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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 June 2011 (09.06.2011)

PCT

(10) International Publication Number
WO 2011/068403 A2

(51) International Patent Classification:
C07D 239/94 (2006.01) *A61P 35/00* (2006.01)
A61K 31/498 (2006.01)

(21) International Application Number:
PCT/NL2010/050809

(22) International Filing Date:
2 December 2010 (02.12.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/265,888 2 December 2009 (02.12.2009) US
61/266,282 3 December 2009 (03.12.2009) US

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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, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/068403 A2

(54) Title: NOVEL N-{3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMJNE SALTS

(57) Abstract: The present invention relates to novel ethanesulfonate, isethionate, bromide, malonate, L-lactate, and succinate salts and polymorphs thereof of N-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (Erlotinib). The invention also relates to pharmaceutical compositions containing Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate, succinate salts and to the methods of treating hyperproliferative disorders such as cancer, by administering the Erlotinib salts.

Title: NOVEL N-(3-ETHYNYLPHENYLAMINO)-6,7-BIS(2-METHOXYETHOXY)-4-QUINAZOLINAMINE SALTS

Field of the Invention

The present invention relates to novel salts and polymorphs thereof of N-(3-ethynylphenylamino)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (Erlotinib). The invention also relates to pharmaceutical compositions containing Erlotinib salts and to the methods of treating hyperproliferative disorders such as cancer, by administering Erlotinib salts.

Background of the invention

The present invention relates to novel salts of Erlotinib and polymorphs of theses salts. This quinazolamine compounds are useful in the treatment of hyperproliferative disorders such as cancers in mammals.

United States patent number 5,747,498 filed May 28, 1996, refers to Erlotinib hydrochloride which, the patent application discloses, is an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as the epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of proliferative disorders such as cancers in humans. United States patent number 6,706,721, filed April 08, 1999 refers to Erlotinib mesylate salt. US patent publication 2002/006,443 discloses the solubility of the mesylate salt of Erlotinib being in the range of approximately 30 µg/mL to 100 µg/mL. The hydrochloric and mesylate compound have very limited solubility in aqueous compositions which limits their bioavailability and gives rise to an undesirable strong food effect. Limited solubility also limits the dosing route and formulation to a solid oral dosage form. However mesylates have an inherent problem in the way that a toxic impurity in the form of ethyl methanesulfonate can be formed in certain circumstances.

Hence there remains a need for Erlotinib based compounds that overcome the above described disadvantages. One advantage of the novel salts is that they are all more soluble in aqueous compositions than the above mentioned hydrochloride compound, and thus the novel salts of the present invention will posses increased

bioavailability, a reduction of the food effect and can be formulated for possible dosing routes. Furthermore, the toxic effect of ethyl methanesulfonate can be avoided.

Summary of the invention

The present inventors have found different salts and/or solid forms of Erlotinib which are useful for the treatment of proliferative disorders. It has been found that these salts and solid forms possess certain advantages over the prior art hydrochloride and mesylate compounds. It has been found that providing the novel salts in crystalline from provides for an enhanced stability until administration as a liquid and may be easier I the purification step at the end of the synthesis process. It has been found that the salts of the present invention are more soluble in aqueous compositions than the above mentioned hydrochloride, and thus the novel salts of the present invention will posses increased bioavailability, a reduction of the food effect and can be formulated for possible dosing routes. In particular, the invention relates to Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate in anhydrous and hydrated forms and polymorphic forms thereof.

Detailed Description of the Invention

The present invention relates to anhydrous and hydrated salts of Erlotinib.

One embodiment of the present invention relates to the ethanesulfonate salt of Erlotinib.

Another embodiment of the present invention relates to the isethionate salt of Erlotinib.

Another embodiment of the present invention relates to the bromide salt of Erlotinib.

Another embodiment of the present invention comprises the malonate salt of Erlotinib.

Another embodiment of the present invention comprises the L-lactate salt of Erlotinib.

Another embodiment of the present invention comprises the succinate salt of Erlotinib.

The invention further relates to a pharmaceutical composition for the treatment of hyperproliferative disorder, specifically non-small cell lung cancer and bronchioalveolar cancer, in a mammal, including a human, which comprises a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate and a pharmaceutical acceptable carrier. In one embodiment, said pharmaceutical composition is for the treatment of cancers.

The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal, including a human, which comprises a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate and a pharmaceutical acceptable carrier.

The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a mammal, including a human, which comprises a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate salt and a pharmaceutical acceptable carrier.

The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal, including a human, which comprises a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate salt and a pharmaceutical acceptable carrier. In one embodiment, said pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetes retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

The invention also relates to a method of treating hyperproliferative disorder in a mammal, including a human, which comprises administering to said mammal a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate salt. In one embodiment said method relates to the treatment of cancer such as brain, lung, squamous cell, bladder, gastric, pancreatic,

breast, neck, head, renal (such as kidney), ovarian, prostate, colorectal, oesophageal, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of non-cancerous hyperproliferative disorder such being benign hyperplasia of the skin (e.g. psoriasis) or prostate (e.g. benign prostatic hypertrophy (BPH)).

The invention also relates to a method of treatment of a hyperproliferative disorder in a mammal, including a human, which comprises administering to said mammal a therapeutically effective amount of Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate salt, optionally in combination with an anti-tumor agent selected from the group of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

Patients that can be treated with Erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate and succinate salt according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, BPH, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, ovarian cancer, rectal cancer, cancer of he anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of he cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of he urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphatic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g." renal call carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g. primary CNS lymphoma, spinal axis tumors, brainstem gliomas or pituitary adenomas).

Brief description of the Figures and Tables

Figure 1A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib ethanesulfonate ERET ULT-1

Figure 1B illustrates the DSC thermogram of Erlotinib ethanesulfonate ERET ULT-1

Figure 1C illustrates the TGA thermogram of Erlotinib ethanesulfonate ERET ULT-1

Figure 2A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib ethanesulfonate ERET ULT-2

Figure 2B illustrates the DSC thermogram of Erlotinib ethanesulfonate ERET ULT-2

Figure 2C illustrates the TGA thermogram of Erlotinib ethanesulfonate ERET ULT-2

Figure 2D illustrates the Raman spectrogram of Erlotinib ethanesulfonate ERET ULT-2

Figure 2E illustrates the FT-IR spectrogram of Erlotinib ethanesulfonate ERET ULT-2

Table 2A Characteristic Raman peaks of Erlotinib ethanesulfonate ERET ULT-2

Table 2B Characteristic FT-IR peaks of Erlotinib ethanesulfonate ERET ULT-2

Figure 3A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-1

Figure 3B illustrates the DSC thermogram of Erlotinib isethionate ERIS ULT-1

Figure 3C illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-1

Figure 3D illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-1

Figure 3E illustrates the Raman spectrogram of Erlotinib isethionate ERIS ULT-1

Figure 3F illustrates the FT-IR spectrogram of Erlotinib isethionate ERIS ULT-1

Table 3A Characteristic Raman peaks of Erlotinib isethionate ERIS ULT-1

Table 3B Characteristic FT-IR peaks of Erlotinib isethionate ERIS ULT-1

Figure 4A illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-2

Figure 4B illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-2

Figure 4C illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-2

Figure 5A illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-3

Figure 5B illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-3

Figure 5C illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-3

Figure 6 illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-4

Figure 7A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-1

Figure 7B illustrates the DSC thermogram of Erlotinib bromide ERBR ULT-1

Figure 7C illustrates the TGA thermogram of Erlotinib bromide ERBR ULT-1

Figure 7D illustrates the Raman spectrogram of Erlotinib bromide ERBR ULT-1

Figure 7E illustrates the FT-IR spectrogram of Erlotinib bromide ERBR ULT-1

Table 7A Characteristic Raman peaks of Erlotinib bromide ERBR ULT-1

Table 7B Characteristic FT-IR peaks of Erlotinib bromide ERBR ULT-1

Figure 8 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-2

Figure 9A illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-3

Figure 9B illustrates the TGA thermogram of Erlotinib bromide ERBR ULT-3

Figure 10 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-4

Figure 11 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-5

Figure 12A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib malonate ERMO ULT-1

Figure 12B illustrates the DSC thermogram of Erlotinib malonate ERMO ULT-1

Figure 12C illustrates the TGA thermogram of Erlotinib malonate ERMO ULT-1

Figure 12D illustrates the Raman spectrogram of Erlotinib malonate ERMO ULT-1

Figure 12E illustrates the FT-IR spectrogram of Erlotinib malonate ERMO ULT-1

Table 12A Characteristic Raman peaks of Erlotinib malonate ERMO ULT-1

Table 12B Characteristic FT-IR peaks of Erlotinib malonate ERMO ULT-1

Figure 13 illustrates the X-Ray Powder Diffraction pattern of Erlotinib malonate ERMO ULT-2

Figure 14 illustrates the X-Ray Powder Diffraction pattern of Erlotinib L-lactate ERLA ULT-1

Figure 15A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-1

Figure 15B illustrates the DSC thermogram of Erlotinib succinate ERSC ULT-1

Figure 15C illustrates the TGA thermogram of Erlotinib succinate ERSC ULT-1

Figure 15D illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib succinate ERSC ULT-1

Figure 15E illustrates the Raman spectrogram of Erlotinib succinate ERSC ULT-1

Figure 15F illustrates the FT-IR spectrogram of Erlotinib succinate ERSC ULT-1

Table 15A Characteristic Raman peaks of Erlotinib succinate ERSC ULT-1

Table 15B Characteristic FT-IR peaks of Erlotinib succinate ERSC ULT-1

Figure 16 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-2

Figure 17 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-3

Figure 18 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-4

Figure 19A illustrates the X-Ray Powder Diffraction pattern of Erlotinib free base

Figure 19B illustrates the DSC thermogram of Erlotinib free base

Figure 19C illustrates the TGA thermogram of Erlotinib free base

Figure 19D illustrates the FT-IR spectrogram of Erlotinib free base

Table 19A Characteristic FT-IR peaks of Erlotinib free base

Erlotinib ethanesulfonate.

Erlotinib ethanesulfonate may be prepared as described in examples 1 and 2. Erlotinib ethanesulfonate has been found also in 2 distinct polymorphs, depicted herein as ERET ULT-1 – 2.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. The solvent (ethylacetate, water) was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. Ethanesulfonic acid was added drop wise in a ratio of 1.1 with respect to the free base of Erlotinib to the above reaction mass under stirring with a speed of 200 rpm. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration under vacuum with a 5 μm filter and/or by evaporation. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Dry solid was analyzed by XRPD.

The polymorphs ERET ULT-1 – 2 are characterized by the diffraction peaks found in the XRPD patterns shown below. The XRPD is essentially as shown in Figures 1A and 2A.

ERET ULT-1 – 2 are found as anhydrous forms, as indicated by the results of the DSC and TGA analyses shown in Figures 1B, 1C and 2B, 2C.

ERET ULT-1		
Peak table for sud 21.9 c : K6		
Peak ID	Angle (2θ)	
1	5.42	H
2	6.94	M
3	8.65	L

4	10.78	L
5	13.16	L
6	16.17	L
7	18.94	M
8	20.62	L
9	21.76	L
10	23.82	L
11	25.32	L
		L<40<M<60<H

ERET ULT-2		
Peak table for SUD41		
Peak ID	Angle (2θ)	
1	5.9	L
2	8.36	L
3	10.18	L
4	11.73	H
5	13.02	L
6	13.27	L
7	16.8	L
8	16.89	M
9	17.09	M
10	17.88	H
11	18.81	M
12	19.57	L
13	19.87	L
14	20.05	M
15	20.44	M
16	20.72	L
17	21.57	L
18	22.21	L

ERET ULT-2		
Peak table for SUD41		
Peak ID	Angle (2θ)	
19	23.62	L
20	23.98	H
21	24.72	M
22	25.16	L
23	25.38	L
24	25.72	L
25	26.01	L
26	26.29	L
27	26.73	H
28	27.84	L
29	28.15	L
30	28.93	L
31	29.56	L
32	30.06	L
33	30.49	L
34	31.09	L
35	31.72	L
36	32.77	L
37	33.94	L
38	34.22	L
39	34.62	L
40	36.38	L
		L<35<M<60<H

It has been found that polymorph ERET ULT-2 of Erlotinib ethanesulfonate is more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in H2O. The solubility is respectively 14.7 mg/mL, compared to 0.9 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib ethanesulfonate salt at room temperature. Approximately 20 mg of Erlotinib ethanesulfonate salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

Erlotinib isethionate.

Erlotinib isethionate may be prepared as described in examples 3 – 6. Erlotinib isethionate has been found also in 4 distinct polymorphs, depicted herein as ERIS ULT-1 – 4.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 2-hydroxy-ethanesulfonic acid (isethionic acid) was added in a ratio of 1.1 – 1.4 with respect to the free base of Erlotinib Subsequently, solvent (methanol, tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, 1,4-dioxane, 3-methyl-1-butanol, ethanol, ethylacetate, tert-butyl methyl ether, methanol/water, methylacetate) was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently the vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor or if no solid was present, the solvent was evaporated. The supernatant solution was also evaporated. All resulting solids were dried and analyzed by XRPD.

The polymorphs ERIS ULT-1 – 4 are characterized by the diffraction peaks found in the XRPD patterns shown below (Figures 3A-5A, 6). ERIS ULT-1 and ERIS ULT-3 are found as hydrates, as indicated by the results of the TGA analyses shown in Figures 3C, 3D, 5B and 5C. ERIS ULT-2 is found as anhydrate, as indicated by the TGA results shown in Figures 4B, 4C.

ERIS ULT-1		
Peak table for SUD 26		
Peak ID	Angle (2θ)	
1	7.31	L
2	7.43	M
3	7.65	M
4	8.3	M
5	11.37	L
6	11.8	L
7	12.61	L
8	14.81	L
9	15.06	L
10	15.91	M
11	16.09	L
12	16.4	L
13	16.66	L
14	20.26	M
15	20.58	M
16	20.92	L
17	21.84	L
18	22.06	L
19	22.24	L
20	22.6	M
21	22.8	M
22	23.11	L
23	23.37	H
24	23.72	L

ERIS ULT-1		
Peak table for SUD 26		
Peak ID	Angle (2θ)	
25	24.47	L
26	24.9	H
27	25.78	L
28	26.27	H
29	27.11	H
30	27.65	L
31	28.55	L
32	29.09	L
33	29.58	L
34	30.41	L
35	30.94	L
		L<40<M<60<H

ERIS ULT-2		
Peak table for co 03.1 c : K8		
Peak ID	Angle (2θ)	
1	5.7	L
2	8.18	L
3	12.26	M
4	13.14	L
5	16.34	L
6	17.14	L
7	17.7	M
8	18.54	M
9	19.1	M
10	20.62	L
11	21.39	L

ERIS ULT-2		
Peak table for co 03.1 c : K8		
Peak ID	Angle (2θ)	
12	23.04	L
13	24.58	H
14	26.5	M
15	29.15	L
16	30.2	L
17	31.26	L
		L<35<M<60<H

ERIS ULT-3		
Peak table for co 03.1 c : H8		
Peak ID	Angle (2θ)	
1	5.38	L
2	6.54	H
3	7.3	M
4	13.38	L
5	14.48	L
6	15.63	L
7	17.86	L
8	19.18	L
9	19.58	L
10	20.54	L
11	21.35	L
12	21.9	L
13	22.83	L
14	24.31	L
15	25.05	L
16	26.02	M

ERIS ULT-3		
Peak table for co 03.1 c : H8		
Peak ID	Angle (2θ)	
17	27.22	L
18	28.52	L
19	29.57	L
		L<40<M<60<H

ERIS ULT-4		
Peak table for co 03.2 c : H8		
Peak ID	Angle (2θ)	
1	5.22	H
2	6.38	L
3	7.08	L
4	10.43	L
5	17.26	L
6	18.16	L
7	19.17	L
8	20.42	L
9	22.18	L
10	24.62	M
11	27.45	L
		L<35<M<60<H

The polymorphs ERIS ULT-1 and ERIS ULT-2 of Erlotinib isethionate are more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in H2O. The solubility of ERIS ULT-1 and ERIS ULT-2 is respectively 1.7 mg/mL and 7.7 mg/mL compared to 0.9 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib isethionate salt at room temperature. Approximately 20 mg of Erlotinib ethanesulfonate salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

Erlotinib bromide.

