and 3 under accelerated conditions (40 °C and 75% RH).

DETAILED DESCRIPTION OF THE INVENTION

[0012] The present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically

acceptable salt thereof, and a non-metallic salt lubricant:

, wherein said non-metallic salt lubricant is selected from the group consisting of fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc, and a mixture thereof.



(I).

[0013] Each ingredient of the inventive pharmaceutical composition is described in detail as follows.

(a) Pharmaceutically active ingredient

[0014] The pharmaceutical composition according to the present invention comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof as a pharmaceutically active ingredient.

[0015] The compound of formula (I) (hereinafter referred to as the code name "HM781-36B"), as disclosed in Korea Patent Laid-open Publication No. 2008-0107294, can selectively and effectively inhibit the growth of cancer cells and the development of drug resistance induced by the EGFR and its mutants, while causing no adverse side effects.

[0016] The pharmaceutically acceptable salt of the compound of formula (I) includes, but is not limited to, an acid-addition salt of an inorganic or organic acid. Examples of the inorganic acid-addition salt may include salts of hydrochloric acid, sulfuric acid, disulfonic acid, nitric acid, phosphoric acid, perchloric acid, or bromic acid; examples of the organic acid-addition salt may include salts of formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, benzoic acid, citric acid, maleic acid, malonic acid, malic acid, tartaric acid, gluconic acid, lactic acid, gestisic acid, fumaric acid, lactobionic acid, salicylic acid, phthalic acid, embonic acid, aspartic acid, glutamic acid, camsylic acid, besylic acid, or acetylsalicylic acid (aspirin). The pharmaceutically acceptable salt may also include metal salts derived from alkali metals such as calcium, sodium, magnesium, strontium, potassium.

[0017] In the present invention, the compound of formula (I) may be employed in an amount ranging from 0.1 to 50% by weight, preferably 0.5 to 10% by weight, based on the total weight of the composition. The compound may be contained in the composition in an amount ranging from 0.1 mg to 100 mg, preferably 0.5 to 50 mg, per 1 dosage unit of the composition.

(b) Non-metallic salt lubricant

[0018] Lubricants are ingredients added to improve the compression process of granules, and they are considered as a critical excipient, which plays important roles in the manufacture of solid compressed compositions. Advantages of employing lubricants include an improved flow of the powder or granular materials, which allows them to be more readily filled in a die; a reduced friction of the powder or granular materials as well as that between the powder or granular materials and the punch or the die; and enhanced compressibility and dischargeability of the tablets. Lubricants can be categorized as shown in Table 1.

<Table 1>

Category	Lubricant
Fatty acid metal salts	calcium stearate, magnesium stearate, sodium stearyl fumarate, zinc stearate
Fatty acid esters	glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl trimyristate, glyceryl tristearate, sucrose fatty acid ester
Fatty acids & alcohols	palmitic acid, palmitoyl alcohol, stearic acid, stearyl alcohol
Oils	hydrogenated castor oil, mineral oil, hydrogenated vegetable oil
Others	fumaric acid, polyethylene glycol (PEG 4000 & PEG 6000), polytetrafluoroethylene, talc

[0019] The pharmaceutical composition of the present invention comprising a compound of formula (I) is characterized by the use of a non-metallic salt lubricant in order to prevent the formation of the related compound IV, which may otherwise be formed due to a metallic salt if it is contained in the composition.

[0020] The term "non-metallic salt lubricant" according to the present invention refers to a lubricant that is free of metallic materials, e.g., such metallic salts as calcium stearate, magnesium stearate, sodium stearayl fumarate, zinc stearate, and the like. Examples of the non-metallic salt lubricant according to the present invention may include fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc.

[0021] The enhanced storage stability of the inventive pharmaceutical composition can be achieved by employing such non-metallic salt lubricants.

[0022] Specifically, examples of the non-metallic salt lubricant, which can be used in the present invention, may include, but are not limited to, fatty acid esters (*e.g.*, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl trimyristate, glyceryl tristearate, sucrose fatty acid ester); fatty acids (*e.g.*, palmitic acid, stearic acid); oils (*e.g.*, hydrogenated castor oil, mineral oil, hydrogenated vegetable oil) polyethylene glycol (*e.g.*, PEG 4000 or PEG 6000); starch; and talc. The non-metallic salt lubricants may be used solely or as a mixture thereof.

