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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 March 2020 (12.03.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/049429 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *C07D 405/04* (2006.01)

(21) International Application Number:
PCT/IB2019/057324

(22) International Filing Date:
30 August 2019 (30.08.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201821032977 03 September 2018 (03.09.2018) IN

(71) Applicant: **BDR PHARMACEUTICALS INTERNATIONAL PRIVATE LIMITED** [IN/IN]; 407-408, Sharda Chambers, New Marine Lines, Mumbai 400020 (IN).

(72) Inventors: **SHAH, Dharmesh Mahendrabhai**; 2301, Sterling Tower, H.g. Marg, Gamdevi, Mumbai 400007 (IN). **BADIGER, Aravind Manappa**; C-404, Iskon Heights, Gotri Road, Vadodara 390021 (IN). **SHARMA, Mukeshkumar Subhashchandra**; B-11, Omkarnagar Society,i/s Tagore Nagar, Old Padra Road, Vadodara 390007 (IN). **TRIVEDI, Madhavkumar Dilipbhai**; B-301, Kishan Galaxy, Canal Road, Off. Vasna-bhayli Road, Vadodara 391410 (IN). **PATEL, Harikrishnabhai Vinubhai**; Near The Ideal High School, At & Po: Kothamba, TA: Lunavada, Mahisagar 389220 (IN). **PATEL, Prashant Karamshibhai**; 106/A, Kubernagar-1, 202, Gangotri Apartment, Katargam Darwaja, Surat 395004 (IN). **GANDHI, Prashant Kanaiyalal**; Bank Road, Kachhiyawad, Mahemdabad, Kheda 387130 (IN). **PANCHAL, Nimitkumar Harishchandra**; E-105, The Rise-1, Vasna-bhayli Canal Road, B/h Bright Day CBSE School, Vadodara 390012 (IN).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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 the identity of the inventor (Rule 4.17(i))*

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

WO 2020/049429 A1

(54) Title: NOVEL COMPOSITION OF LAPATINIB OF ORAL SOLID DOSAGE FORM AND METHOD OF MANUFACTURING THEREOF

(57) Abstract: The present invention discloses a novel pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof preferably oral solid dosage form of a tablet with pharmaceutically acceptable excipients and method of preparation thereof. The pharmaceutical composition of present invention comprises lapatinib ditosylate monohydrate with one or more pharmaceutically acceptable excipients selected from the group comprising of at least one diluent, at least one disintegrant, at least one binder, at least one lubricant, wherein the composition does not comprise microcrystalline cellulose and sodium starch glycolate. The pharmaceutical composition according to the present invention is economical and advanced dosage form over existing dosage form, with less side effects and time efficient, especially for large scale production, whereby the pharmaceutical composition shows a desired dissolution profile and higher stability with minimum use of excipients.

NOVEL COMPOSITION OF LAPATINIB OF ORAL SOLID DOSAGE FORM AND METHOD OF MANUFACTURING THEREOF

FIELD OF THE INVENTION:

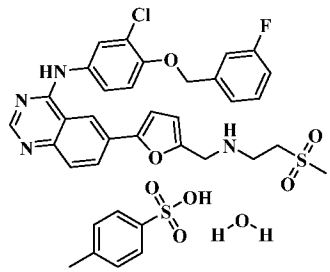
The present invention relates to novel oral solid dosage pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof, preferably in a tablet dosage form. Further, the present invention discloses the process for preparing the same. The present invention provides an economical and advanced dosage form over existing dosage form.

BACKGROUND OF THE INVENTION:

Lapatinib is a small molecule of dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor (EGFR) pathways. It is orally active drug for breast cancer and used for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2).

It is present as the monohydrate of the ditosylate salt, with chemical name N-{3-chloro-4-[(3-fluorophenyl)methoxy]phenyl}-6-(5-{[(2-ethanesulfonylethyl) amino] methyl}furan-2-yl)quinazolin-4-amine and molecular formula $C_{29}H_{26}ClFN_4O_4S$ $(C_7H_8O_3S)_2$ H_2O and a molecular weight of 943.5.

Structurally, lapatinib ditosylate monohydrate is represented as below:



LAPATINIB

Lapatinib is disclosed in US patent no. WO1999035146 and is marketed under the brand name of TYKERB® (by Glaxo Smith Kline) which is of 250 mg, orange colored, oval shaped -biconvex, film-coated tablet for oral administration. Each 250 mg tablet of TYKERB® contains lapatinib ditosylate monohydrate or 250 mg lapatinib free base along with the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate and for coating

of orange film-coat, FD&C yellow no. 6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80 and titanium dioxide.