Erlotinib bromide may be prepared as described in examples 7-11 Erlotinib bromide has been found also in 5 distinct polymorphs, depicted herein as ERBR ULT-1 – 5.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 48 % hydrobromic acid in ACS reagent was added together with the solvent (methylacetate, methanol, tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, 1,4-dioxane, 3-methyl-1-butanol, ethanol, ethylacetate, water, acetone/water, 2,2,2-trifluoroethanol, tert-butyl methyl ether, ethanol/water, methanol/water) in a ratio of 1.1 – 1.2 with respect to the free base of Erlotinib. The final concentration of Erlotinib free base in the solvent was approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL). The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor or if no solid was present, the solvent was evaporated. The supernatant solution was also evaporated. All resulting solids were dried and analyzed by XRPD.

The polymorphs ERBR ULT-1 – 5 are characterized by the diffraction peaks found in the XRPD patterns shown below (Figures 7-11).

ERBR ULT-1 and ERBR ULT-3 are found as anhydrate forms, as indicated by the results of the TGA analyses shown in Figures 7C, 9B.

ERBR ULT-1		
Peak table for SUD1		
Peak ID	Angle (2θ)	
1	6.23	H
2	7.84	L
3	9.55	M
4	11.39	L
5	12.47	L
6	13.37	L
7	14.76	L
8	15.67	L
9	16.95	L
10	17.63	L
11	20.19	M
12	20.67	L
13	20.93	L
14	21.11	L
15	21.85	L
16	22.43	M
17	22.96	M
18	23.83	L
19	23.94	M
20	24.43	M
21	24.65	M
22	25.12	H
23	25.90	L
24	26.50	L

ERBR ULT-1		
Peak table for SUD1		
Peak ID	Angle (2θ)	
25	26.75	L
26	26.95	L
27	28.60	L
28	28.95	L
29	29.70	L
30	32.66	L
31	34.72	L
32	40.08	L
		L<35<M<60<H

ERBR ULT-2		
Peak table for co 03.1 c : L4		
Peak ID	Angle (2θ)	
1	5.66	H
2	9.58	L
3	12.74	L
4	15.18	L
5	16.99	L
6	13.58	L
7	18.7	M
8	19.1	L
9	20.42	L
10	22.42	M
11	23.38	M
12	23.86	H
13	24.54	M
14	25.18	M

ERBR ULT-2		
Peak table for co 03.1 c : L4		
Peak ID	Angle (2θ)	
15	25.62	M
16	26.44	L
17	27.29	L
18	28.5	M
19	29.22	L
20	30.58	L
21	31.06	L
22	32.17	L
23	37.57	L
		L<40<M<60<H

ERBR ULT-3		
Peak table for co 03.2 c : K4		
Peak ID	Angle (2θ)	
1	6.26	H
2	7.78	L
3	9.3	M
4	13.33	L
5	15.5	L
6	16.74	L
7	18.17	L
8	18.66	L
9	19.7	M
10	20.5	L
11	21	L
12	22.06	M
13	22.94	H

ERBR ULT-3		
Peak table for co 03.2 c : K4		
Peak ID	Angle (2θ)	
14	23.9	M
15	24.34	M
16	24.98	M
17	26.34	M
18	28.26	M
19	28.87	L
20	29.37	L
21	30.49	L
22	30.99	L
23	32.04	L
24	33.29	L
25	34.1	L
26	35.09	L
27	36.77	L
28	38.14	L
29	40.15	L
		L<35<M<60<H

ERBR ULT-4		
Peak table for co 04.0 c : H5		
Peak ID	Angle (2θ)	
1	5.9	H
2	8.14	L
3	11.3	L
4	11.66	M
5	12.68	L
6	16.31	L

ERBR ULT-4		
Peak table for co 04.0 c : H5		
Peak ID	Angle (2θ)	
7	17.9	L
8	18.87	L
9	21.1	L
10	22.63	L
11	23.34	L
12	23.82	M
13	25.98	M
14	27.14	M
15	28.42	L
16	29.17	L
17	31.84	L
		L<25<M<60<H

ERBR ULT-5		
Peak table for co 04.1 c : H5		
Peak ID	Angle (2θ)	
1	6.22	H
2	8.38	L
3	11.78	M
4	14.68	L
5	16.85	L
6	18.14	L
7	18.7	L
8	19.44	L
9	20.36	L
10	20.92	L
11	22.63	L

ERBR ULT-5		
Peak table for co 04.1 c : H5		
Peak ID	Angle (2θ)	
12	23.13	L
13	24.62	M
14	25.25	L
15	26.46	M
16	27.82	L
17	28.59	L
18	29.46	L
		L<25<M<60<H

Polymorph ERBR ULT-1 of Erlotinib bromide is more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in H2O. The solubility of ERBR ULT-1 is 2.1 mg/mL compared to 0.9 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib bromide salt at room temperature. Approximately 20 mg of Erlotinib bromide salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

Erlotinib malonate.

Erlotinib malonate may be prepared as described in examples 12, 13 Erlotinib malonate has been found also in 2 distinct polymorphs, depicted herein as ERMO ULT-1 in anhydrate form and ERMO ULT-2.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base malonic acid was added in a ratio of 1.1 – 1.4 with respect to the free base of Erlotinib Subsequently, solvent (methylacetate, acetonitrile, ethanol/water, methanol/water, tetrahydrofuran/water, acetonitrile/water, methanol, acetone/water, 1,4-dioxane) was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor or if no solid was present, the solvent was evaporated. The supernatant solution was also evaporated. All resulting solids were dried and analyzed by XRPD.

The polymorphs ERMO ULT-1 – 2 are characterized by the diffraction peaks found in the XRPD patterns shown below. The XRPD is essentially as shown in Figures 12A, 13.

ERMO ULT-1		
Peak table for SDU 25		
Peak ID	Angle (2θ)	
1	6.68	H
2	8.85	L
3	9.31	L
4	12.07	L
5	13.29	L
6	15.98	L
7	16.78	L
8	17.43	L
9	18.91	M
10	19.36	M
11	20.17	L

ERMO ULT-1		
Peak table for SDU 25		
Peak ID	Angle (2θ)	
12	20.44	L
13	21.05	L
14	21.67	M
15	22.85	L
16	23.09	L
17	23.70	L
18	24.70	L
19	24.89	L
20	26.68	H
21	26.90	H
22	27.69	L
23	28.25	M
		L<35<M<60<H

ERMO ULT-2		
Peak table for co 11.1 c : H4		
Peak ID	Angle (2θ)	
1	2.26	L
2	5.42	H
3	8.26	M
4	10.82	L
5	14.3	M
6	16.5	M
7	17.86	M
8	20.81	L
9	21.74	L
10	22.46	M

ERMO ULT-2		
Peak table for co 11.1 c : H4		
Peak ID	Angle (2θ)	
11	24.06	H
12	25.14	M
13	25.78	H
		L<40<M<60<H

It has been found that polymorph ERMO ULT-1 of Erlotinib malonate is more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in H2O. The solubility is 1.6 mg/mL compared to 0.9 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib malonate salt at room temperature. Approximately 20 mg of Erlotinib malonate salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

Erlotinib L-lactate.

Erlotinib L-lactate may be prepared as described in example 14 Erlotinib L-lactate has been found also in 1 distinct polymorph, depicted herein as ERLA ULT-1.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base Lactic acid was added in a ratio of 1.2 – 6.1 with respect to the free base of Erlotinib Subsequently, solvent (methylacetate, 1,2-dimethoxyethane, 3-methyl-1-butanol, ethanol, ethylacetate) was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor or if no solid was present, the solvent was evaporated. The supernatant solution was also evaporated. All resulting solids were dried and analyzed by XRPD.

The polymorph ERLA ULT-1 is characterized by the diffraction peaks found in the XRPD patterns shown below. The XRPD is essentially as shown in Figure 20.

ERLA ULT-1		
Peak table for co 22.0 c : J2		
Peak ID	Angle (2θ)	
1	6.46	H
2	7.83	L
3	12.41	L
4	12.81	L
5	15.84	L
6	16.66	L
7	18.2	L
8	19.48	L
9	20.42	L
10	21.03	L
11	21.7	L
12	22.58	M
13	23.53	L
14	24.64	L
15	26.24	L
16	25.66	M

ERLA ULT-1		
Peak table for co 22.0 c : J2		
Peak ID	Angle (2θ)	
17	26.75	L
18	27.2	L
19	29.24	L
		L<20<M<60<H

It has been found that ERLA ULT-1 polymorph of Erlotinib L-lactate is more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in H2O. The solubility is 14.9 mg/mL compared to 0.9 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib L-lactate salt at room temperature. Approximately 20 mg of Erlotinib L-lactate salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

Erlotinib succinate.

Erlotinib succinate may be prepared as described in example 15-18. Erlotinib succinate has been found also in 4 distinct polymorphs, depicted herein as ERSC ULT-1 – 4 in anhydrate and hydrate forms.

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base succinic acid was added in a ratio of 0.9 – 1.9 with respect to the free base of Erlotinib Subsequently, solvent (2,2,2-trifluoroethanol, ethylacetate, water, ethanol/water, methanol/water, acetone/water, acetonitrile/water, tetrahydrofuran/water, methylacetate, methanol, tetrahydrofuran, acetonitrile, 1,4-dioxane, 3-methyl-1-butanol, ethanol, tert-butyl methyl ether) was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor or if no solid was present, the solvent was evaporated. The supernatant solution was also evaporated. All resulting solids were dried and analyzed by XRPD.

In the case of polymorph ERSC ULT-2, about 50 mg of Erlotinib free base was solid dosed in a stainless steel vial. To the free base succinic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, about 5µL of solvent (2-propanol, isopropyl acetate, n-heptane, water) was added and the vials were sealed and shaken for at least 20 minutes and up till 90 minutes at a frequency of 30 s^{-1}. Solid material was analyzed by XRPD.

The polymorphs ERSC ULT-1 – 4 are characterized by the diffraction peaks found in the XRPD patterns shown below. The XRPD is essentially as shown in Figures 21-24.

ERSC ULT-1		
Peak table for SUD36		
Peak ID	Angle (2θ)	
1	7.34	M
2	7.45	H
3	8.04	M

ERSC ULT-1		
Peak table for SUD36		
Peak ID	Angle (2θ)	
4	11.64	L
5	12.05	L
6	14.40	L
7	14.71	L
8	14.95	L
9	15.15	L
10	15.90	M
11	16.35	L
12	16.54	L
13	19.91	L
14	20.38	M
15	20.84	L
16	21.27	L
17	21.50	L
18	21.77	L
19	22.15	L
20	22.51	L
21	22.69	M
22	22.87	L
23	23.27	L
24	23.94	H
25	24.26	L
26	25.26	M
27	25.67	L
28	26.70	M
29	27.51	H
30	28.46	L
31	29.08	L
		L<35<M<60<H

ERSC ULT-2		
Peak table for grc 06.4 c : L4		
Peak ID	Angle (2θ)	
1	6.54	H
2	7.34	H
3	9.82	L
4	11.36	L
5	12.88	L
6	14.77	L
7	18.74	M
8	19.67	L
9	20.46	M
10	22.17	L
11	22.78	M
12	23.94	L
13	25.18	M
14	26.3	M
15	27.02	L
16	27.58	L
17	28.62	L
18	29.3	L
19	31.29	L
		L<40<M<60<H

ERSC ULT-3		
Peak table for co 07.0 c : C2		
Peak ID	Angle (2θ)	
1	6.62	H
2	7.97	L

ERSC ULT-3		
Peak table for co 07.0 c : C2		
Peak ID	Angle (2θ)	
3	13.04	L
4	15.2	L
5	16.31	M
6	17.71	L
7	19.21	L
8	19.91	L
9	21.07	M
10	21.73	L
11	22.63	L
12	24.49	L
13	25.49	M
14	26.34	M
15	27.45	L
16	28.95	L
17	30.31	L
		L<15<M<60<H

ERSC ULT-4		
Peak table for co 16.0 c : G3		
Peak ID	Angle (2θ)	
1	3.7	M
2	6.66	M
3	7.46	H
4	8.28	L
5	13.05	L
6	13.66	L
7	14.54	L

ERSC ULT-4		
Peak table for co 16.0 c : G3		
Peak ID	Angle (2θ)	
8	15.12	L
9	18.5	L
10	19.55	L
11	20.33	L
12	22.15	M
13	22.61	M
14	24.63	M
15	25.29	M
16	25.82	M
17	26.52	M
18	29.38	L
19	31.36	L
		L<20<M<60<H

Polymorph ERSC ULT-1 of Erlotinib succinate is more soluble then the hydrochloric acid salt of Erlotinib as demonstrated by a comparative solubility determination in sodium dihydrogen phosphate buffer, pH=6.8. The solubility is 3.3 mg/mL, compared to <0.01 mg/mL for the hydrochloric acid salt of Erlotinib.

Quantitative solubility determination was performed in water and / or buffers on Erlotinib L-lactate salt at room temperature. Approximately 20 mg of Erlotinib L-lactate salt was weighted in a 1.8 ml screw cap glass vial and 400 µl liquid (water or buffers of pH 3, 5 and 6.8) was added. The vial was then closed and equilibrated for 24 h at room temperature under continuous stirring. The mother liquor was isolated from solids using a Tecan Genesis 200 liquid-handling robot. Subsequently three independent dilutions (factor of 10, 50 and 200) were prepared with Tecan Genesis 200. The dilutions were measured by HPLC (wavelength 245 nm). Further, two separate calibration curves for the HPLC (Agilent HP1100, UV-detector HP DAD) were made from two stock solutions of Erlotinib free base in water (stock concentrations 0.3 mg/ml and 0.5 mg/ml). The solubility was determined from the peak area from the HPLC chromatogram.

The compounds of this present invention are potent inhibitors of the erbB family of oncogenic and prooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly in humans. The compounds of the present invention are also inhibitors of angiogenesis and/or vasculogenesis. In particular, the compounds of the present invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplasic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH). It is expected that a compound of the present invention may possess activity against a range of leukemias and lymphoid malignancies. The compounds of the present invention may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signaling events related to various protein tyrosine kinases are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, glandular, macrophagal, epithelial, stromal, or blastocoelic nature in which aberrant function, expression, activation or signaling of the erbB tyrosine kinases are involved. In addition, the compounds of the present invention may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases that are inhibited by the compounds of the present invention.

Other methods for determining the activity of the compounds of the present invention are described in United States patent number 5,747,498, referred to above.