[0023] Preferably, examplary non-metallic salt lubricants according to the present invention may include sucrose fatty acid ester, hydrogenated vegetable oil, stearic acid, glyceryl behenate, glyceryl palmitostearate, talc, starch, and PEG 6000, more preferably sucrose fatty acid ester and hydrogenated vegetable oil.

[0024] In the present invention, the non-metallic salt lubricant may be employed in an amount ranging from 0.1 to 100 parts by weight, preferably 0.1 to 50 parts by weight, more preferably 0.25 to 10 parts by weight, based on 1 part by weight of the compound of formula (I).

[0025] If the amount of the non-metallic salt lubricant employed is less than 0.1 parts by weight, a tablet formed would not be readily released from the die cast or may stick to the die cast during the tablet formation. On the other hand, if the amount is greater than 100 parts by weight, a tablet would suffer from such problems as capping or delamination. Moreover, since lubricants are in general hydrophobic, if they are employed in a large amount, they may cause such unintended problems as a delayed disintegration and a low dissolution rate.

(c) Pharmaceutically acceptable additives

[0026] The pharmaceutical composition of the present invention may further comprise pharmaceutically acceptable additives and can be formulated into a variety of administration forms, preferably an oral administration form. Representative examples of the formulation for oral administration may include powder, tablet, pill, capsule, liquid, suspension, emulsion, syrup, and granule, preferably tablet and capsule, but are not limited thereto.

[0027] In the present invention, the pharmaceutically acceptable additives may include a diluent, a binder, a disintegrant.

[0028] Examples of the diluent may include microcrystalline cellulose, lactose, mannitol, calcium phosphate; examples of the binder may include povidone, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), sodium carboxymethyl cellulose; and examples of the disintegrant may include crospovidone, sodium croscarmellose, sodium starch glycolate.

[0029] The diluent may be used in an amount ranging from 20 to 95% by weight, the binder may be used in an amount ranging from 1 to 10% by weight, and the disintegrant may be used in an amount ranging from 1 to 30% by weight, based on the total weight of the composition.

[0030] The pharmaceutical composition of the present invention may be coated with a coating substrate to prevent the composition from being in direct contact with the hand or skin of a user.

[0031] The coating substrate that can be used in the present invention may include a rapid release coating substrate, an enteric coating substrate, or a sustained release coating substrate. The rapid release coating substrate may be selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol graft

polymer (Kollocoat IR®, BASF), and a mixture thereof. The enteric coating substrate may be selected from the group consisting of (meth)acrylate copolymer (Eudragit®, EVONIK), hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, and a mixture thereof. The sustained release coating substrate may be selected from the group consisting of cellulose acetate, ethyl cellulose, polyvinyl acetate, and a mixture thereof.

[0032] The coating substrate may be coated on the surface of the composition in an amount ranging from 1 to 50 parts by weight, preferably 1 to 30 parts by weight, based on 100 parts by weight of the uncoated core.

[0033] The present invention also provides a method for preparing the pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a non-metallic salt lubricant, wherein said non-metallic salt lubricant is selected from the group consisting of fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc, and a mixture thereof.

[0034] A formulation of the pharmaceutical composition comprising the above-mentioned ingredients can be prepared by the following method, which comprises the steps of:

1. (1) mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof with such a pharmaceutically acceptable additive as a diluent and a binder, and granulating the mixture to obtain granules;
2. (2) mixing the granules prepared in step (1) with such a pharmaceutically acceptable additive as a diluent and a disintegrant, and adding a non-metallic salt lubricant thereto to obtain mixed granules; and
3. (3) subjecting the mixed granules prepared in step (2) to a formulating step.