The recommended dosage of TYKERB® for advanced or metastatic breast cancer is 1250 mg (5 tablets) given orally once daily on days 1-21 continuously in combination with capecitabine 2000 mg/m2/day (administered orally in 2 doses approximately 12 hours apart) on days 1-14 in a repeating 21-day cycle.

Breast cancer is the commonest form of cancer in women worldwide and second leading cause of cancer-related death in American women. Although treatment with chemotherapy, endocrine therapy and targeted therapy has significantly improved outcomes for women with early stage disease, overall survival for women with metastatic disease remains poor with a five-year survival rate of only 15% underscoring the need for novel therapeutic strategies.

PCT publication no. WO2010023187 discloses a pharmaceutical composition with a high percentage of lapatinib as active pharmaceutical ingredient present in an amount of more than 60% by weight based on the total weight of the composition.

WO2014128107 exemplifies a pharmaceutical composition comprises lapatinib as an active ingredient along with one binder, one disintegrant, one lubricant, and one filler, wherein the filler comprises microcrystalline cellulose in an amount of 10 to 30% by weight, relative to the total weight of the pharmaceutical composition.

WO 2010/023188 discloses pharmaceutical compositions comprising lapatinib or a pharmaceutically acceptable salt thereof wherein a unit dose of the composition contains 1200 to 1300 mg of the active pharmaceutical ingredient calculated as the free base.

WO2007143483 reveals a method of treating cancer by administration of a combination of pyrimidine derivatives and quinazoline derivatives, more particularly combination of pazopanib and lapatinib for treatment of cancer.

Indian patent application 970/MUM/2014 claims a pharmaceutical composition comprising lapatinib and one or more pharmaceutically acceptable excipients wherein the composition comprises nanosized lapatinib, having the particle size an average of less than about 2000 nm.

Lapatinib formulations available currently in the market generally use microcrystalline cellulose and magnesium stearate as excipients. Microcrystalline cellulose is a widely used excipient and used in many pill and tablet formulations. However, there are certain disadvantages and side effects there of the microcrystalline cellulose.

It should be noted that the mannitol is inert excipient and is readily water soluble excipient. Cellulose derivatives when used as major component in the formulation have tendency to swell and result into higher variation when products are subjected to dissolution or pK studies. Being water soluble excipient, mannitol do not hinder the absorption of product and hence would be reduction in drug loss. Mannitol provides quite good compressibility as well and imparts adequate density to formulation, thereby making the formulation process more robust and advantageous and importantly scalability becomes quite smooth. Hence mannitol has definitely advantage over using cellulose derivatives. Cellulose derivatives in many cases are reported to have more variable processing parameters and pose challenges in commercial manufacturing process. The extent of use of such excipients becomes a limiting factor and hence excipients like mannitol enjoys better advantages.

Sodium starch glycolate also like most other excipients and bulk additives is not healthy in high doses. Sodium starch glycolate was found to lengthen disintegration time when utilized at high concentrations. Further, it is found that depending on the source, it can cause adverse effects on certain individuals. People with allergy to corn or with celiac disease may experience adverse effects.

To overcome such instances, the present invention discloses a novel pharmaceutical composition of lapatinib that exclude the excipients like microcrystalline cellulose and sodium starch glycolate. Therefore, it is technically advanced and improved over existing prior arts.

OBJECT OF THE INVENTION

The primary object of the present invention is to provide a novel pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof for oral solid dosage form.

Another object of the present invention is to provide the pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof for oral solid dosage form, preferably a tablet dosage form.

Another object of the present invention is to provide an economical and advanced dosage form over existing dosage form and with less side effects.

Yet another object of the present invention is to provide a pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof without the use of microcrystalline cellulose and sodium starch glycolate.

Yet another object of the present invention is to provide a pharmaceutical composition of lapatinib active ingredient wherein lapatinib is in micro sized form have a particle size distribution D_{90} with ranging from 5 to 50 μm, preferably 5 to 20 μm and more preferably 5-15 μm.

Yet another object of the present invention is to provide a pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof having excellent dissolution profile and higher stability with minimum use of excipients.

Yet another object of the present invention is to provide a novel process for preparation of oral solid dosage pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof.

Still another object of the present invention is to provide a pharmaceutical composition comprising lapatinib for the use in treatment of advanced or metastatic breast cancer.