Administration of the compounds of the present invention (hereinafter the active compound(s)") can be effected by any method that enables delivery of the compounds to he site of action. These methods include oral routes intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular and infusion), topical, and rectal administration. The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration and the judgment of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg

human, this would amount to about 0.0S to about 7 g/day, preferably about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such larger doses are first divided into several smaller doses by administration throughout the day. The active compound may be applied as a sole therapy or may involve one or more other antitumor substances, for example those selected from, for example, mitotic inhibitors. For example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fuorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European patent Application No. 239362 such as N-(5-[N-(3,4dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for examples interferon; and anti-hormones, for example anti-estrogens such as Nolvadex™ (Tamoxifen) or for example anti-androgens such as Casodex™. Such conjoint treatment may be achievable by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet capsule, pill, powder, sustained release formulations, solution, suspension for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjutants, etc. Exemplary parenteral administration forms include solutions or suspensions of the active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired. Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrant such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia.

Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound herein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof. Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent to those skilled in this art. For examples, see Reminqton's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975). The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

Examples

Experimental conditions

X-ray Powder Diffraction:

XRPD patterns were obtained using a T2 high-throughput XRPD set-up by Avantium technologies, The Netherlands. The plates were mounted on a Bruker GADDS diffractometer equipped with a Hi-Star area detector. The XRPD platform was calibrated using Silver Behenate for the long d-spacings and Corundum for the short d spacings.

Data collection was carried out at room temperature using monochromatic CuK(alpha)radiation (1.54178 Å) in the two-theta region between 1.5 °and 41.5 °. The diffraction pattern of each well is collected in two two-theta ranges ($1.5° \leq 2\theta \leq 21.5°$ for the first frame, and $19.5° \leq 2\theta \leq 41.5°$ for the second) with an exposure time of 120 s for each frame. One of ordinary skill in the art understands that experimental differences may arise due to differences in instrumentation, sample preparation, or other factors. Typically XRPD data are collected with a variance of about 0.3 degrees two-theta, preferable about 0.2 degrees, more preferably 0.1 degrees, even

more preferable 0.05 degrees. This has consequences for when X-ray peaks are considered overlapping.

High-resolution X-ray Powder Diffraction:

The High resolution powder patterns were collected on the D8 Advance system in the Brag-Brentano geometry equipped with LynxEye solid state detector. The radiation used for collecting the data was CuK(alpha1 = 1.54056 A) monochromatized by the Germanium crystal. The patterns were collected in various 2θ ranges, starting from about 2 4 °2θ until about 60-65 °2θ, with a step in the ragne of 0.04-0.16 °2θ without further processing. All patterns were taken at Room Temperature, approximately 295K.

Single-crystal X-ray diffraction

Suitable single crystals were selected and glued to a glass fibre, which was then mounted on an X-ray diffraction goniometer. X-ray diffraction data were collected for these crystals at a temperature of 120K and at room temperature, using a KappaCCD system and MoK□ radiation, generated by a FR590 X-ray generator (Bruker Nonius, Delft, The Netherlands).

Unit-cell parameters and crystal structures were determined and refined using the software package MaXus.

Thermal analysis:

Melting properties were obtained from DSC thermograms, recorded with a heat flux DSC822e instrument (Mettler-Toledo GmbH, Switzerland). The DSC822e was calibrated for temperature and enthalpy with a small piece of indium (m.p. = 156.6°C; delta-H(f) = 28.45 J/g). Samples were sealed in standard 40 microliter aluminum pans and heated in the DSC from 25°C to 300°C, at a heating rate of 20°C/min. Dry N2 gas, at a flow rate of 50 ml/min, was used to purge the DSC equipment during measurement.

Mass loss due to solvent or water loss from the crystals was determined by TGA/SDTA. Monitoring of the sample weight, during heating in a TGA/SDTA851e instrument (Mettler-Toledo GmbH, Switzerland), resulted in a weight vs. temperature curve. The TGA/SDTA851e was calibrated for temperature with indium and aluminium.

Samples were weighed into 100 microliter aluminium crucibles and sealed. The seals were pin-holed and the crucibles heated in the TGA from 25°C to 300°C at a heating rate of 20°C/min. Dry N2 gas is used for purging. Melting point determinations based on DSC have a variability of +/- 2.0 degrees Celsius, preferably 1.0 degrees Celsius.

Raman spectroscopy:

The Raman spectra were collected with a Raman microscope mW (Kaiser Opticals Inc) at 0.96 cm-1 resolution using a laser of 780 nm and a power output of 100.

Erlotinib free base

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art. Dry solid was analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 19A – 19D.

Example 1

Preparation of Erlotinib ethanesulfonate polymorph ERET ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. Ethylacetate was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. Ethanesulfonic acid was added drop wise in a ratio of 1.1 with respect to the free base of Erlotinib to the above reaction mass under stirring with a speed of 200 rpm. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration under vacuum with a 5 μm filter. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 -

5 h. Dry solid was analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 1A – 1E.

Example 2

Preparation of Erlotinib ethanesulfonate polymorph ERET ULT-2

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. Water was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. Ethanesulfonic acid was added drop wise in a ratio of 1.1 with respect to the free base of Erlotinib to the above reaction mass under stirring with a speed of 200 rpm. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by evaporation. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Dry solid was analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 2A – 2E.

Example 3

Preparation of Erlotinib isethionate polymorph ERIS ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. To the free base 2-hydroxy-ethanesulfonic acid (isethionic acid) was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, ethylacetate was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently the reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration

under vacuum with a 5 μm filter. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Subsequently, the solids were dispensed in water and the resulting slurry was stirred at room temperature for at least 1 day and up till 5 days. Solid material was separated from water, dried as mentioned above and analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 3A – 3F.

Example 4

Preparation of Erlotinib isethionate polymorph ERIS ULT-2

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 2-hydroxy-ethanesulfonic acid (isethionic acid) was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, ethylacetate was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Dry solid was analyzed by XRPD and TGA(MS). Analytical data are presented in Figures 4A – 4C.

Example 5

Preparation of Erlotinib isethionate polymorph ERIS ULT-3

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 2-hydroxy-ethanesulfonic acid (isethionic acid) was added in a ratio of 1.2 with respect to the free base of Erlotinib. Subsequently, methylacetate was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free

base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Dry solid was analyzed by XRPD and TGA(MS). Analytical data are presented in Figures 5A – 5C.

Example 6

Preparation of Erlotinib isethionate polymorph ERIS ULT-4

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 2-hydroxy-ethanesulfonic acid (isethionic acid) was added in a ratio of 1.2 with respect to the free base of Erlotinib. Subsequently, methylacetate was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Subsequently, the solids were dispensed in water and the resulting slurry was stirred at room temperature for at least 1 day and up till 5 days. Solid material was separated from water, dried and analyzed by XRPD (Figure 6).

Example 7

Preparation of Erlotinib bromide polymorph ERBR ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. Ethylacetate was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. 48 % of hydrobromic acid in ACS reagent was added drop wise in a ratio of 1.1 with respect to the free base of Erlotinib to the above reaction mass under stirring with a speed of 200 rpm. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently the reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration under vacuum with a 5 μm filter. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Dry solid was analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 7A – 7F.

Example 8

Preparation of Erlotinib bromide polymorph ERBR ULT-2

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 48 % hydrobromic acid in ACS reagent was added together with acetone/water 50:50 in a ratio of 1.1 – 1.2 with respect to the free base of Erlotinib. The final concentration of Erlotinib free base in the solvent was approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL). The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Dry solid was analyzed by XRPD (Figure 8).

Example 9

Preparation of Erlotinib bromide polymorph ERBR ULT-3

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 48 % hydrobromic acid in ACS reagent was added together with methanol/water 50:50 in a ratio of 1.1 with respect to the free base of Erlotinib. The final concentration of Erlotinib free base in the solvent was approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL). The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Dry solid was analyzed by XRPD (Figure 9A).

Example 10

Preparation of Erlotinib bromide polymorph ERBR ULT-4

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 48 % hydrobromic acid in ACS reagent was added together with methanol in a ratio of 1.1 with respect to the free base of Erlotinib. The final concentration of Erlotinib free base in methanol was approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL). The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor. The solvent from the mother liquor was evaporated and the remaining solid was dried and analyzed by XRPD (Figure 10). Drying was carried out at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection.

Example 11

Preparation of Erlotinib bromide polymorph ERBR ULT-5

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base 48 % hydrobromic acid in ACS reagent was added together with methanol in a ratio of 1.1 with respect to the free base of Erlotinib. The final concentration of Erlotinib free base in methanol was approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL). The vials were sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor. The solvent from the mother liquor was evaporated and the remaining solid was dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. Subsequently, the solids were exposed to 40°C and 75% relative humidity for 48 h and re-analyzed by XRPD (Figure 11).

Example 12

Preparation of Erlotinib malonate polymorph ERMO ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. To the free base malonic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, ethanol/water 50:50 was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently the reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration under vacuum with a 5 μm filter. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Subsequently, the solids were dispensed in water and the resulting slurry was stirred at room temperature for at least 1 day and up till 5 days. Solid material was separated from water, dried as mentioned

above and analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 12A – 12F.

Example 13

Preparation of Erlotinib malonate polymorph ERMO ULT-2

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base malonic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib Subsequently, methanol/water 50:50 was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vial was sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently the vial was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor. The solvent from the mother liquor was evaporated and the remaining solid was dried and analyzed by XRPD. Drying was carried out at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. The XRPD pattern is presented in Figure 13.

Example 14

Preparation of Erlotinib L-lactate polymorph ERLA ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base Lactic acid was added in a ratio of 1.2 with respect to the free base of Erlotinib Subsequently, methylacetate was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vial was sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vials were allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-

38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. The XRPD pattern is presented in Figure 14.

Example 15

Preparation of Erlotinib succinate polymorph ERSC ULT-1

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 1 g of Erlotinib free base was weighted in a 50 mL glass reactor in the Mettler Toledo MultiMax^{MT} device equipped with mechanical stirring. To the free base succinic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, ethanol/water 50:50 was added to a final concentration of approximately 50 mg/mL of Erlotinib free base. The reactor was heated from rT to 60°C with a rate of 1°C/min and kept at 60°C for 60 minutes. Subsequently the reactor was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Stirring speed during the temperature profile was 300 rpm. Solid material was obtained by filtration under vacuum with a 5 μm filter. The solids were dried at 20 -25 °C at 200 mbar for approximately 1 day and additionally at 40°C and 200 mbar for about 4 - 5 h. Dry solid was analyzed by XRPD and additional analytical methods. Analytical data are presented in Figures 15A – 15F.

Example 16

Preparation of Erlotinib succinate polymorph ERSC ULT-2

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 50 mg of Erlotinib free base was solid dosed in a stainless steel vial. To the free base succinic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, about 5μL of water was added and the vial was sealed and

shaken for at least 20 minutes and up till 90 minutes at a frequency of 30 s^{-1}. Solid material was analyzed by XRPD (Figure 16).

Example 17

Preparation of Erlotinib succinate polymorph ERSC ULT-3

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base succinic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, ethanol was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vial was sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vial was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. The XRPD pattern is presented in Figure 17.

Example 18

Preparation of Erlotinib succinate polymorph ERSC ULT-4

Erlotinib hydrochloride salt was obtained from Jinan Sky-worth Pharmaceutical Group. The free base of Erlotinib was obtained from the hydrochloride salt by standard conversion known to a person skilled in the art.

About 40 mg of Erlotinib free base was solid dosed in a 1.8 mL glass vial. To the free base succinic acid was added in a ratio of 1.1 with respect to the free base of Erlotinib. Subsequently, 1,2-dimethoxyethane was added to a final concentration of approximately 50 mg/mL (range of 48.8 – 52.9 mg/mL) of Erlotinib free base. The vial was sealed and heated from rT to 60°C with a rate of 10°C/min and kept at 60°C for 60 minutes. Subsequently vial was allowed to cool to 5°C at rate of 1°C/hr and kept at 5°C for 35-38 hr. Solid material was separated from the mother liquor and dried at 20 -25 °C at 200 mbar for at least 1 day and up till 6 days. If remaining solid was still wet further

drying was done at 20-25 °C at 5 mbar until sample was completely dry as judged by visual inspection. The XRPD pattern is presented in Figure 18.

Example 19

Comparative pharmacokinetic study of erlotinib solid forms and erlotinib mesylate salt

Batches of the solid forms of erlotinib and erlotinib mesylate salt are prepared with comparable crystal size by sieving through a [mu]M sieve. Small cellulose capsules are filled with approximately 15 mg of the solid forms . Twelve Male wistar rats of approximately 300 grams each are dosed one capsule by oral gavage followed by 1 mL of tap water. At regular intervals a small quantity of blood is sampled from each rat by a tail vein puncture. Blood samples are immediately frozen in Liquid N2 for further processing. After all samples are collected, plasma preparations are made of each sample. The plasma samples are further worked up for analysis by LC-MS-MS for their content of erlotinib. Efficiency of extraction is determined by comparison by spiking rat plasma samples with known amounts of erlotinib. The concentration of erlotinib is quantified in each sample by means of LC-MS-MS against a calibration curve. The results of the comparative pharmacokinetic are presented. From the PK data bioequivalency of the erlotinib sold forms to the mesylate and/or chloride salt of erlotinib can be determined.

Example 20

Study of the food effect of erlotinib solid forms

The effects of food on the pharmacokinetics of erlotinib are investigated. In a single-dose study 150 mg of erlotinib, either the mesylate salt, the hydrochloride salt or the solid forms described herein are administered under either fasting or fed conditions. The area under the plasma concentration-time curve is determined by the geometric mean ratio (GMR) observed under fed or fasted conditions. In another study, identical doses of erlotinib, either the mesylate salt, the hydrochloride salt or the solid forms described herein are administered daily for 8 days, either 7 days of fasting followed by feeding on day 8, or the reverse sequence. The plasma concentration-time curve is determined to determine the food effect of the various erlotinib forms. These studies provide an indication that the solid forms described herein can play a role in controlling

the fact that food can substantially increase plasma exposure to erlotinib. As the clinical practice allows only for a maximum tolerated dose of erlotinib, the use of other forms of erlotinib may lower the food effect of erlotinib resulting in that erlotinib may be taken also under conditions of fed or reduced fasting thereby alleviating discomfort for patients.