[0035] In one embodiment of the present invention, the inventive pharmaceutical composition can be prepared by admixing a compound of formula (I) and mannitol in a solution of povidone in purified water, subjecting the prepared mixture to wet granulation, and then drying the resulting granules. The prepared granules can be formed into a tablet by mixing the prepared granules with mannitol and Crospovidone, adding a non-metallic salt lubricant thereto, and then tableting the mixed granules by a tablet, wherein said non-metallic salt lubricant is selected from the group consisting of fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc, and a mixture thereof.

[0036] The various steps related with the formulation of the pharmaceutical composition of the present invention can be conducted according to conventional techniques known in the art. Further, the method of the present invention may further comprise the step of coating the formulation prepared in step (3) with the above-mentioned coating substrates for convenient storage and ease of use.

[0037] The pharmaceutical composition of the present invention can effectively inhibit the growth of cancer cells by comprising the compound of formula (I), which selectively and effectively inhibits the growth of cancer cells and the development of drug resistance induced by the EGFR and its mutants. Also, the pharmaceutical composition of the present invention can inhibit the formation of impurities (*i.e.*, the related compounds IV) to less than 0.5% by weight under extreme conditions (e.g., kept in an airtight HDPE container at 60 °C for 4 weeks), and under accelerated conditions (e.g., kept in an airtight HDPE container at 40°C/75% RH for 6 months) by comprising the non-metallic salt lubricant. Therefore, the pharmaceutical composition of the present invention can enhance the efficacy and improve the stability of the compound of formula (I).

[0038] Therefore, the present invention provides a method to stabilize a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof, comprising adding the non-metallic salt lubricant to the pharmaceutical, wherein said non-metallic salt lubricant is selected from the group consisting of fatty acid esters, fatty acids, oils, polyethylene glycols (PEGs), starch, talc, and a mixture thereof.

Examples

Examples 1 to 8: Preparation of pharmaceutical compositions comprising non-metallic salt lubricants

[0039] Pharmaceutical compositions of Examples 1 to 3 were prepared by employing a compound of formula (I) (hereinafter, referred to as "HM781-36B," Dongwoo Syntech Co., Ltd., Korea); mannitol (Roquette); Povidone® (BASF); Crospovidone®

(BASF); and sucrose fatty acid ester (Daiichi Kogyo Seiyaku, Japan), hydrogenated vegetable oil (Lubritab®, JRS Pharma), or stearic acid (Emery Oleochemicals.), as a non-metallic salt lubricant, in accordance with the composition and the amount (unit: mg) described in Table 2.

[0040] Specifically, HM781-36B and mannitol were mixed and the mixture was subjected to a wet-granulation process by a conventional method with employing a binder solution of Povidone dissolved in purified water. The wet granules thus obtained were dried, mixed with mannitol and Crospovidone, and subsequently added with a lubricant, which was previously sieved through a 30 mesh screen, to prepare a final mixture. The final mixture thus prepared was formed into a tablet having a hardness of about 5 to 10 kp by a tablet machine (Sejong, Korea) according to a conventional method.

<Table 2>

			Ex.1	Ex. 2	Ex. 3
Wet granule	Mixture	HM781-36B	0.5	0.5	0.5
		Mannitol	50	50	50
	Binder	Povidone	1.5	1.5	1.5
		<Purified water>	<10>	<10>	<10>
Mixture		Mannitol	42	42	42
		Crospovidone	5	5	5
Final mixture		Sucrose fatty acid ester	2	-	-
		Hydrogenated vegetable oil	-	2	-
		Stearic acid	-	-	1
Total weight			101	101	100

[0041] Pharmaceutical compositions of Examples 4 to 8 were prepared by the same method as above by employing a compound of formula (I) (HM781-36B, Dongwoo Syntech Co., Ltd., Korea); mannitol (Roquette); Povidone® (BASF); Crospovidone® (BASF); and glyceryl behenate (Compritol 888 ATO®, Gattefosse), glyceryl palmitostearate (Compritol HD5®, Gatefosse), talc (Nippon Talc Corp., Japan), starch (Roquette), or PEG 6000 (Sanyo Chemical, Japan), as a non-metallic salt lubricant, in accordance with the composition and the amount (unit: mg) described in Table 3.