Another object of the present invention is to provide process for the preparation of pharmaceutical composition comprising lapatinib ditosylate and hydroxyl propyl methylcellulose (suitable for hot melt extrusion) and other suitable excipients, which then was encapsulated in hard gelatin capsule dosage form wherein faster dissolution of the lapatinib is obtained in recommended dissolution media.

Another object of the present invention is to improve the solubility of lapatinib by complexation with cyclodextrin and its various modified derivatives. The inclusion complex obtained was mixed with other suitable excipients and encapsulated or compressed to form lapatinib tablets 250mg / 500mg tablet.

SUMMARY OF THE INVENTION

The present invention discloses a novel pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof preferably oral solid dosage form of a tablet with pharmaceutically acceptable excipients and method of preparation thereof. The pharmaceutical composition of present invention comprises lapatinib ditosylate monohydrate with one or more pharmaceutically acceptable excipients selected from the group comprising of at least one diluent, at least one disintegrant, at least one binder, at least one lubricant, wherein the composition does not comprise microcrystalline cellulose and sodium starch glycolate. In the present invention, lapatinib ditosylate is in micro sized form have a particle size distribution D_{90} with ranging from 5 to 50 μm, preferably 5 to 20 μm and more preferably 5-15 μm and the particle size is tightly controlled that enhances the drug dissolution of the drug product.

The pharmaceutical composition according to the present invention is economical and advanced dosage form over existing dosage form, with less side effects and time efficient, especially for large-scale production, whereby the pharmaceutical composition shows a desired dissolution profile and higher stability with minimum use of excipients.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1: illustrates particle size distribution curve of micro sized particles of lapatinib ditosylate monohydrate of the present invention.

DETAILED DESCRIPTION OF THE INVENTION:

The nature of the invention is clearly described in the specification. The invention has various components and they are clearly described in the following pages of the complete specification. The present invention will now be disclosed by describing certain preferred and optional embodiments, to facilitate various aspects thereof.

The present invention discloses a novel pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof preferably oral solid dosage form of a tablet. The pharmaceutical composition of the present invention comprises lapatinib preferably ditosylate monohydrate with one or more pharmaceutically acceptable excipients selected from the group consisting of at least one diluent, at least one disintegrant, at least one binder, at least one lubricant, wherein the composition does not comprise microcrystalline cellulose and sodium starch glycolate.

In accordance with the present invention, a novel pharmaceutical composition comprising lapatinib as an active ingredient and one or more pharmaceutically acceptable excipients including diluents/filler, disintegrants, binders, lubricants, but not limited thereof.

In one preferred embodiment of the present invention comprises lapatinib ditosylate monohydrate as an active ingredient along with pharmaceutically acceptable excipients selected from lactose, mannitol, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), povidone, croscarmellose sodium, magnesium stearate.

General composition for 250 mg tablet of lapatinib of the present invention is as under:

Sr. No.	Ingredients for Oral Solid Dosage of Lapatinib	Range (%w/w)
1.	Active Ingredient	25-50%
2.	Diluent /filler	35-50%
3.	Binder	2-10%
4.	Disintegrant	2-10%
5.	Lubricant	0.25-1.5%
6.	Coating	2-4%
7.	Purified water	Q.S.

The pharmaceutical composition of the present invention comprises lapatinib as active ingredient in the dosage form in range from 25% to 50% w/w.

Another embodiment of present invention discloses 500 mg tablet of lapatinib. General composition for 500 mg tablet of lapatinib of the present invention is as below:

Sr. No.	Ingredients for Oral Solid Dosage of Lapatinib	Range (%w/w)
1.	Active Ingredient	55-80%
2.	Diluent /filler	15-30%
3.	Binder	2-10%
4.	Disintegrant	2-10%
5.	Lubricant	0.25-1.5%
6.	Coating	2-4%
7.	Purified water	Q.S.

The novel pharmaceutical composition of lapatinib oral dosage form of comprises a lapatinib, more preferably lapatinib ditosylate monohydrate as an active ingredient along with pharmaceutically acceptable excipients selected from lactose, mannitol, Soluplus®, Pharmaburst®500, dicalcium phosphate, Polyplasdone®XL, povidone, Hypromellose, croscarmellose sodium, magnesium stearate.

The present invention discloses an immediate-release formulation of lapatinib ditosylate monohydrate for oral dosage form. As lapatinib having very less solubility in water, the active ingredient used in the present invention is micronized and the particle size is tightly controlled that enhances the drug dissolution of the drug product. Further, in the present invention, ditosylate salt is used which exhibited good compression characteristics.