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CLAIMS

1. Salt of Erlotinib, wherein the salt is selected from the group consisting of ethanesulfonate, isethionate, bromide, malonate, L-lactate, succinate.
2. Salt of Erlotinib according to claim 1, wherein the salt is the ethanesulfonate salt.
3. Salt of Erlotinib according to claim 1, wherein the salt is the isethionate salt.
4. Salt of Erlotinib according to claim 1, wherein the salt is the bromide salt.
5. Salt of Erlotinib according to claim 1, wherein the salt is the malonate salt.
6. Salt of Erlotinib according to claim 1, wherein the salt is the L-lactate salt.
7. Salt of Erlotinib according to claim 1, wherein the salt is the succinate salt.
8. Salt of Erlotinib ETHANESULFONATE according to claim 2, wherein the salt is the Form ERET ULT-1, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.42, 6.94, 8.65, 10.78, 13.16, 16.17, 18.94, 20.62, 21.76, 23.82, 25.32 (2θ) +/- 0.3.
9. Salt of Erlotinib ETHANESULFONATE according to claim 2, wherein the salt is the Form ERET ULT2, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.9, 8.36, 10.18, 11.73, 13.02, 13.27, 16.8, 16.89, 17.09, 17.88, 18.81, 19.57, 19.87, 20.05, 20.44, 20.72, 21.57, 22.21, 23.62, 23.98, 24.72, 25.16, 25.38, 25.72, 26.01, 26.29, 26.73, 27.84, 28.15, 28.93, 29.56, 30.06, 30.49, 31.09, 31.72, 32.77, 33.94, 34.22, 34.62, 36.38 (2θ) +/- 0.3.
10. Salt of Erlotinib isethionate according to claim 3, wherein the salt is the Form ERIS ULT-1, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 7.31, 7.43, 7.65, 8.3, 11.37, 11.8, 12.61, 14.81, 15.06, 15.91, 16.09, 16.4, 16.66, 20.26, 20.58, 20.92, 21.84, 22.06, 22.24, 22.6, 22.8, 23.11, 23.37, 23.72, 24.47, 24.9, 25.78, 26.27, 27.11, 27.65, 28.55, 29.09, 29.58, 30.41, 30.94 (2θ) +/- 0.3.
11. Salt of Erlotinib isethionate according to claim 3, wherein the salt is the Form ERIS ULT2, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.7, 8.18, 12.26, 13.14, 16.34, 17.14, 17.7, 18.54, 19.1, 20.62, 21.39, 23.04, 24.58, 26.5, 29.15, 30.2, 31.26 (2θ) +/- 0.3.

12. Salt of Erlotinib isethionate according to claim 3, wherein the salt is the Form ERIS ULT3, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.38, 6.54, 7.3, 13.38, 14.48, 15.63, 17.86, 19.18, 19.58, 20.54, 21.35 (2θ) +/- 0.3.

13. Salt of Erlotinib isethionate according to claim 3, wherein the salt is the Form ERIS ULT4, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.22, 6.38, 7.08, 10.43, 17.26, 18.16, 19.17, 20.42, 22.18, 24.62, 27.45 (2θ) +/- 0.3.

14. Salt of Erlotinib bromide according to claim 4, wherein the salt is the Form ERBR ULT-1, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.23, 7.84, 9.55, 11.39, 12.47, 13.37, 14.76, 15.67, 16.95, 17.63, 20.19, 20.67, 20.93, 21.11, 21.85, 22.43, 22.96, 23.83, 23.94, 24.43, 24.65, 25.12, 25.90, 26.50, 26.75, 26.95, 28.60, 28.95, 29.70, 32.66, 34.72, 40.08 (2θ) +/- 0.3.

15. Salt of Erlotinib bromide according to claim 4, wherein the salt is the Form ERBR ULT2, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.66, 9.58, 12.74, 15.18, 16.99, 13.58, 18.7, 19.1, 20.42, 22.42, 23.38, 23.86, 24.54, 25.18, 25.62, 26.44, 27.29, 28.5, 29.22, 30.58, 31.06, 32.17, 37.57 (2θ) +/- 0.3.

16. Salt of Erlotinib bromide according to claim 4, wherein the salt is the Form ERBR ULT3, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.26, 7.78, 9.3, 13.33, 15.5, 16.74, 18.17, 18.66, 19.7, 20.5, 21, 22.06, 22.94, 23.9, 24.34, 24.98, 26.34, 28.26, 28.87, 29.37, 30.49, 30.99, 32.04, 33.29, 34.1, 35.09, 36.77, 38.14, 40.15 (2θ) +/- 0.3.

17. Salt of Erlotinib bromide according to claim 4, wherein the salt is the Form ERBR ULT4, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 5.9, 8.14, 11.3, 11.66, 12.68, 16.31, 17.9, 18.87, 21.1, 22.63, 23.34, 23.82, 25.98, 27.14, 28.42, 29.17, 31.84 (2θ) +/- 0.3.

18. Salt of Erlotinib bromide according to claim 4, wherein the salt is the Form ERBR ULT5, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.22, 8.38, 11.78, 14.68, 16.85, 18.14, 18.7,

19.44, 20.36, 20.92, 22.63, 23.13, 24.62, 25.25, 26.46, 27.82, 28.59, 29.46 (2θ) +/- 0.3.

19. Salt of Erlotinib malonate according to claim 5, wherein the salt is the Form ERMO ULT-1, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.68, 8.85, 9.31, 12.07, 13.29, 15.98, 16.78, 17.43, 18.91, 19.36, 20.17, 20.44, 21.05, 21.67, 22.85, 23.09, 23.70, 24.70, 24.89, 26.68, 26.90, 27.69, 28.25, (2θ) +/- 0.3.

20. Salt of Erlotinib malonate according to claim 5, wherein the salt is the Form ERMO ULT2, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 2.26, 5.42, 8.26, 10.82, 14.3, 16.5, 17.86, 20.81, 21.74, 22.46, 24.06, 25.14, 25.78, (2θ) +/- 0.3.

21. Salt of Erlotinib L-lactate according to claim 6, wherein the salt is the Form ER ULTY, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.46, 7.83, 12.41, 12.81, 15.84, 16.66, 18.2, 19.48, 20.42, 21.03, 21.7, 22.58, 23.53, 24.64, 26.24, 25.66, 26.75, 27.2, 29.24, (2θ) +/- 0.3.

22. Salt of Erlotinib succinate according to claim 7, wherein the salt is the Form ERSC ULT-1, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 7.34, 7.45, 8.04, 11.64, 12.05, 14.40, 14.71, 14.95, 15.15, 15.90, 16.35, 16.54, 19.91, 20.38, 20.84, 21.27, 21.50, 21.77, 22.15, 22.51, 22.69, 22.87, 23.27, 23.94, 24.26, 25.26, 25.67, 26.70, 27.51, 28.46, 29.08, (2θ) +/- 0.3.

23. Salt of Erlotinib succinate according to claim 7, wherein the salt is the Form ERSC ULT2, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.54, 7.34, 9.82, 11.36, 12.88, 14.77, 18.74, 19.67, 20.46, 22.17, 22.78, 23.94, 25.18, 26.3, 27.02, 27.58, 28.62, 29.3, 31.29, (2θ) +/- 0.3.

24. Salt of Erlotinib succinate according to claim 7, wherein the salt is the Form ERSC ULT3, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 6.62, 7.97, 13.04, 15.2, 16.31, 17.71, 19.21, 19.91, 21.07, 21.73, 22.63, 24.49, 25.49, 26.34, 27.45, 28.95, 30.31, (2θ) +/- 0.3.

25. Salt of Erlotinib succinate according to claim 7, wherein the salt is the Form ERSC ULT4, characterized by one, two, three, four, five, six, seven or eight peaks selected from the group consisting of 3.7, 6.66, 7.46, 8.28, 13.05, 13.66, 14.54, 15.12, 18.5, 19.55, 20.33, 22.15, 22.61, 24.63, 25.29, 25.82, 26.52, 29.38, 31.36, (2θ) +/- 0.3.

26. Method for the preparation of Erlotinib salts and solid forms as defined in claims 1-25, comprising the steps of

- combining erlotinib free base with about 1.1 – 1.2 equivalent of acid;
- adding solvent to a concentration of about 50 mg/ml;
- warming the mixture to about 60 degrees Celsius at a rate of about 1-10 degrees/minute;
- keeping the mixture at about 60 degrees Celsius for a period between about 30-90 minutes;
- allowing the mixture to cool to about 5 degrees Celsius at a rate of about 1-10 degrees/minute;
- keeping the mixture for about 10-50 hours;
- optionally evaporating the liquid;
- isolating the solid;
- drying the solid, optionally at reduced pressure;

wherein the acids and solvents are:

Erlotinib Salt	Acid	Solvent
ethanesulfonate	Ethanesulfonic acid	ethylacetate, water
isethionate	isethionic acid	methanol, tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, 1,4-dioxane, 3-methyl-1-butanol, ethanol, ethylacetate, tert-butyl methyl ether, methanol/water, methylacetate
bromide	hydrobromic acid	methylacetate, methanol, tetrahydrofuran, acetonitrile, 1,2-

		dimethoxyethane, 1,4-dioxane, 3-methyl-1-butanol, ethanol, ethylacetate, water, acetone/water, 2,2,2-trifluoroethanol, tert-butyl methyl ether, ethanol/water, methanol/water
malonate	malonic acid	methylacetate, acetonitrile, ethanol/water, methanol/water, tetrahydrofuran/water, acetonitrile/water, methanol, acetone/water, 1,4-dioxane
L-lactate	Lactic acid	methylacetate, 1,2-dimethoxyethane, 3-methyl-1-butanol, ethanol, ethylacetate
succinate	succinic acid	2,2,2-trifluoroethanol, ethylacetate, water, ethanol/water, methanol/water, acetone/water, acetonitrile/water, tetrahydrofuran/water, methylacetate, methanol, tetrahydrofuran, acetonitrile, 1,4-dioxane, 3-methyl-1-butanol, ethanol, tert-butyl methyl ether

27. Pharmaceutical composition comprising any of the erlotinib salts of claims 1-25 together with a pharmaceutically acceptable carrier.

28. Use of a pharmaceutical composition comprising any of the erlotinib salts of claims 1-25 as a medicament.

29. Use of any of the erlotinib salts of claims 1-25 in the preparation of a medicament for:

- the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal, including a human;
- the treatment of hyperproliferative disorder, specifically non-small cell lung cancer and bronchioalveolar cancer, in a mammal, including a human;
- the prevention of blastocyte implantation in a mammal, including a human;

- the treatment of a disease related to vasculogenesis or angiogenesis in a mammal, including a human;

- the treatment of a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetes retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer in a mammal, including a human;

- the treatment of cancer selected from the group consisting of brain, lung, squamous cell, bladder, gastric, pancreatic, breast, neck, head, renal (kidney), ovarian, prostate, colorectal, oesophageal, gynaecological or thyroid cancer in a mammal, including a human;

- the treatment of non-cancerous hyperproliferative disorder selected from the group consisting of benign hyperplasia of the skin (psoriasis) or prostate (benign prostatic hypertrophy (BPH));

- the treatment of psoriasis, BPH, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynaecologic tumors (uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphatic lymphomas, cancer of the bladder, cancer of the kidney or urethra (renal call carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (primary CNS lymphoma, spinal axis tumors, brainstem gliomas or pituitary adenomas.

30. Use of any of the erlotinib salts and solid forms of claims 1-25 in:

- the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal, including a human;

- the treatment of hyperproliferative disorder, specifically non-small cell lung cancer and bronchioalveolar cancer, in a mammal, including a human;

- the prevention of blastocyte implantation in a mammal, including a human;

- the treatment of a disease related to vasculogenesis or angiogenesis in a mammal, including a human;

- the treatment of a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetes retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer in a mammal, including a human;

- the treatment of cancer selected from the group consisting of brain, lung, squamous cell, bladder, gastric, pancreatic, breast, neck, head, renal (kidney), ovarian, prostate, colorectal, oesophageal, gynaecological or thyroid cancer in a mammal, including a human;

- the treatment of non-cancerous hyperproliferative disorder selected from the group consisting of benign hyperplasia of the skin (psoriasis) or prostate (benign prostatic hypertrophy (BPH));

- the treatment of psoriasis, BPH, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynaecologic tumors (uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or

acute leukemia, solid tumors of childhood, lymphatic lymphomas, cancer of the bladder, cancer of the kidney or urethra (renal call carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (primary CNS lymphoma, spinal axis tumors, brainstem gliomas or pituitary adenomas.

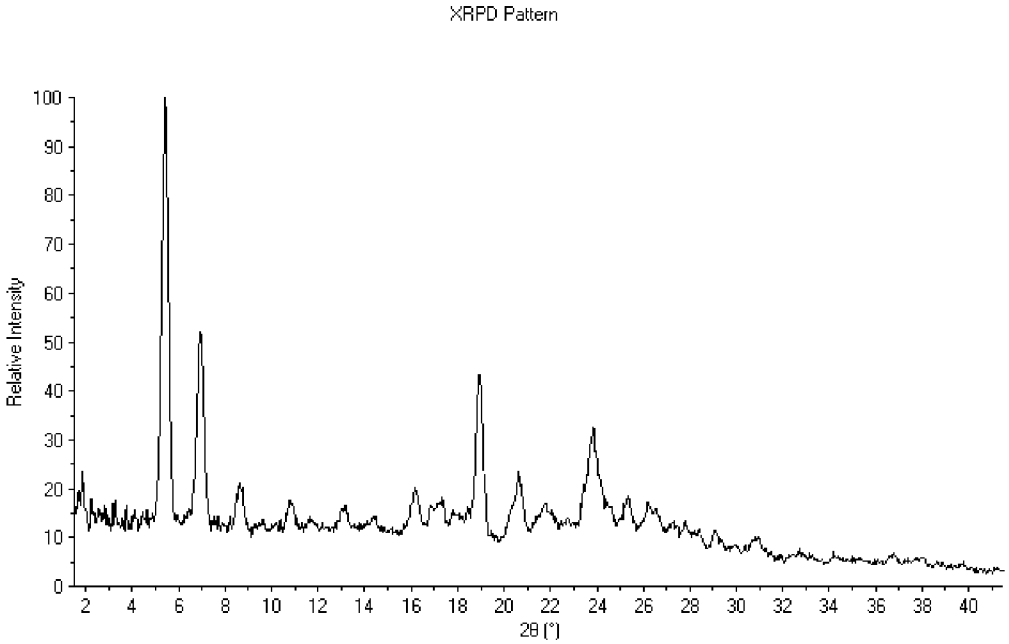
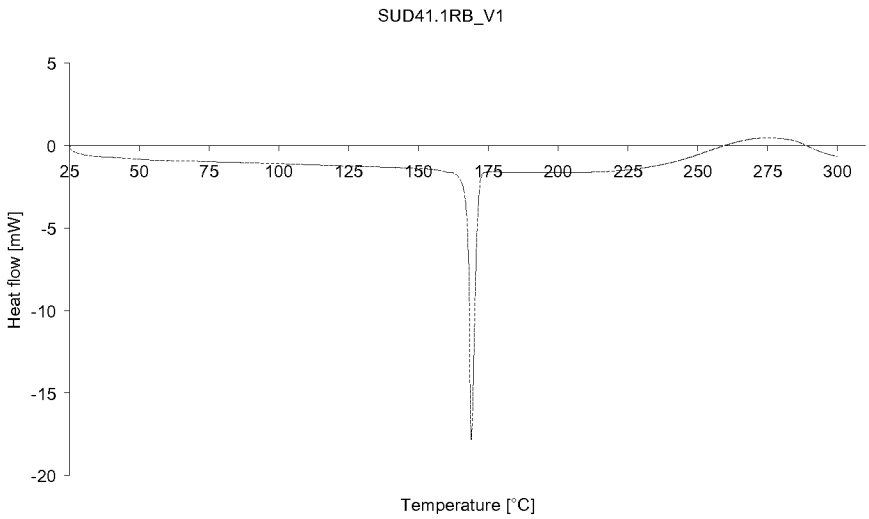
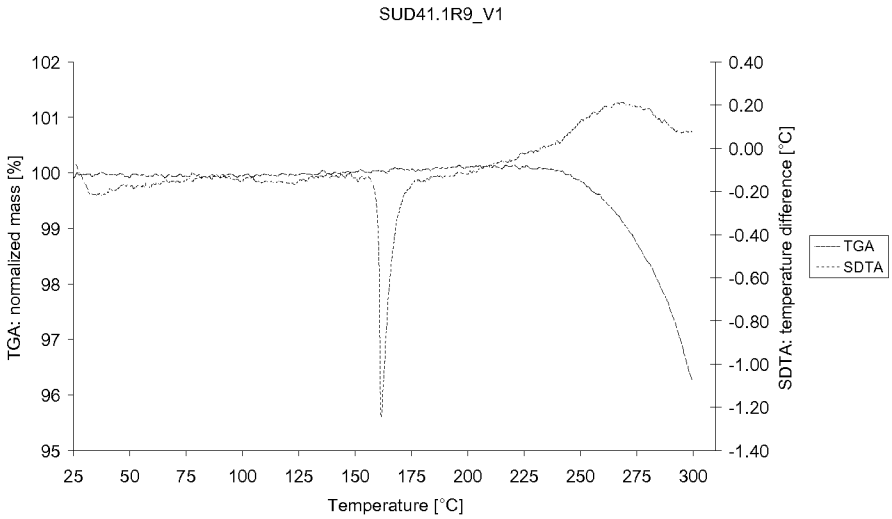