<Table 3>

			Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8
Wet granule	Mixture	HM781-36B	0.5	0.5	0.5	0.5	0.5
		Mannitol	50	50	50	50	50
	Binder	Povidone	1.5	1.5	1.5	1.5	1.5
		<Purified water>	<10>	<10>	<10>	<10>	<10>
Mixture		Mannitol	42	42	42	42	42
		Crospovidone	5	5	5	5	5
Final mixture		Glyceryl behenate	2	-	-	-	-
		Glyceryl palmitostearate	-	2	-	-	-
		Talc	-	-	3	-	-
		Starch	-	-	-	5	-
		PEG 6000					3
Total weight			101	101	102	104	102

[0042] Pharmaceutical compositions of Examples 9 to 15 were prepared by the same method as above by employing a compound of formula (I) (HM781-36B, Dongwoo Syntech Co., Ltd., Korea); mannitol (Roquette); Povidone® (BASF); Crospovidone® (BASF); and glyceryl monostearate (Capmul GMS-50), palmitoyl alcohol (Landz International Company Ltd., China), stearyl alcohol (Lubrizol Advanced Materials, U.S.), hydrogenated castor oil (BASF), mineral oil (Alfa Aesar, U.S.), fumaric acid (Merck), or silicon dioxide (Grace Davison, U.S.), as a non-metallic salt lubricant, in accordance with the composition and the

amount (unit: mg) described in Table 4.

<Table 4>

			Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 15
Wet granule	Mixture	HM781-36B	0.5	0.5	0.5	0.5	0.5	0.5	0.5
		Mannitol	50	50	50	50	50	50	50
	Binder	Povidone	1.5	1.5	1.5	1.5	1.5	1.5	1.5
		<Purified water>	<10>	<10>	<10>	<10>	<10>	<10>	<10>
Mixture		Mannitol	42	42	42	42	42	42	42
		Crospovidone	5	5	5	5	5	5	5
Final mixture		Glyceryl monostearate	5	-	-	-	-	-	-
		Palmitoyl alcohol	-	5	-	-	-	-	-
		Stearyl alcohol	-	-	5	-	-	-	-
		Hydrogenated castor oil	-	-	-	5	-	-	-
		Mineral oil	-	-	-	-	5	-	-
		Fumaric acid	-	-	-	-	-	5	-
		Silicon dioxide	-	-	-	-	-	-	2
Total weight			104	104	104	104	104	104	101

Comparative Examples 1 to 4: Preparation of pharmaceutical compositions comprising metallic salt lubricants

[0043] The procedures of the above Examples were repeated by employing the composition and the amount (unit: mg) described in Table 5, to prepare pharmaceutical compositions of Comparative Examples 1 to 4 comprising metallic salt lubricants.

<Table 5>

			Comp. Ex. 1	Comp. Ex. 2	Comp. Ex. 3	Comp. Ex. 4
Wet granule	Mixture	HM781-36B	0.5	0.5	0.5	0.5
		Mannitol	50	50	50	50
	Binder	Povidone	1.5	1.5	1.5	1.5
		<Purified water>	<10>	<10>	<10>	<10>
Mixture		Mannitol	42	42	42	42
		Crospovidone	5	5	5	5
Final mixture		Magnesium stearate	1	-	-	-
		Calciumstearate	-	1	-	-
		Sodium stearyl fumarate	-	-	1	-
		Zinc stearate	-	-	-	1
Total weight			100	100	100	100

Test Example: Measurement of the related compound formed

[0044] In order to evaluate the storage stability of the pharmaceutical compositions prepared in Examples 1 to 8 and Comparative Examples 1 to 4, the pharmaceutical compositions were each packaged with 1 g of silica gel in an HDPE bottle and stored in a chamber (60 °C). After 2 and 4 weeks, respectively, the related compound IV, a major degradation product of HM781-36B, was extracted by 60% acetonitrile as a solvent, and then HPLC analyses were performed. The results of Examples 1 to 8 are shown in Table 6 and Fig. 1, and those of Comparative Examples 1 to 4 are shown in Table 7 and Fig. 2.