Inventors of the present invention provides a pharmaceutical composition of lapatinib which would be considered as patient compliant due its better dissolution profile which ultimately leads to enhanced bioavailability.

Inventors of the present invention have developed the formulation of lapatinib that comprises lapatinib, preferably ditosylate, more preferably in its monohydrate form with one or more pharmaceutically acceptable excipients selected from at least one diluent, at least one disintegrant, at least one binder, at least one lubricant; wherein diluent is preferably selected from lactose, mannitol, Soluplus®; binder is preferably selected from povidone, HPMC; disintegrant is preferably selected from croscarmellose sodium, Polyplasdone® XL (crospovidone), and lubricant is preferably selected from magnesium stearate, sucrose stearate or sodium stearyl fumarate.

The amount of lubricant magnesium stearate in the tablet of the present invention is adjusted to avoid sticking to the tableting tools. Further, the film coated tablet of the present invention facilitate swallowing and patient compliance.

This composition of the present invention lacks excipients including microcrystalline cellulose and sodium starch glycolate that are present in innovator's product. Microcrystalline cellulose is insoluble in water and avoidance of that has enhanced the solubility and bioavailability of the composition of the present invention. Therefore, solubility of the active ingredient is increased. The present invention resulted in achieving good dissolution profile with minimum use of excipients. Therefore, stability of solid dosage forms of the present invention is quite higher.

In further aspect of the present invention, diluents may be selected from the group consisting of dextrates, dextrin, dextrose, fructose, 1-O-α-D-glucopyranosyl-D-mannitol, glyceryl palmitostearate, hydrogenated vegetable oil, kaolin, lactitol, lactose, lactose monohydrate,

maltitol, mannitol, maltodextrin, maltose, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), pregelatinized starch, sodium chloride, sorbitol, starches, sucrose, talc and xylitol or a mixture of one or more of said diluents.

Disintegrants used for the preparation of solid oral dosage form are selected from the group consisting of carboxymethyl cellulose, low substituted hydroxypropyl cellulose, powdered cellulose, croscarmellose sodium, Polyplasdone® XL (crospovidone), methylcellulose, polacrilin potassium, sodium alginate or a mixture of one or more of said disintegrants.

Lubricants may be selected from the group consisting of calcium stearate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, stearic acid, talc, zinc stearate and magnesium stearate or a mixture of one or more of said lubricants.

The binders may be selected from the group consisting of hydroxyl propyl methyl cellulose (HPMC or hypromellose), polyvinyl pyrrolidone (povidone), hydroxyl propyl cellulose, polyvinyl alcohol, methyl cellulose, ethyl cellulose, gum arabic, alginic acid, polyethylene glycol (PEG), pregelatinized starch (PGS) and the like.

Glidants, if used, may be selected from the group consisting of colloidal silica, hydrophobic colloidal silica and magnesium trisilicate, such as talc; preferably, the glidants are selected from the group consisting of colloidal silica and hydrophobic colloidal silica.

Solvents may be selected from the group consisting of short chain and long chain alcohols, acetone, and methylene dichloride (MDC).

Coating mixture (Opadry®) or Tabcoat® of present invention is consisting of hypomellose as film-forming agent, macrogol as plasticizer and polysorbate 80 as wetting agent. Further, titanium dioxide, yellow ferric oxide and red ferric oxide are used as colorants.

The excipients used as listed above; however, it is not limited to the said excipients only.

In the present invention, the term “lapatinib” is not only limited to “lapatinib” per se but also includes in broader way its pharmaceutically acceptable derivatives thereof. These derivatives include pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable isomers, pharmaceutically acceptable prodrugs, pharmaceutically acceptable enantiomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable esters, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc. Preferably, lapatinib is present in the form of lapatinib ditosylate monohydrate in the present invention.

In the present invention, active ingredient lapatinib have a particle size distribution D_{90} with ranging from 5 to 50 μm, preferably 5 to 15 μm.

The present invention thus provides a pharmaceutical composition comprising lapatinib wherein the particle size of Lapatinib ditosylate is along with the unique formulation designed in such a way that lead to provide better dissolution profile and solubility of the drug. As per the observation of inventor of the present invention that the particle size between range of 5 to 50 μm, preferably 5 to 15 μm gives better dissolution profile than highly reduced particle size.

In general scenario, it is reported that when particle size is highly reduced gives better dissolution profile of the drug. However, as per the inventors of the present invention contradicts with the above statement and observed that the composition of the present invention and moderately reduced particle size and not highly reduced particle size of the present product i.e. 5 to 50 μm are complimentary to each other in term to get better dissolution and purity profile under stability.