Figure 1A illustrates the X-Ray Powder Diffraction pattern of Erlotinib ethanesulfonate ERET ULT-1



SUD41.1RB_V1
DSC (10 ºC/min)
Onset: 167.54 °C
Peak:168.96 °C

Figure 1B illustrates the DSC thermogram of Erlotinib ethanesulfonate ERET ULT-1



SUD41.1R9_V1
TGA (10 ºC/min)
Mass loss ~0.1% for T<170 ºC

Figure 1C illustrates the TGA thermogram of Erlotinib ethanesulfonate ERET ULT-1

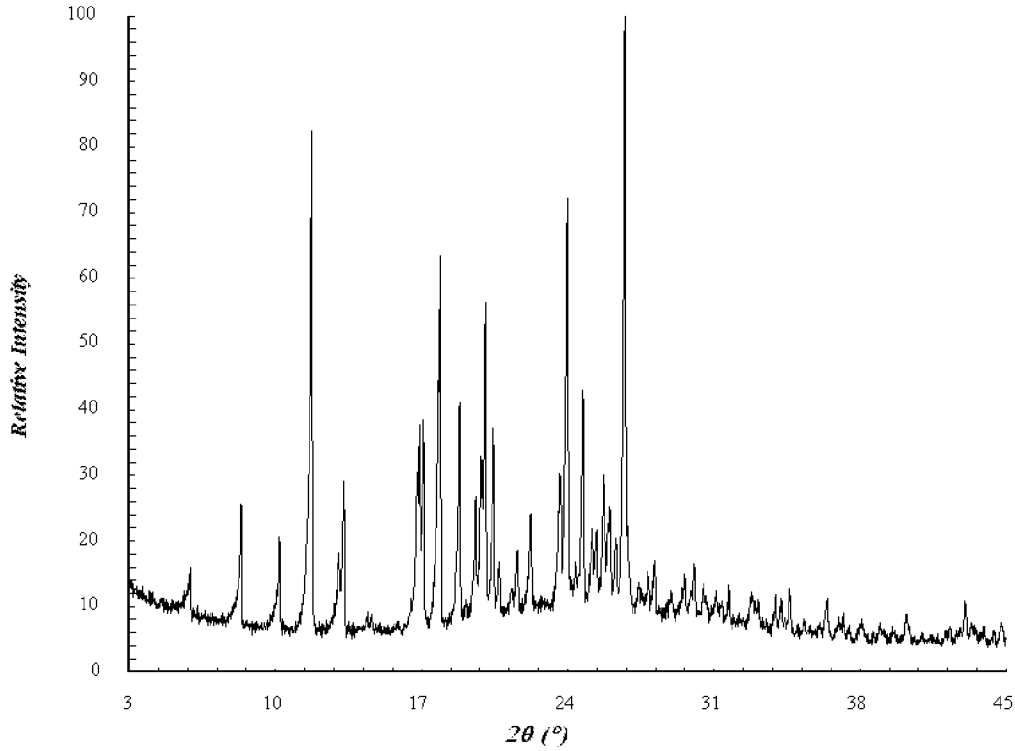
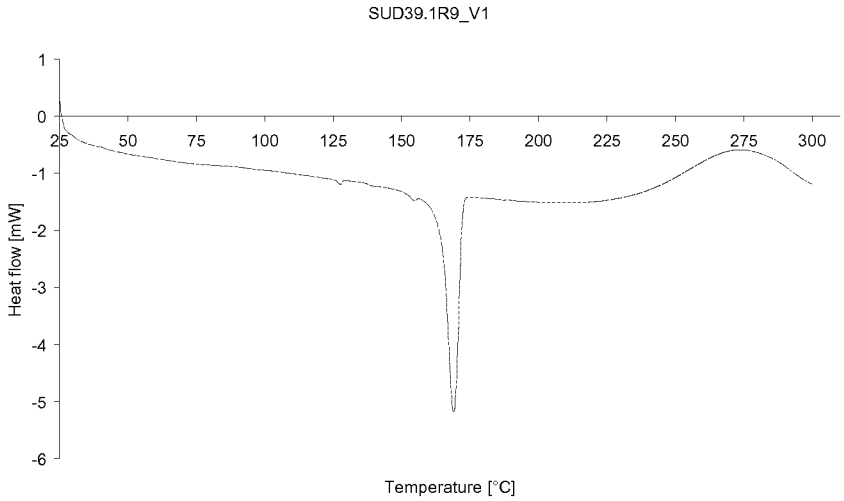
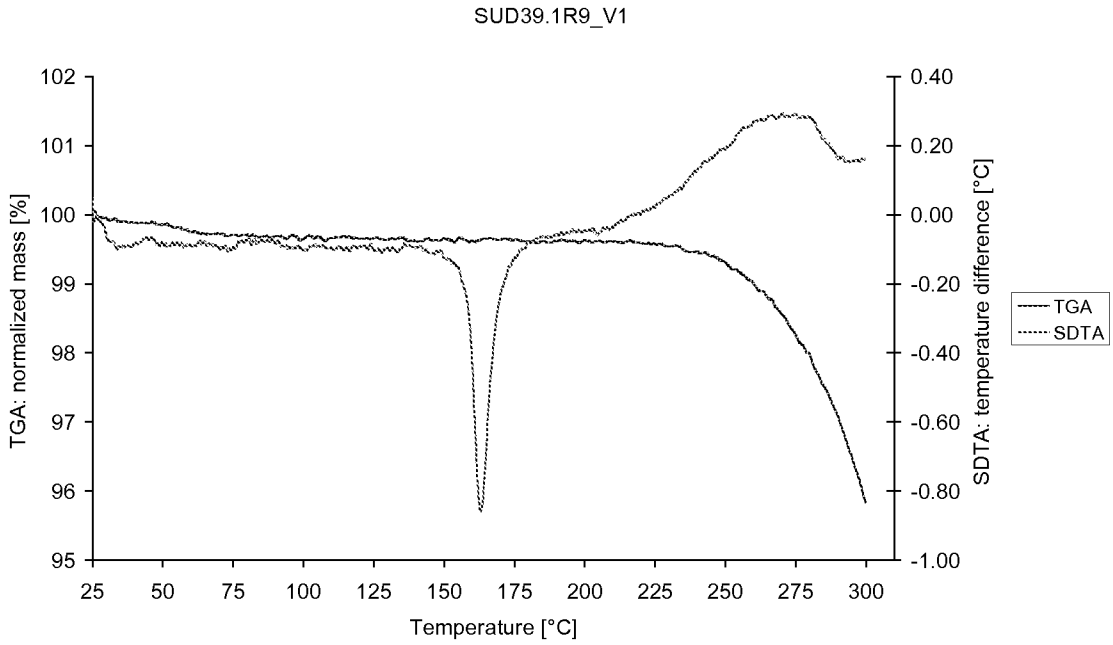


Figure 2A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib ethanesulfonate ERET ULT-2



SUD39.1R9_V1
DSC (10 ºC/min)
Onset: 164.5 °C
Peak: 169.08 °C

Figure 2B illustrates the DSC thermogram of Erlotinib ethanesulfonate ERET ULT-2



SUD39.1R9_V1
TGA (10 ºC/min)
Mass loss ~0.3% for T<170 ºC

Figure 2C illustrates the TGA thermogram of Erlotinib ethanesulfonate ERET ULT-2

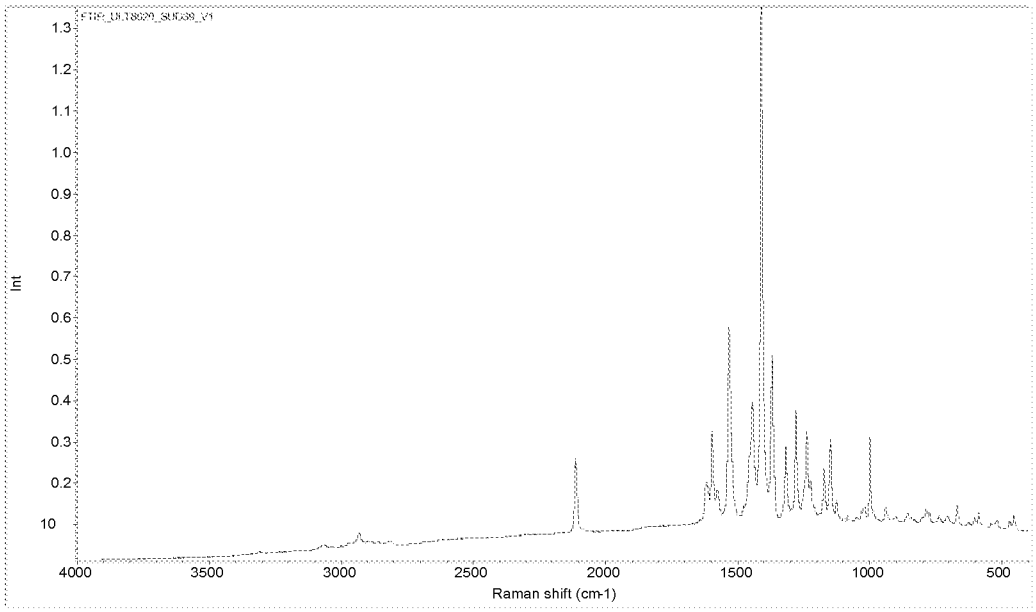


Figure 2D illustrates the Raman spectrogram of Erlotinib ethanesulfonate ERET ULT-2

Table 2A Characteristic Raman peaks of Erlotinib ethanesulfonate ERET ULT-2

Wavenumber (cm^{-1})	Intensity	H>40000>M>30000>L
998.6	30678.303	M
1148.2	30613.902	M
1172.4	23244.225	L
1237.7	32137.625	M
1278.9	37342.883	M
1317.3	28240.537	L
1368.7	50723.551	H
1409.3	134891.5	H
1444.1	39543.156	M
1532.1	57675.109	H
1596.2	32048.08	M
2112.6	25545.547	L

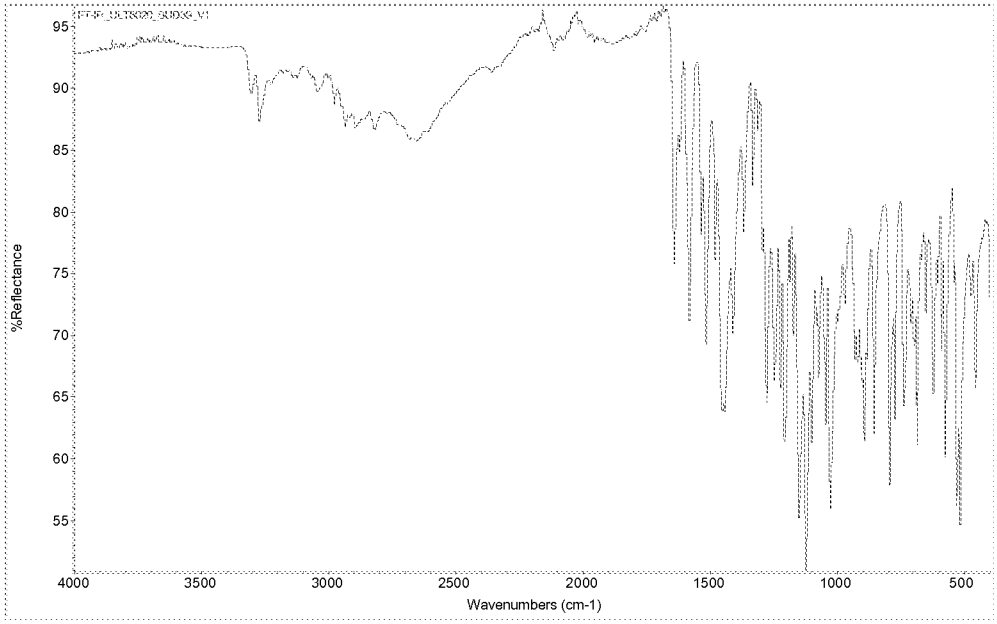


Figure 2E illustrates the FT-IR spectrogram of Erlotinib ethanesulfonate ERET ULT-2

Table 2B Characteristic FT-IR peaks of Erlotinib ethanesulfonate ERET ULT-2

Wavenumber	%reflectance	L>75>M>60>H	Wavenumber	%reflectance	L>75>M>60>H
454.9	73.698	M	1099.7	61.124	M
473.6	72.177	M	1121.9	50.825	H
515	66.654	M	1148.5	54.863	H
528	66.863	M	1171	69.789	M
572	68.362	M	1183.7	74.181	M
586.3	75.186	L	1205.6	61.222	M
603.6	72.033	M	1221.2	65.414	M
619.7	77.42	L	1244.9	65.928	M
651.5	79.627	L	1274.4	64.412	M
684.8	75.126	L	1291.9	76.784	L
695.8	77.429	L	1312.8	86.469	L
708.2	75.987	L	1331.4	81.774	L
735.7	78.522	L	1365.9	78.098	L
771.8	63.153	M	1408.5	69.876	M
791.7	80.151	L	1449	63.554	M
854.1	78.356	L	1478	75.659	L
891.3	76.252	L	1513.9	69.146	M
917.9	72.952	M	1535.1	78.112	L
928.4	76.861	L	1580.6	70.829	M
967.4	72.268	M	1639.4	75.677	L
1024.2	55.846	H	2654.9	85.63	L
1043.5	62.65	M	3271.3	87.207	L
1071.7	66.181	M			