<Table 6>

Ex.	1	2	3	4	5	6	7	8
Initial	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.05
2 weeks, 60 °C	0.26	0.23	0.17	0.27	0.21	0.15	0.18	0.37
4 weeks, 60 °C	0.34	0.35	0.31	0.38	0.36	0.26	0.29	0.45

<Table 7>

Comp. Ex.	1	2	3	4
Initial	0.04	0.04	0.04	0.04
2 weeks, 60 °C	1.52	0.98	1.60	1.09
4 weeks, 60 °C	2.46	2.25	3.41	1.98

[0045] In order to observe the changes of stability of the pharmaceutical compositions prepared in accordance with Examples 1 and 2 and Comparative Examples 1 and 3 against temperature and humidity, the pharmaceutical compositions were exposed to 40 °C and 75% RH. After 1 and 2 weeks, respectively, the related compound IV, a major degradation product of HM781-36B, was extracted by 60% acetonitrile as a solvent, and then HPLC analyses were performed. The results are shown in Table 8 and Fig. 3.

<Table 8>

	Ex. 1	Ex. 2	Comp. Ex. 1	Comp. Ex. 3
Initial	0.05	0.04	0.04	0.04
1 week 40°C/75% RH	0.12	0.10	0.73	0.32
2 weeks 40°C/75% RH	0.16	0.15	1.18	0.51

[0046] In order to observe the changes of stability of the pharmaceutical compositions prepared in accordance with Examples 1 and 2 and Comparative Examples 1 and 3 against temperature and humidity under accelerated conditions, the compositions were exposed to 40 °C and 75% RH in sealed HDPE containers for 1, 3 and 6 months. The related compound IV of each composition was extracted by 60% acetonitrile as a solvent, and then HPLC analyses were performed. The results are shown in Table 9 and Fig. 4.

<Table 9>

	Ex. 1	Ex. 2	Comp. Ex. 1	Comp. Ex. 3
Initial	0.05	0.04	0.04	0.04
1 month ACLTD 40°C	0.15	0.14	0.31	0.28
3 months ACLTD 40°C	0.17	0.15	0.41	0.32
6 months ACLTD 40°C	0.20	0.18	0.62	0.58

[0047] As shown in Tables 6 to 9 and Figs. 1 to 4, the formation of the related compound IV was reduced by about 4 to 10 times or more in the pharmaceutical compositions comprising any of the non-metallic salt lubricants compared with the pharmaceutical compositions comprising the metallic salt lubricants. Thus, the storage stability of the pharmaceutical compositions containing HM781-36B as an active ingredient can significantly be enhanced by adding any of the non-metallic salt lubricants to the pharmaceutical compositions.

[0048] According to the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the limits of unknown and known impurities are prescribed as 0.2% and 0.5%, respectively. The pharmaceutical compositions of Examples 1 and 2 according to the present invention showed satisfactory results of less than 0.5% at 40 °C in an accelerated stability test as described in the ICH guideline. In contrast, the pharmaceutical compositions of Comparative Examples 1 and 3 comprising conventional metallic salt lubricants exceeded the predetermined limits of the ICH guideline.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

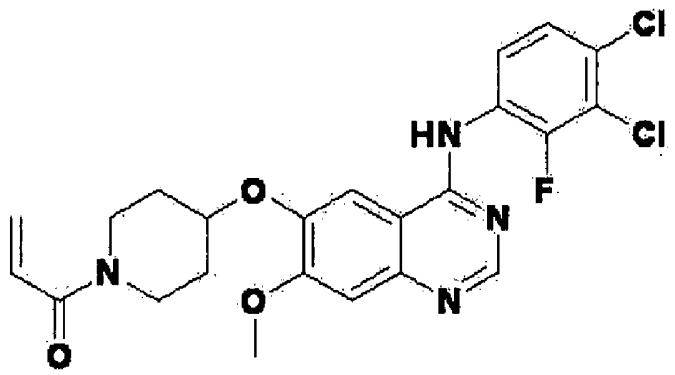
- KR20080107294 [0006] [0015]

Non-patent literature cited in the description

- **A. WELLS**Int. J. Biochem. Cell Biol., 1999, vol. 31, 637-643 [0002]
- **C.H. GOW et al.**PLoS Med., 2005, vol. 2, 9e269- [0005]

Patentkrav

1. Farmaceutisk sammensætning, som omfatter en forbindelse med formlen (I) eller et farmaceutisk acceptabelt salt deraf; og et smøremiddel valgt blandt smøremiddel uden metal,
hvor smøremidlet uden metalsalt er valgt fra gruppen bestående af fedtsyreestere, fedtsyrer, olier, polyethylenglycoler (PEG'er), stivelse, talkum og en blanding deraf



(I).