The pharmaceutical composition comprising lapatinib according to the present invention is administered orally through the solid dosage forms including tablets, capsules (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units), MUPS (multiple unit pellet systems), disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates, sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates), powders for reconstitution and sprinkles, however, other dosage forms such as controlled release formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations and the like.

Preferably, the pharmaceutical composition comprising lapatinib according to the present invention may be administered in a solid oral dosage form of a tablet including film coated tablet, sugar coated tablet, chewable tablet, delayed release tablet, , multiple compressed tablet, enteric coated tablets, effervescent tablet, dispensing tablet.

Method of Manufacturing

The present invention also discloses a method of manufacturing the oral solid dosage pharmaceutical composition of lapatinib or a pharmaceutically acceptable salt thereof.

In the present process, a wet granulation process preferably with water as granulating agent is used.

The process of the present invention is divided in different following steps as below:

(a) Sifting and dry mixing

Lapatinib API and other excipients are sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG) or any other suitable granulator. Then, dry mixing is done of the blend for 5 minutes.

(b) Binder solution preparation

Binder is added to granulating fluid water under stirring. Stirring is continued till uniform solution is formed.

(c) Granulation

During the granulation stage, dry mixture of the blend prepared in step (a), is blended in rapid mixer granulator (RMG) by adding binder solution prepared in stage (b) at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules are kneaded for 30 seconds in rapid mixer granulator (RMG).

(d) Drying

After completing the granulation, the wet granules prepared in step (c) are dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.

Solvent is evaporated during the drying stage.

(e) Sifting and Blending

Dried granules prepared in step (d) are sifted using 20# sieve, milling of the oversize granules are done using clit mill.

Then, sifted and milled dried granules are blended along with disintegrant and blended for 10 minutes.

(f) Lubrication

Lubricant is added in the blend prepared in step (e) and lubrication is carried out for 3 minutes.

(g) Compression

Above prepared lubricated blend is compressed using suitable punch set at 900 mg tablet weight.

(h) Coating

Then, coating of core tablets is carried out using suitable coating mixture (Opadry®) until the weight gain on core tablet is 3%.

The present invention can be described by way of example or strategy only. It is to be recognized that modifications falling within the scope and spirit of the description or claims, which would be obvious to a person skilled in the art based upon the disclosure herein, are also considered to be included within the scope of this disclosure.

EXAMPLES:

Example: 1 Lapatinib formulation preparation 1

Table: 1 Lapatinib tablet formula: 1

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Lactose monohydrate	387.00 mg
Binder solution	
Povidone K30	58.50 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib composition (Example: 1)

1) Lapatinib API and lactose monohydrate were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Dry blend was granulated in rapid mixer granulator (RMG) by adding binder solution of povidone K30 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.

5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 2 Lapatinib formulation preparation 2

Table: 2 Lapatinib tablet formula: 2

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Mannitol	387.00 mg
Binder solution	
Povidone K30	58.50 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 2)

1) Lapatinib API and mannitol were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding binder solution of povidone K30 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.

4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 3 Lapatinib formulation preparation 3

Table: 3 Lapatinib tablet formula: 3

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Lactose monohydrate	349.70 mg
Soluplus®	37.30 mg
Binder solution	
Povidone K30	58.50 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 3)

1) Lapatinib API, lactose monohydrate and Soluplus® were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding binder solution of povidone K30 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).

3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 4 Lapatinib formulation preparation 4

Table: 4 Lapatinib tablet formula: 4

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Mannitol	349.70 mg
Soluplus®	37.30 mg
Binder solution	
Povidone K30	58.50 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 4)

1) Lapatinib API, mannitol and Soluplus® were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.

2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding binder solution of povidone K30 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 5 Lapatinib formulation preparation 5

Table: 5 Lapatinib tablet formula: 5

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Lactose (Flowlac®100)	387.00 mg
Povidone K30	58.50 mg
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 5)

1) Lapatinib API, lactose (Flowlac® 100) and Povidone K30 were sifted using appropriate size sieve and transferred to blender followed by mixing for 30 minutes.