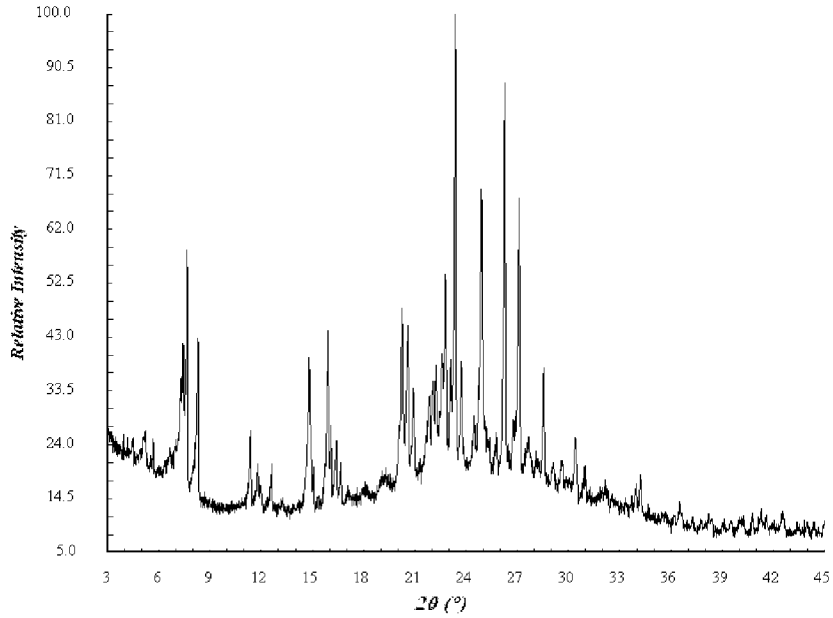
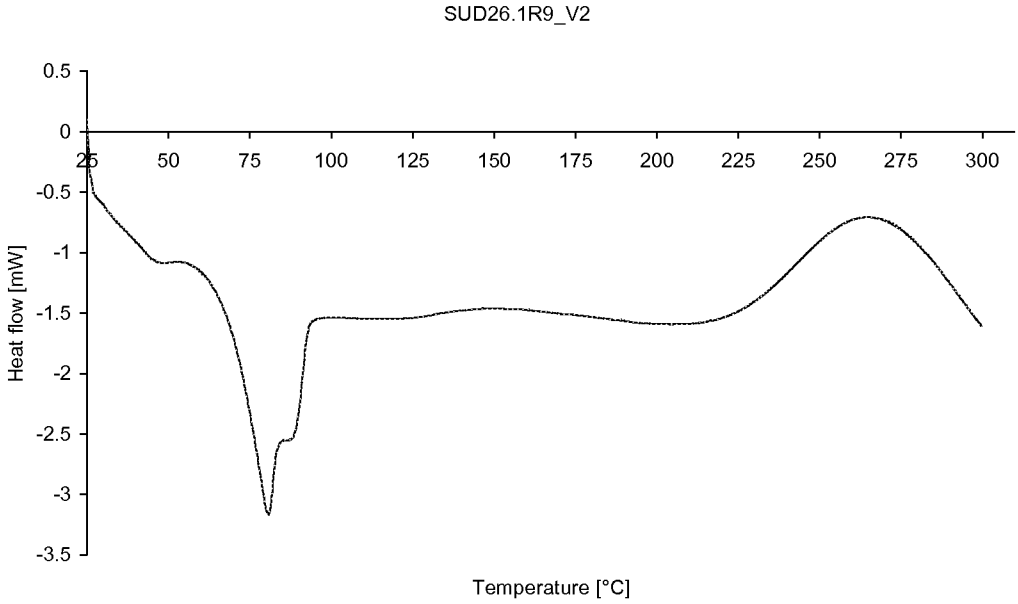
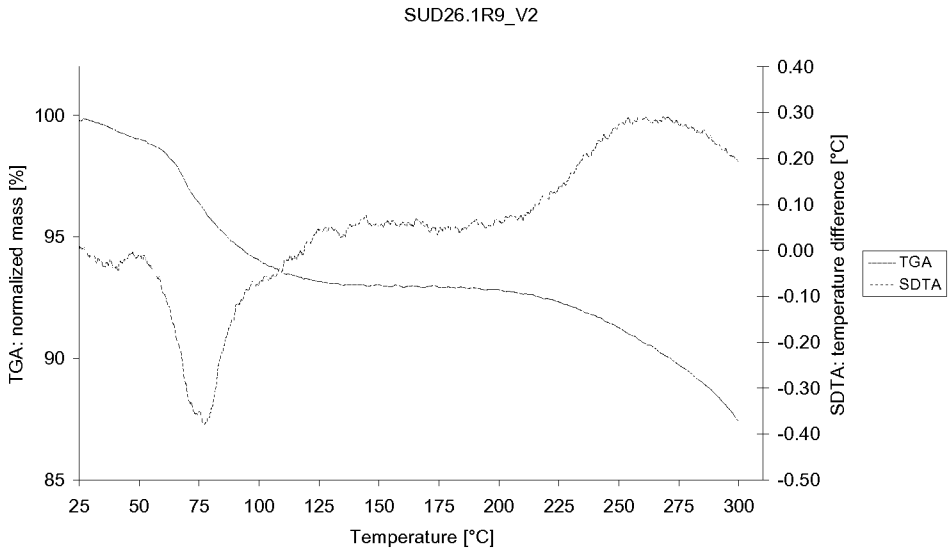


Figure 3A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-1

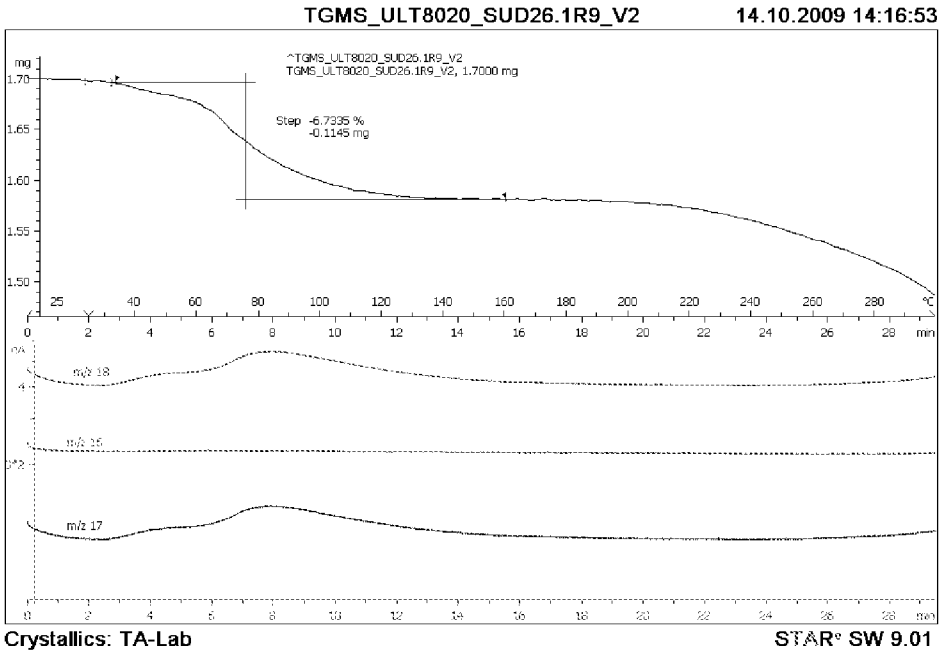


SUD26.1R9_V2
DSC (10 ºC/min)
Onset:67.99 ºC
Peak: 80.72ºC

Figure 3B illustrates the DSC thermogram of Erlotinib isethionate ERIS ULT-1



SUD25.1R7_V1
TGA (10 ºC/min) Mass loss ~6.7% for T<125 ºC
Figure 3C illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-1



SUD26.1R9
TG-MS (10 ºC/min)
Mass loss ~0.5% for T<170 ºC
Solvents detected: Water

Figure 3D illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-1

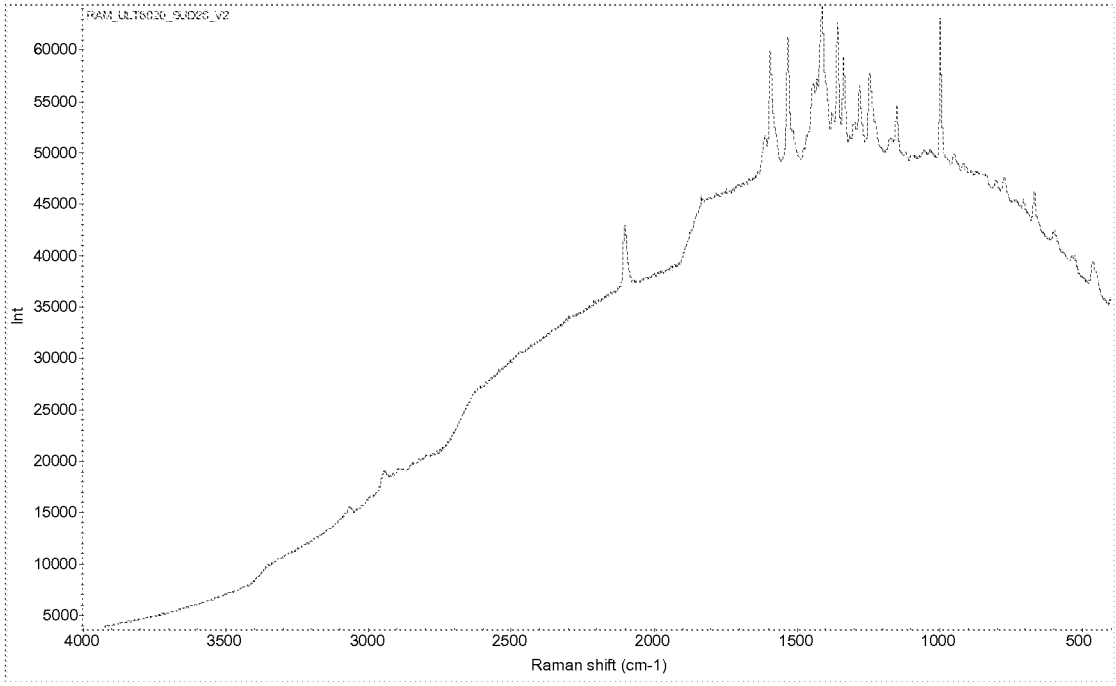


Figure 3E illustrates the Raman spectrogram of Erlotinib isethionate ERIS ULT-1

Table 3A Characteristic Raman peaks of Erlotinib isethionate ERIS ULT-1

Wavenumber (cm^{-1})	Intensity	H>60000>M>50000>L
668.1	46196.469	L
997.8	62993.844	H
1151	54655.43	M
1245.1	57809.016	M
1281.3	56471.051	M
1336.3	59321.32	M
1357.9	62584.18	H
1410.7	64216.422	H
1532	61161.758	H
1593	59786.738	M
2103.6	42819.277	L

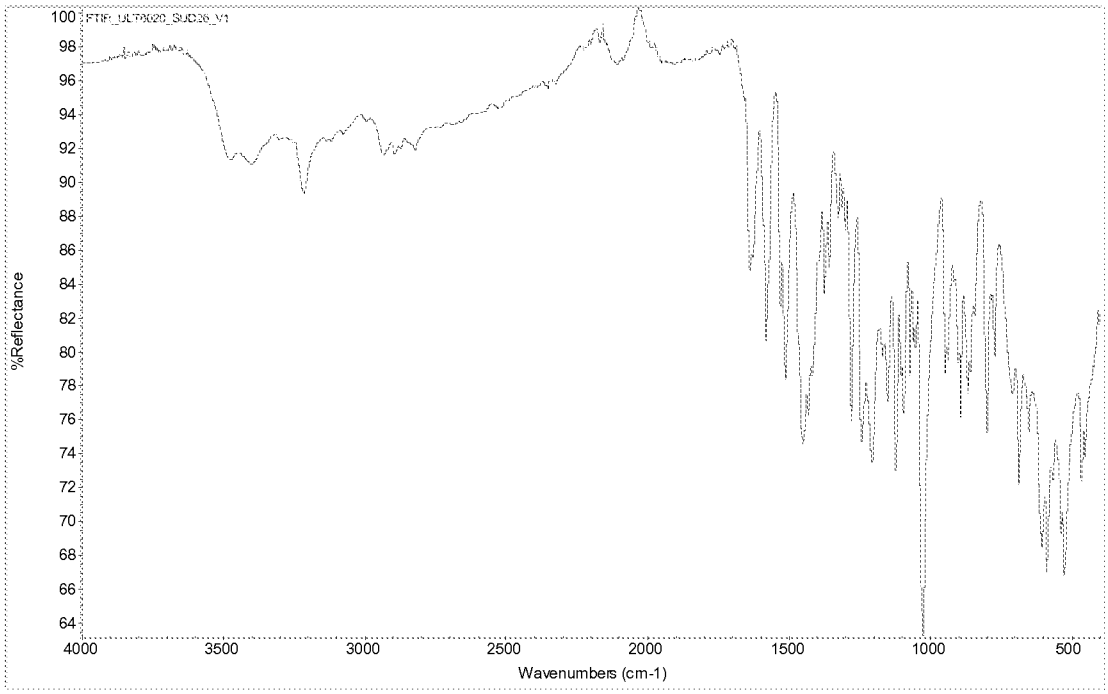


Figure 3F illustrates the FT-IR spectrogram of Erlotinib isethionate ERIS ULT-1

Table 3B Characteristic FT-IR peaks of Erlotinib isethionate ERIS ULT-1

Wavenumber	%reflectance	L>75>M>60>H	Wavenumber	%reflectance	L>75>M>60>H
452.5	73.698	L	1205.4	73.271	M
463.6	72.177	L	1241.6	74.597	M
525.7	66.654	M	1278.4	75.877	L
586.3	66.863	M	1299.2	87.098	L
603.9	68.362	M	1326.4	87.835	L
652.3	75.186	L	1357.6	84.877	L
686.1	72.033	M	1373.9	83.183	L
708	77.42	L	1449.9	74.498	M
772	79.627	L	1510.9	78.208	L
797.9	75.126	L	1530.1	82.502	L
867.5	77.429	L	1580.1	80.535	L
892.5	75.987	L	1638	84.724	L
946.5	78.522	L	2935.5	91.55	L
1024.5	63.153	M	3216	89.257	L
1050.6	80.151	L	3398.7	91.004	L
1071.1	78.356	L			
1094	76.252	L			
1122.5	72.952	M			
1150.7	76.861	L			