2. Farmaceutisk sammensætning ifølge krav 1, hvor smøremidlet uden metalsalt er valgt fra gruppen bestående af glycerylbehenat, glycerylpalmitostearat, glycerylmonostearat, glyceryltrimyristat, glyceryltristearat, saccharose-fedtsyreester, palmitinsyre, stearinsyre, alkohol, hydrogeneret ricinusolie, mineralolie, hydrogeneret vegetabilsk olie, PEG 4000, PEG 6000 og en blanding deraf.

3. Farmaceutisk sammensætning ifølge krav 2, hvor smøremidlet uden metalsalt er saccharose-fedtsyreester eller hydrogeneret vegetabilsk olie.

4. Farmaceutisk sammensætning ifølge krav 1, hvor forbindelsen med formlen (I) er indeholdt i en mængde i intervallet fra 0,1 mg til 100 mg pr. 1 doseringsenhed af sammensætningen.

5. Farmaceutisk sammensætning ifølge krav 1, hvor smøremidlet uden metalsalt er indeholdt i en mængde i intervallet fra 0,1 til 100 vægtdele baseret på 1 vægtdel af forbindelsen med formlen (I).

6. Farmaceutisk sammensætning ifølge krav 1, som yderligere omfatter et farmaceutisk acceptabelt tilsætningsstof valgt fra gruppen bestående af et fortyndingsmiddel, et bindemiddel, et desintegrationsmiddel og en blanding deraf.

7. Farmaceutisk sammensætning ifølge krav 6, hvor fortyndingsmidlet er indeholdt i en mængde i intervallet fra 20 til 95 vægtprocent baseret på den samlede vægt af sammensætningen.

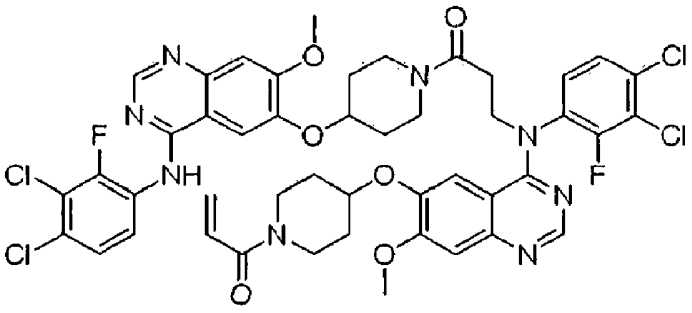
8. Farmaceutisk sammensætning ifølge krav 6, hvor bindemidlet er indeholdt i en mængde i intervallet fra 1 til 10 vægtprocent baseret på den samlede vægt af sammensætningen.

9. Farmaceutisk sammensætning ifølge krav 6, hvor desintegrationsmidlet er indeholdt i en mængde i intervallet fra 1 til 30 vægtprocent baseret på den samlede vægt af sammensætningen.

10. Farmaceutisk sammensætning ifølge krav 1, som er overtrukket med et overtrækssubstrat valgt fra gruppen bestående af et overtrækssubstrat til hurtig frigivelse, et enterisk overtrækssubstrat og et overtrækssubstrat til langvarig frigivelse.

11. Farmaceutisk sammensætning ifølge krav 10, hvor overtrækssubstratet er valgt fra gruppen bestående af hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylalkohol, polyvinylalkohol-polyethylenglycol-graftcopolymer, (meth)acrylsyrecopolymer, phthalsyrehydroxypropylmethylcellulose, phthalsyrecelluloseacetat, celluloseacetat, ethylcellulose, polyvinylacetat og en blanding deraf.