2) Then, disintegrant Croscarmellose sodium added to above blend and blended for 10 minutes.
3) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
4) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
5) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 6 Lapatinib formulation preparation 6

Table: 6 Lapatinib tablet formula: 6

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Pharmaburst®500	387.00 mg
Povidone K30	58.50 mg
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 6)

1) Lapatinib API, Pharmaburst®500 and povidone K30 were sifted using appropriate size sieve and transferred to blender and mixed for 30 minutes.
2) Then, disintegrant Croscarmellose sodium added to above blend and blended for 10 minutes.
3) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
4) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
5) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 7 Lapatinib formulation preparation 7

Table: 7 Lapatinib tablet formula: 7

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Dicalcium phosphate	387.00 mg
Binder solution	
Povidone K30	58.50 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 7)

1) Lapatinib API, dicalcium phosphate were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding binder solution of povidone K30 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.

8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 8 Lapatinib formulation preparation 8

Table: 8 Lapatinib tablet formula:8

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	405.00 mg
Lactose monohydrate	423.00 mg
HPMC	22.50 mg
Granulation	
Purified water	Q.S.
Blending	
Croscarmellose sodium	40.50 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	900.00 mg

Manufacturing process for Lapatinib formulation (Example: 8)

1) Lapatinib API, lactose monohydrate and HPMC were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding purified water at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were using, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.
6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.

7) Lubricated blend was compressed using suitable punch set at 900 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

Example: 9 Lapatinib formulation preparation 9

Table: 9 Lapatinib tablet formula: 9

Ingredients	Quantity per Tablet
Dry mixing	
Lapatinib ditosylate monohydrate	810.00 mg
Mannitol	208.12 mg
Croscarmellose sodium	50.00 mg
Binder solution	
Hypromellose E5	27.88 mg
Purified water	Q.S.
Blending	
Croscarmellose sodium	10.00 mg
Lubrication	
Magnesium stearate	9.00 mg
Total Weight	1115.00 mg

Manufacturing process for Lapatinib formulation (Example: 9)

1) Lapatinib API, mannitol and croscarmellose sodium were sifted using appropriate size sieve and transferred to rapid mixer granulator (RMG). Then, dry mixing was done of the blend for 5 minutes.
2) Then, granulation was done of dry blend in rapid mixer granulator (RMG) by adding binder solution of Hypromellose E5 at an impeller speed of 80-100 RPM and chopper speed of 1000-2000 RPM. Wet granules prepared were kneaded for 30 seconds in rapid mixer granulator (RMG).
3) After completing the granulation, the wet granules prepared were dried in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2%.
4) Then after, dried granules prepared were sifted using 20# sieve, milling of the oversize granules were done using clit mill.
5) Then, sifted and milled dried granules were blended along with disintegrant croscarmellose sodium and blended for 10 minutes.

6) Lubricant magnesium stearate was added in the blend prepared in step (5) and lubrication was carried out for 3 minutes.
7) Lubricated blend was compressed using suitable punch set at 1115 mg tablet weight.
8) Then, coating of core tablets was carried out using coating mixture of Opadry® till the weight gain on core tablet was 3%.

DISSOLUTION STUDY

Dissolution rate is a critical property that need to study for final dosage form Comparative dissolution profile of the product of present invention with a reference product (tablet) was studied. Dissolution study of the pharmaceutical dosage of the present invention was carried out by HPLC.

The dissolution method employed in the present invention is USP Apparatus II (paddle) with sinker at 55 RPM in 2% Tween 80 in 0.1 N HCl for 45 min of time duration at (37 ± 0.5) °C. Samples were taken at 10, 15, 30 and 45 minutes. The sample was filtered through a 0.45 µm syringe filter, transferred to HPLC vials and analyzed by HPLC.

The following are the comparative dissolution data of the Lapatinib ditosylate monohydrate tablet of innovator reference product and final product of the present invention.

Table: 10 Comparative dissolution study of Lapatinib tablet of present invention with Innovator product

Lapatinib tablet 250mg		
Media	2% TWEEN 80 in 0.1 N HCl	
Volume	900 ml	
USP apparatus	Type II (paddle) with sinker	
RPM	55	
Time (minutes)	**Reference product Dissolution (%)**	**Product of the present invention (%)**
10	53.4	77
15	77.2	83
30	89.8	92

45	92.4	95
Recovery	99.5	100

Surprisingly it was found from the above data provided in table 10 that the lapatinib tablets of the present invention underwent rapid and complete dissolution initially compare to innovator product and even after 1 month when tested using the USP Apparatus (II) in comparison with the reference product of the innovator. As increase in the solubility and dissolution rates leads to improvement in the bioavailability of the drug with consistency and uniformity.

STABILITY STUDY

The composition in accordance with the present invention was subjected to stability study under stability analysis condition of 25°C±2°C and relative humidity 60%±5%. It was found to be adequately stable, as per general stability requirement under conditions. Moreover, the product is also stable in the similar manner in accelerated stability conditions.