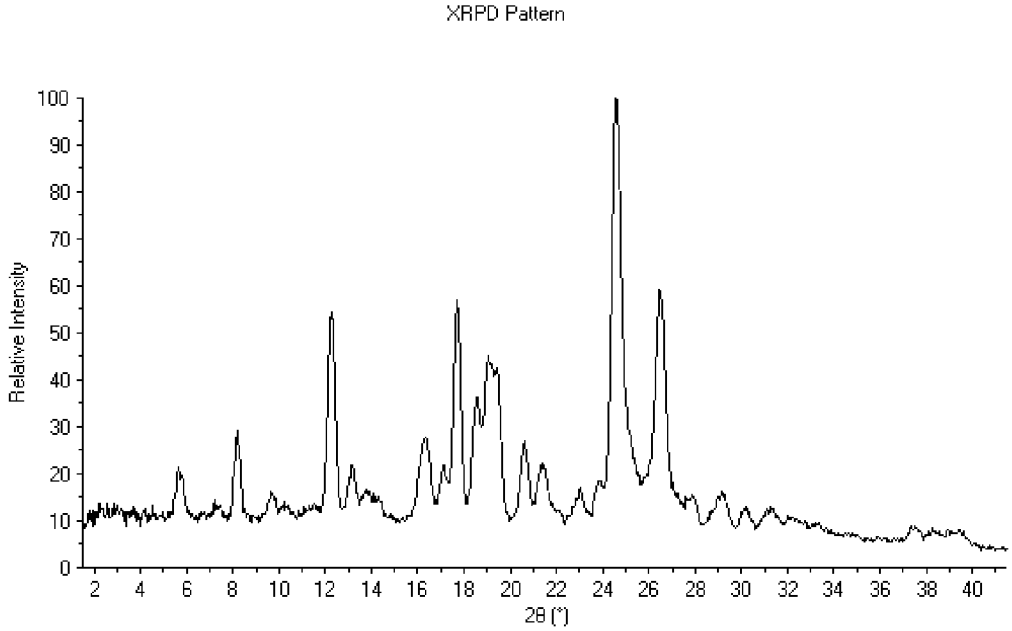
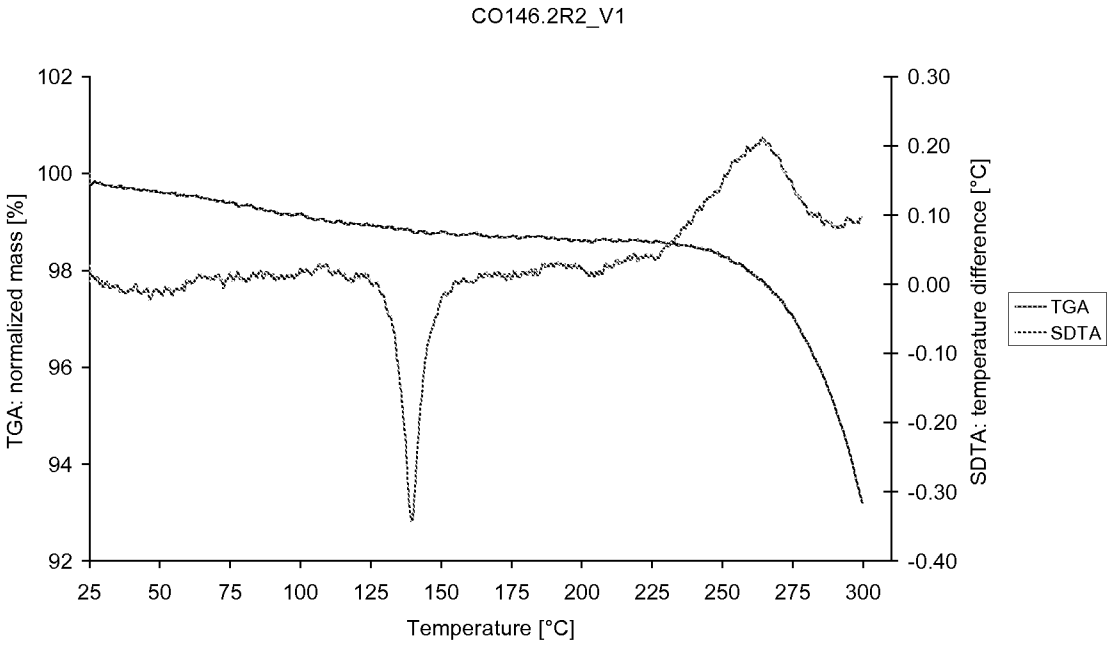
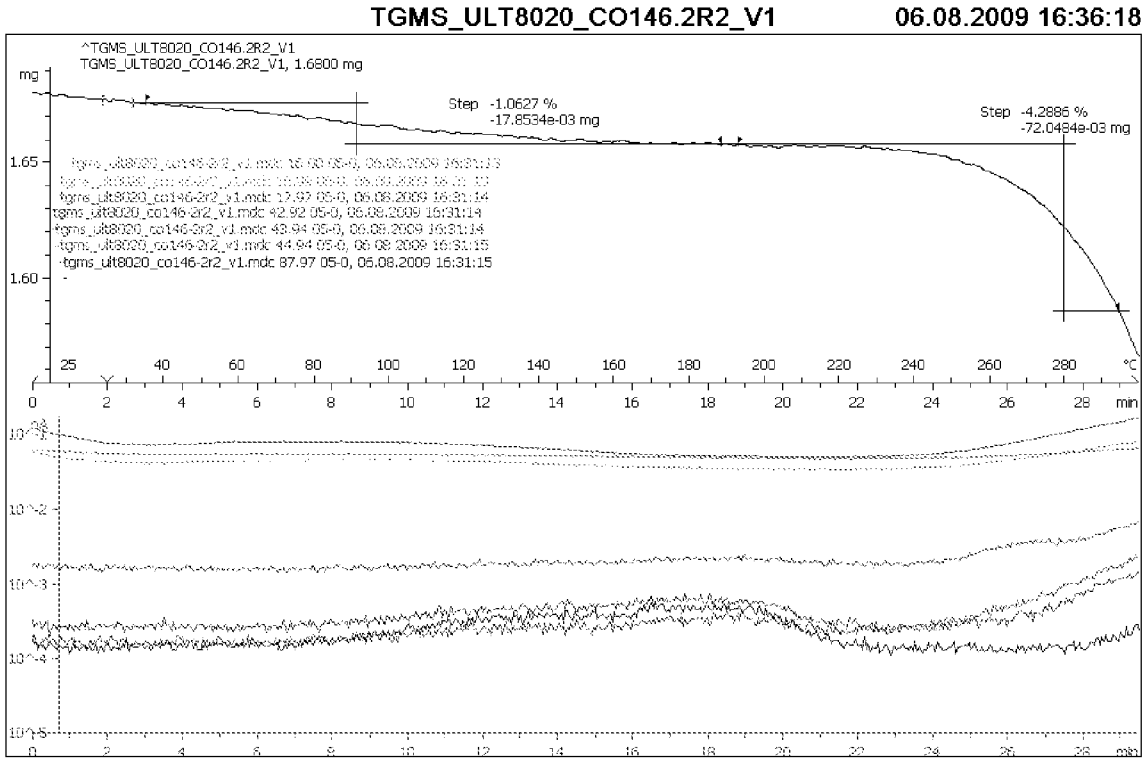


Figure 4A illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-2



CO146.2R2_V1
TGA (10 ºC/min)
Mass loss ~1% for T<180 ºC

Figure 4B illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-2



CO146.2R2_V1
TG-MS (10 ºC/min)
Mass loss ~1% for T<180 ºC
Solvents detected: Water

Figure 4C illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-2

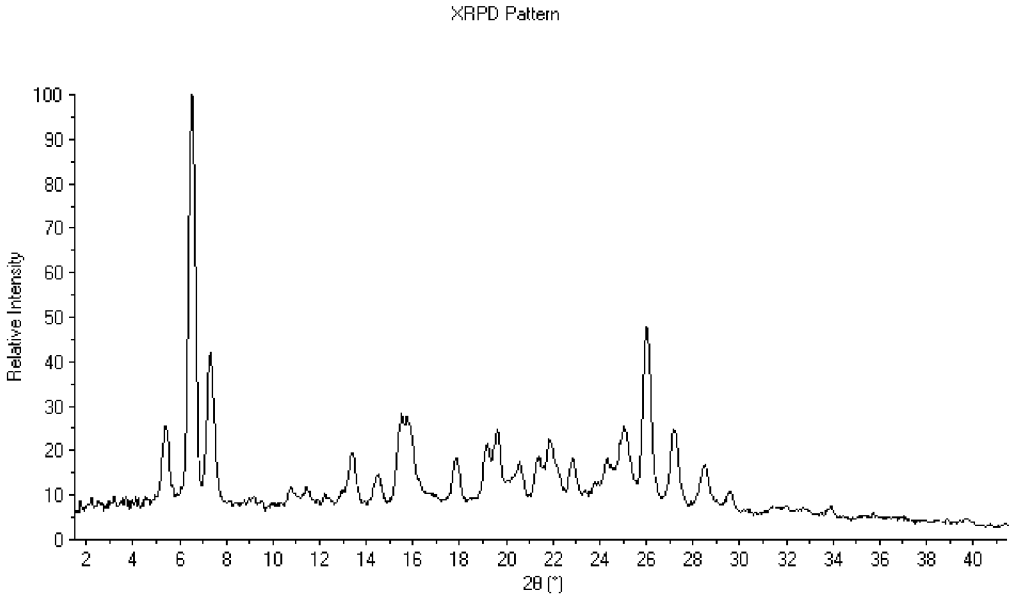
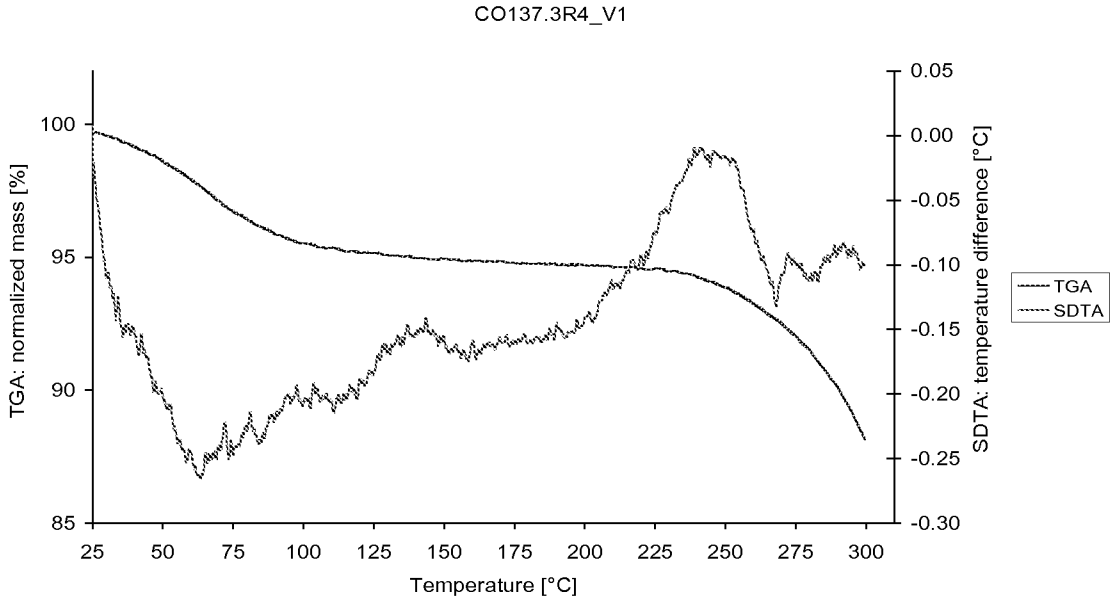
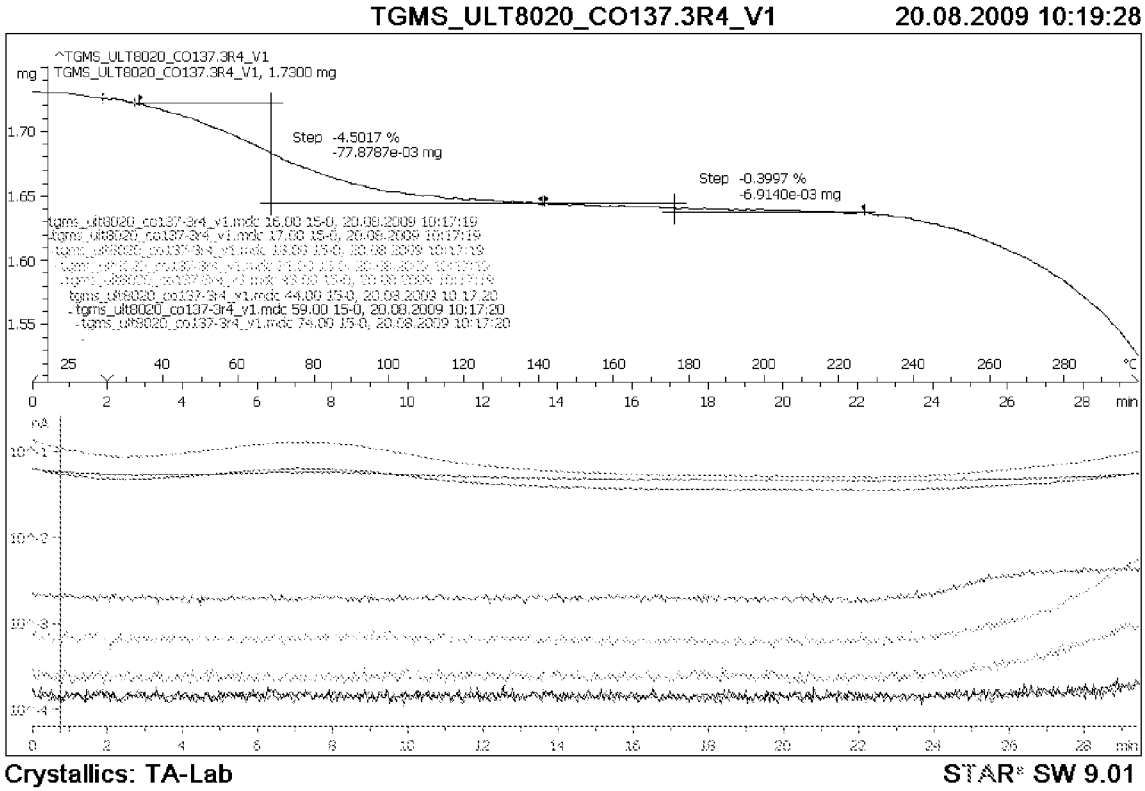


Figure 5A illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-3



CO137.3R4_V1
TGA (10 ºC/min)
Mass loss ~4.5% for T<140 ºC

Figure 5B illustrates the TGA thermogram of Erlotinib isethionate ERIS ULT-3



CO137.3R4
TG-MS (10 ºC/min)
Mass loss ~4.5% for T<140 ºC
Solvents detected: Water

Figure 5C illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib isethionate ERIS ULT-3

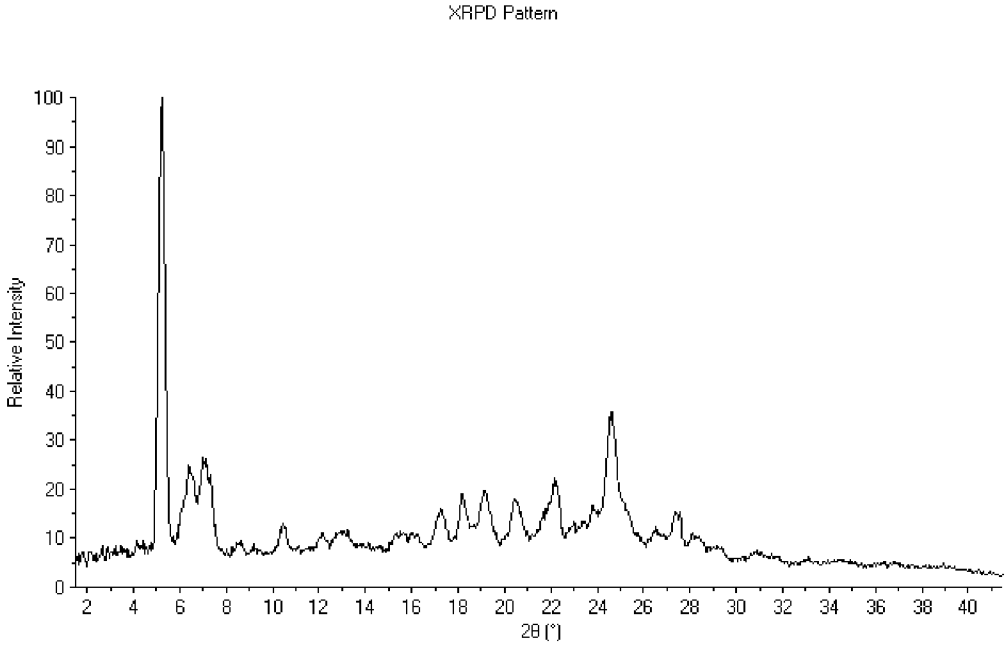


Figure 6 illustrates the X-Ray Powder Diffraction pattern of Erlotinib isethionate ERIS ULT-4