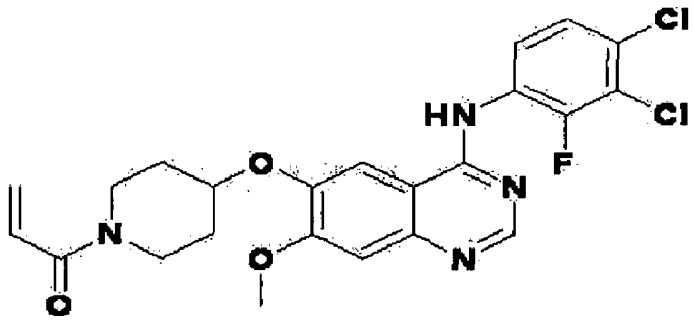
12. Farmaceutisk sammensætning ifølge krav 1, som omfatter mindre end 0,5 vægtprocent af en forbindelse med formlen (II) under ekstreme betingelser, opbevaret i en lufttæt HDPE-beholder ved 60°C i 4 uger, eller under accelererede betingelser, opbevaret i en lufttæt HDPE-beholder ved 40°C og 75% RH i 6 måneder:



(II)

13. Fremgangsmåde til fremstilling af en formulering af den farmaceutiske sammensætning ifølge krav 1, hvilken fremgangsmåde omfatter følgende trin:

(1) at blande en forbindelse med formlen (I) eller et farmaceutisk acceptabelt salt deraf med et farmaceutisk acceptabelt tilsætningsstof og granulere blandingen for at opnå et granulat;
(2) at blande det i trin (1) fremstillede granulat med et farmaceutisk acceptabelt tilsætningsstof og tilsætte et smøremiddel uden metalsalt dertil for at opnå et blandet granulat; og
(3) at underkaste det i trin (2) fremstillede blandede granulat et formuleringstrin

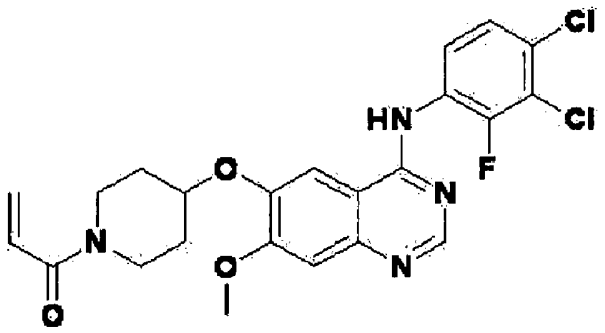


(I).

14. Fremgangsmåde ifølge krav 13, som yderligere omfatter trinet at overtrække den i trin (3) fremstillede formulering med et overtrækssubstrat valgt fra gruppen bestående af et overtrækssubstrat til hurtig frigivelse, et enterisk overtrækssubstrat og et overtrækssubstrat til langvarig frigivelse.

15. Fremgangsmåde til stabilisering af en farmaceutisk sammensætning, som omfatter en forbindelse med formlen (I) eller et farmaceutisk acceptabelt salt deraf, hvilken fremgangsmåde omfatter at tilsætte et smøremiddel uden metalsalt til den farmaceutiske sammensætning:

hvor smøremidlet uden metalsalt er valgt fra gruppen bestående af fedtsyreestere, fedtsyrer, olier, polyethylenglycoler (PEG'er), stivelse, talkum og en blanding deraf



(I).