Table: 11 Stability study of Lapatinib tablet of present invention and its comparison with Innovator reference product

Sr. No.	**Description**	**Initial**	**After 1 month**	**After 2 months**	**After 3 months**	**After 6 months**	**Reference product after 6 months**
1	**Assay (By HPLC)**	101.7%	99.1%	102.4%	103.5%	101.4%	99.64%
2	**Related Substances (%)**						
	Impurity-A	ND	ND	ND	ND	ND	0.037%
	Impurity-B	ND	ND	ND	ND	ND	0.122%
	Impurity-C	ND	ND	ND	ND	ND	0.003%
	Dimer Impurity	ND	0.15%	0.15%	0.02%	ND	0.069%
	Single max. Unknown Impurity	0.08%	0.05%	0.06%	0.11%	0.09%	0.036%
	Total Impurities	0.21%	0.23%	0.30%	0.27%	0.21%	0.4%

3	**Dissolution average**	90.1%	92.2%	90.1%	90.6%	90.3%	91.40%

*ND = Not detected

As indicated in above table, the result of the stability study indicates that lapatinib composition in accordance with the present invention exhibits excellent storage stability.

The invention described herein comprises in various objects as mentioned above and their description in relation to characteristics, compositions and process adopted. While these aspects are emphasised in the invention, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as described.

WE CLAIM:

1. A novel pharmaceutical composition of lapatinib of oral solid dosage form comprising lapatinib or pharmaceutically acceptable salt or polymorph thereof and one or more pharmaceutically acceptable excipients selected from diluents/fillers, disintegrants, binders, lubricants, coating agent, but not limited thereof, wherein the composition lacks excipients including microcrystalline cellulose and sodium starch glycolate.

2. The novel pharmaceutical composition of lapatinib as claimed in claim 1, wherein the composition comprising:

Ingredients for Oral Solid Dosage of Lapatinib	Range (%w/w)
Active Ingredient	25-50%
Diluent /filler	35-50%
Binder	2-10%
Disintegrant	2-10%
Lubricant	0.25-1.5%
Coating	2-4%
Purified water	Q.S.

3. The novel pharmaceutical composition of lapatinib as claimed in claim 1, wherein the composition comprising:

Ingredients for Oral Solid Dosage of Lapatinib	Range (%w/w)
Active Ingredient	55-80%
Diluent /filler	15-30%
Binder	2-10%
Disintegrant	2-10%
Lubricant	0.25-1.5%
Coating	2-4%
Purified water	Q.S.

4. The novel pharmaceutical composition of lapatinib as claimed in claims 1-3, wherein the composition is in solid dosage form preferably selected from tablet, capsule, MUPS (multiple unit pellet system), powder, granules, sachets, pellets, powders for reconstitution and sprinkles.

5. The novel pharmaceutical composition of lapatinib as claimed in claims 1-4, wherein the composition is in solid dosage form preferably a tablet dosage form.

6. The novel pharmaceutical composition of lapatinib as claimed in claims 1 to 5, wherein the content of lapatinib in the dosage form is in range from 25% w/w to 80% w/w.

7. The novel pharmaceutical composition of lapatinib as claimed in claims 1-6, wherein the dosage strength of the composition is 250 mg and 500 mg tablets.

8. The novel pharmaceutical composition of lapatinib as claimed in claims 1-7, wherein lapatinib is in particle size D_{90} ranging from 5 to 50 μm.

9. The novel pharmaceutical composition of lapatinib as claimed in claims 1-8, wherein pharmaceutically acceptable diluent/filler is selected from lactose, lactose monohydrate, mannitol, sorbitol, sucrose; dextrates, dextrin, dextrose, fructose, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), dicalcium phosphate, 1-O-α-D-glucopyranosyl-D-mannitol, glyceryl palmitostearate, hydrogenated vegetable oil, kaolin, lactitol, maltitol, maltodextrin, maltose, pregelatinized starch, sodium chloride, sorbitol, starches, sucrose, talc and xylitol or a mixture of one or more of said diluents, preferably lactose monohydrate, wherein microcrystalline cellulose is not used in the composition.

10. The novel pharmaceutical composition of lapatinib as claimed in claims 1-8, wherein pharmaceutically acceptable disintegrant is selected from carboxymethyl cellulose, low substituted hydroxypropyl cellulose, powdered cellulose, croscarmellose sodium, Polyplasdone® XL (crospovidone), methylcellulose, polacrilin potassium, sodium alginate or a mixture of one or more of said disintegrants, preferably croscarmellose sodium, wherein sodium starch glycolate is not used in the composition.

11. A process for preparation of a novel pharmaceutical composition of lapatinib comprising the following steps:

(a) Sifting and dry mixing

sifting of lapatinib and other excipients using appropriate size sieve and transferring to rapid mixer granulator (RMG) or any other suitable granulator; dry mixing of the blend for 5 minutes;

(b) Binder solution preparation

adding binder to granulating fluid water under stirring continuously till uniform solution formed;

(c) Granulation

blending of dry mixture of the blend prepared in step (a) in rapid mixer granulator (RMG) by adding binder solution prepared in stage (b) at an impeller speed 80-100 RPM and chopper speed of 1000-2000 RPM;

kneading of wet granules for 30 seconds in rapid mixer granulator (RMG);

(d) Drying

after completing the granulation process, drying of the wet granules prepared in step (c) in the fluid bed processor (FBP) at inlet air temperature 45 to 65°C till loss on drying (LOD) of the granules is less than 2% and evaporating the solvent for drying;

(e) Sifting and Blending

sifting of dried granules prepared in step (d) using 20# sieve, milling of the oversize granules using clit mill;

blending of sifted and milled dried granules along with disintegrant and blending for 10 minutes;

(f) Lubrication

adding lubricant in the blend prepared in step (e) and carrying out lubrication for 3 minutes;

(g) Compression

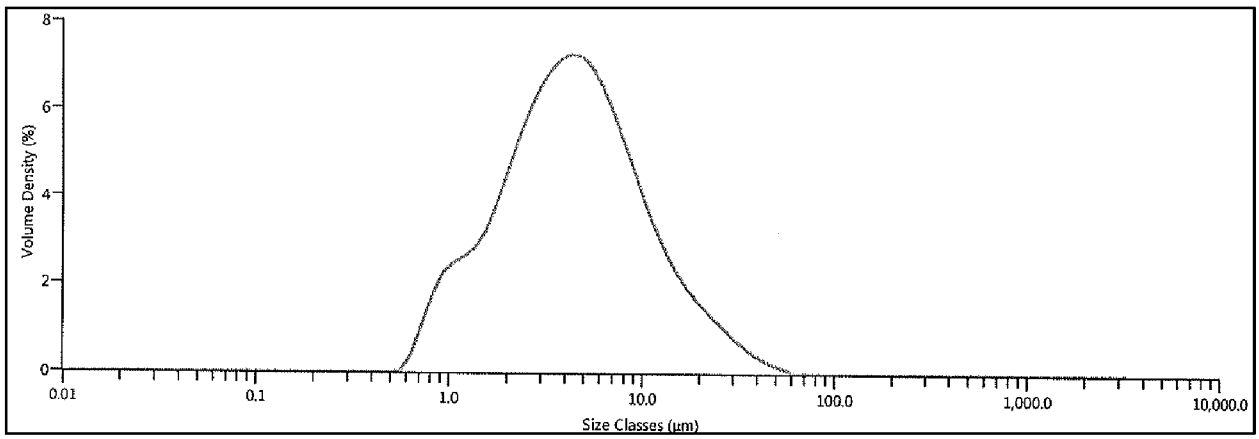
compressing the lubricated blend prepared in step (f) using suitable punch set tablet weight;

(h) Coating

coating of core tablets using suitable coating mixture till the weight gain on core tablet of up to 3%.

12. The process for preparation of a novel pharmaceutical composition of lapatinib as claimed in claim 11, wherein coating mixture is of Opadry® or Tabcoat®.

Figure *1*


Volume Density (%)
8
6
4
2
0
0.01
0.1
1.0
10.0
100.0
1,000.0
10,000.0
Size Classes (µm)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/057324

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/20,C07D405/04 Version=2019.01

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, C07D

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2015145145 A1 (CIPLA LTD[IN]; TURNER CRAIG[GB]) 01 October 2015 claim 1	1-10
X	page 20	11-12
Y	WO2012017448 A2 (HETERO RESEARCH FOUNDATION [IN]) claim 24	1-10

☐ Further documents are listed in the continuation of Box C.

☒ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
23-12-2019	23-12-2019
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Abhas Kumar Bhoi Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2019/057324

Citation	Pub.Date	Family	Pub.Date
WO 2012017448 A2	24-05-2012	EP 2601178 A2	12-06-2013
		US 2013131090 A1	23-05-2013