DRAWINGS

FIG. 1

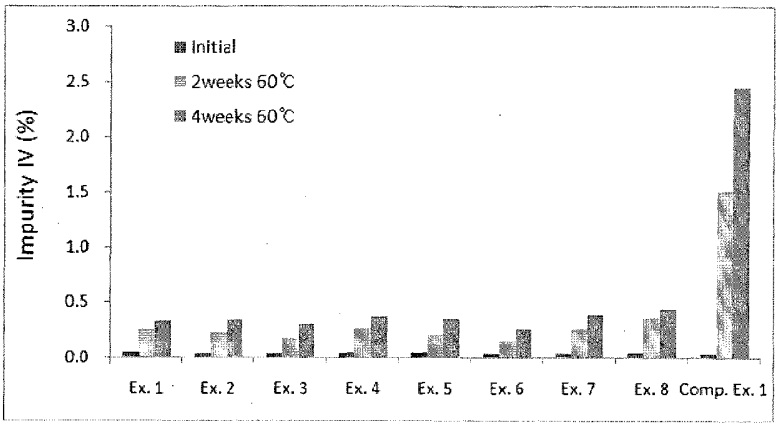


FIG. 2

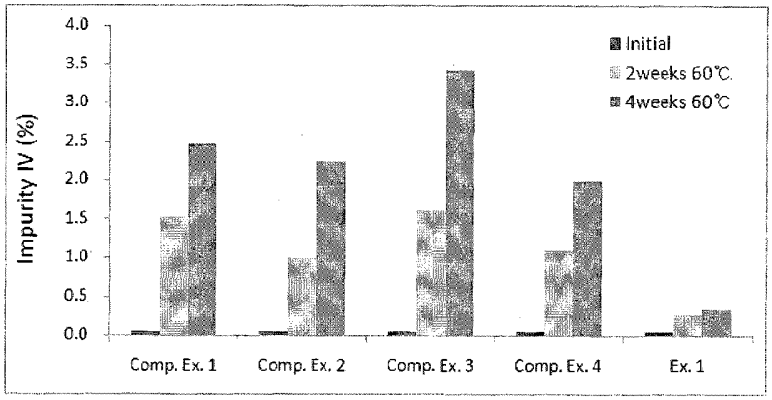


FIG. 3

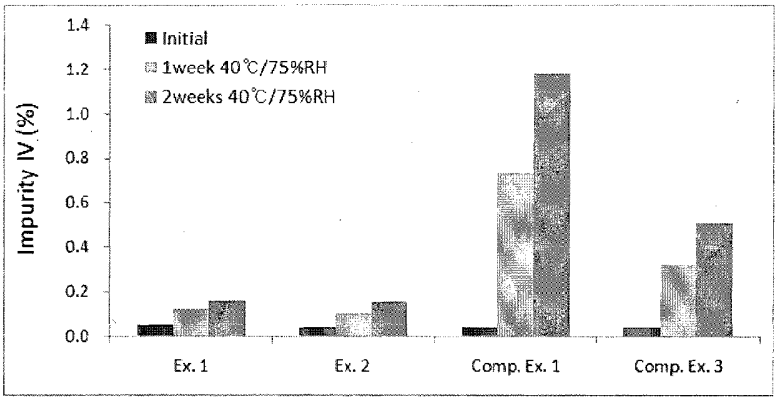
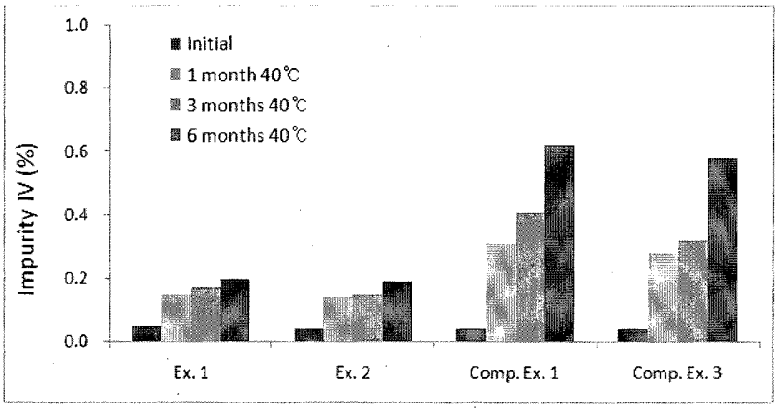

Initial
1week 40℃/75%RH
2weeks 40℃/75%RH
Impurity IV (%)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Ex. 1
Ex. 2
Comp. Ex. 1
Comp. Ex. 3

FIG. 4


Initial
1 month 40℃
3 months 40℃
6 months 40℃
Impurity IV (%)
1.0
0.8
0.6
0.4
0.2
0.0
Ex. 1
Ex. 2
Comp. Ex. 1
Comp. Ex. 3