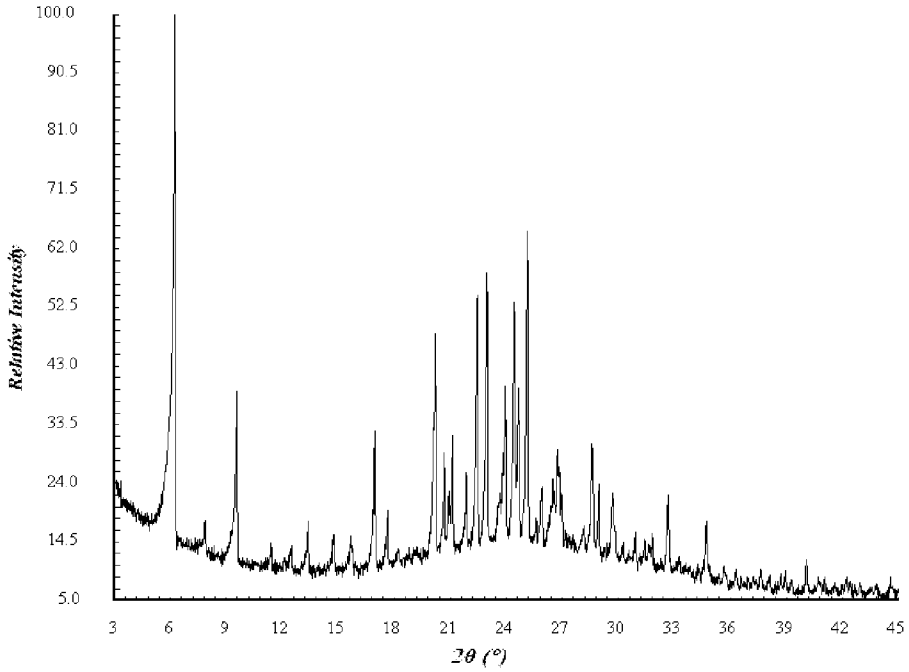
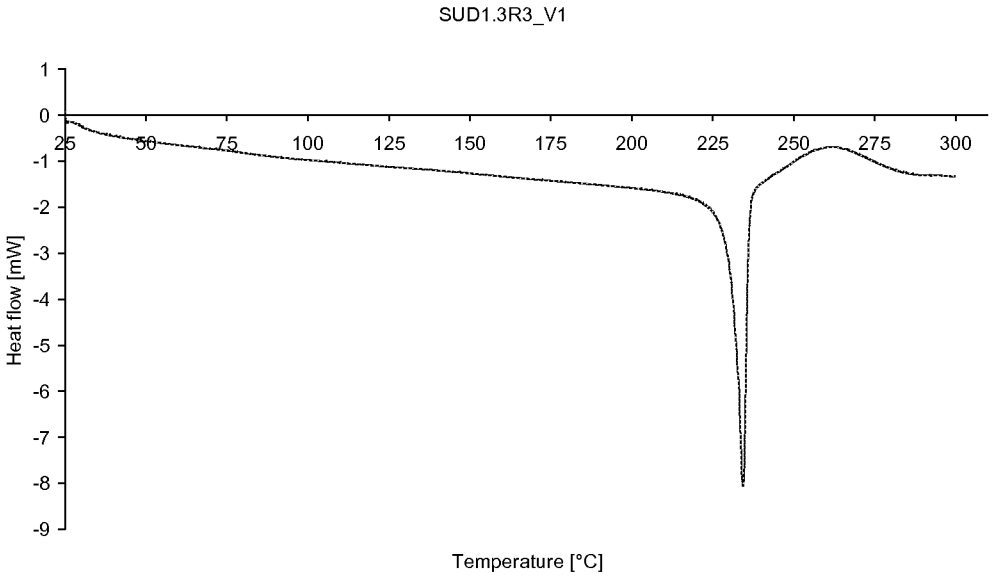
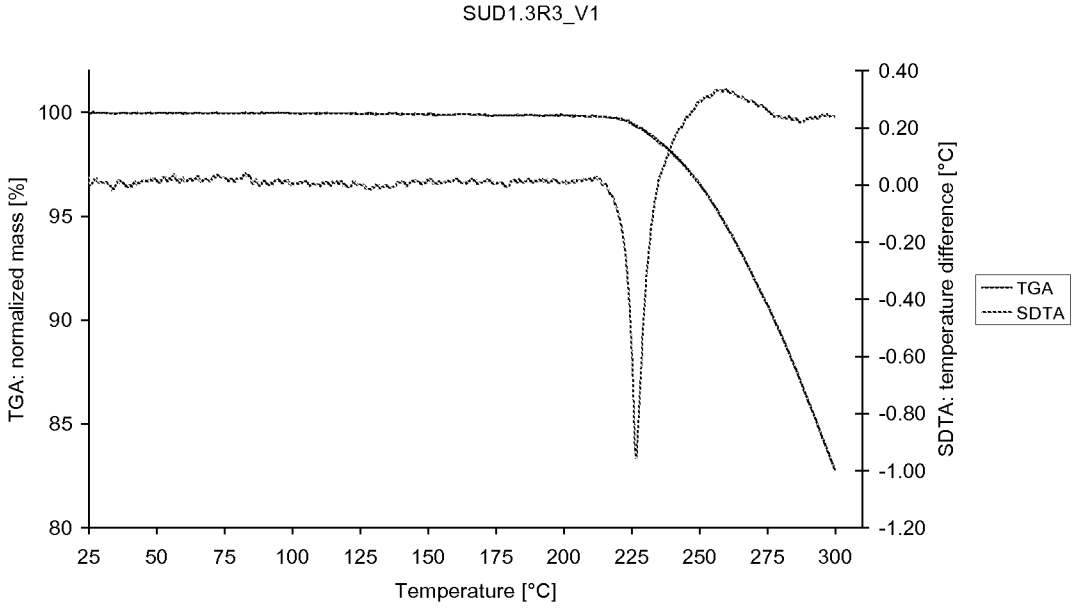


Figure 7A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-1



SUD1.3
DSC (10 ºC/min)
Onset 230.9 °C
Peak: 234.37 °C

Figure 7B illustrates the DSC thermogram of Erlotinib bromide ERBR ULT-1



SUD1.3
TGA (10 ºC/min)
No weight loss for T<150 ºC

Figure 7C illustrates the TGA thermogram of Erlotinib bromide ERBR ULT-1

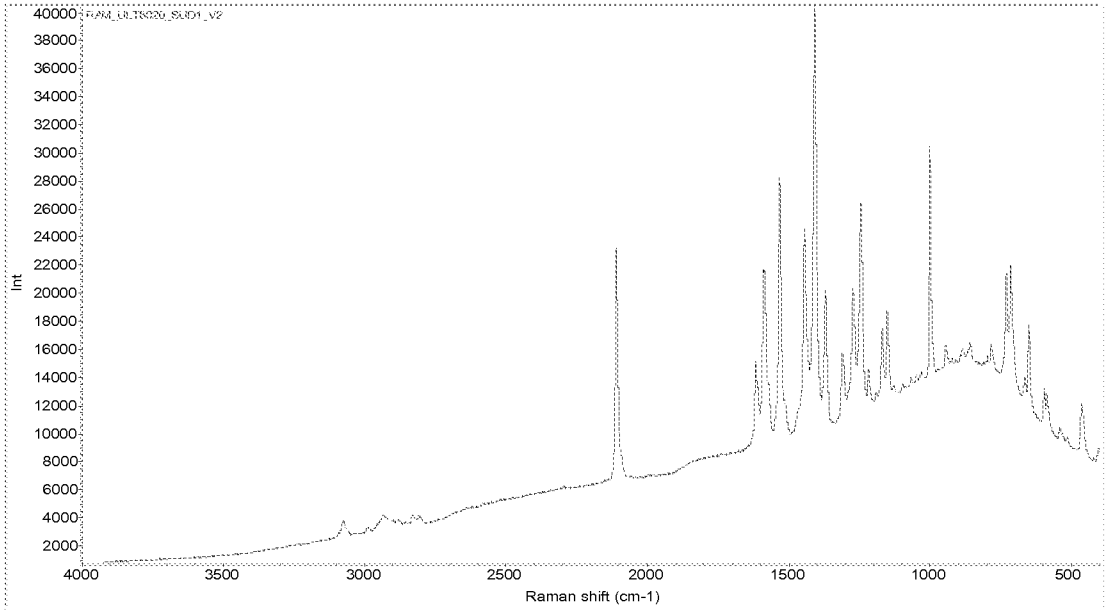


Figure 7D illustrates the Raman spectrogram of Erlotinib bromide ERBR ULT-1

Table 7A Characteristic Raman peaks of Erlotinib bromide ERBR ULT-1

Wavenumber (cm^{-1})	Intensity	H>30000>M>20000>L
192.8	11786.69	L
269	11481.252	L
367.1	10341.108	L
463.6	12010.631	L
596.2	13151.49	L
650.5	17709.32	L
714.1	21894.457	M
729.4	21295.236	M
783.1	16289.318	L
856.9	16356.864	L
999.7	30453.729	H
1150.8	18687.803	L
1169.3	17347.271	L
1217.7	14564.681	L
1244.6	26389.281	M
1272.9	20292.301	M
1309.6	15670.643	L
1370.2	20205.068	M
1408.1	40430.117	H
1444	24533.781	M
1532.3	28141.391	M
1589.4	21686.898	M
1617.8	15057.992	L
2110.9	23073.127	M

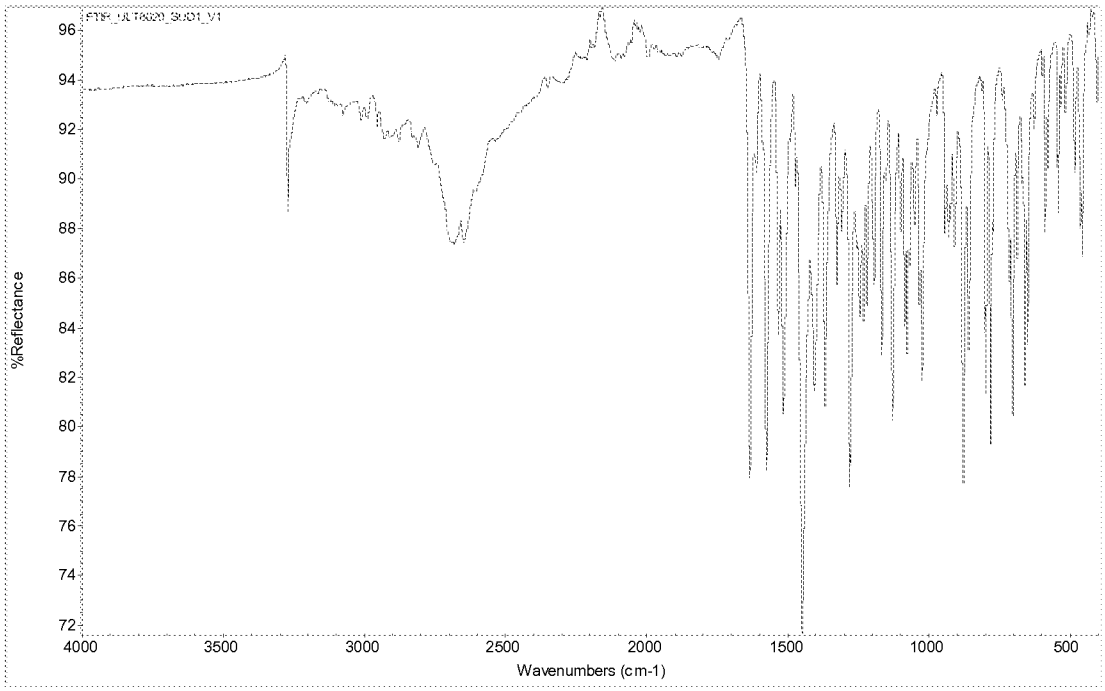


Figure 7E illustrates the FT-IR spectrogram of Erlotinib bromide ERBR ULT-1

Table 7B Characteristic FT-IR peaks of Erlotinib bromide ERBR ULT-1

Wavenumber (cm^{-}	%reflectance	L>85>M>75>H	Wavenumber	%reflectance	H>10000>M>4000>L
455.3	86.812	L	1084.9	83.74	M
462	87.705	L	1099.9	87.743	L
481.5	90.118	L	1127.8	80.136	M
540.1	88.588	L	1166.2	82.724	M
576.9	90.28	L	1193	85.513	L
585.7	87.546	L	1217.8	84.637	M
649.6	83.185	M	1230.5	84.219	M
659.1	81.489	M	1242.9	84.3	M
686.5	86.726	L	1278.3	77.49	M
702.5	80.278	M	1308.4	87.756	L
714.1	85.748	L	1325.2	85.645	L
779.6	79.06	M	1367.6	80.707	M
796.6	81.226	M	1404	81.294	M
858.8	82.946	M	1447	71.541	H
877.4	77.648	M	1471	89.635	L
908.2	87.239	L	1512.9	80.33	M
929.5	87.527	L	1533.1	83.595	M
941.7	87.673	L	1575.2	78.059	M
1021.5	81.684	M	1633	77.828	M
1030.9	84.653	M	2681.4	87.292	L
1048.1	87.984	L	3270.4	88.495	L

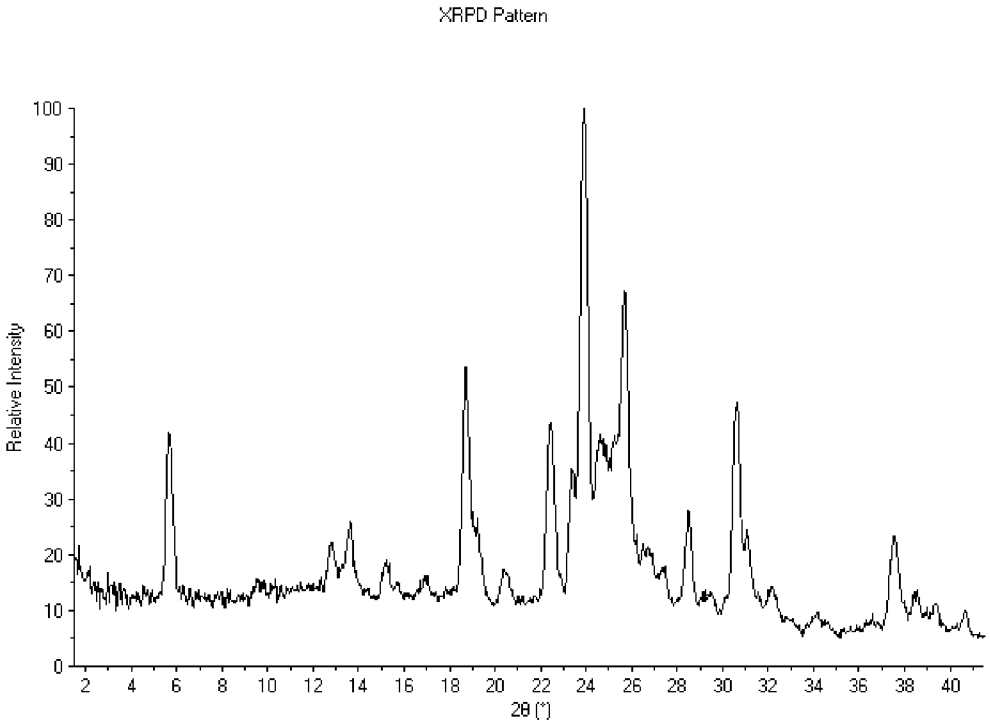


Figure 8 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-2

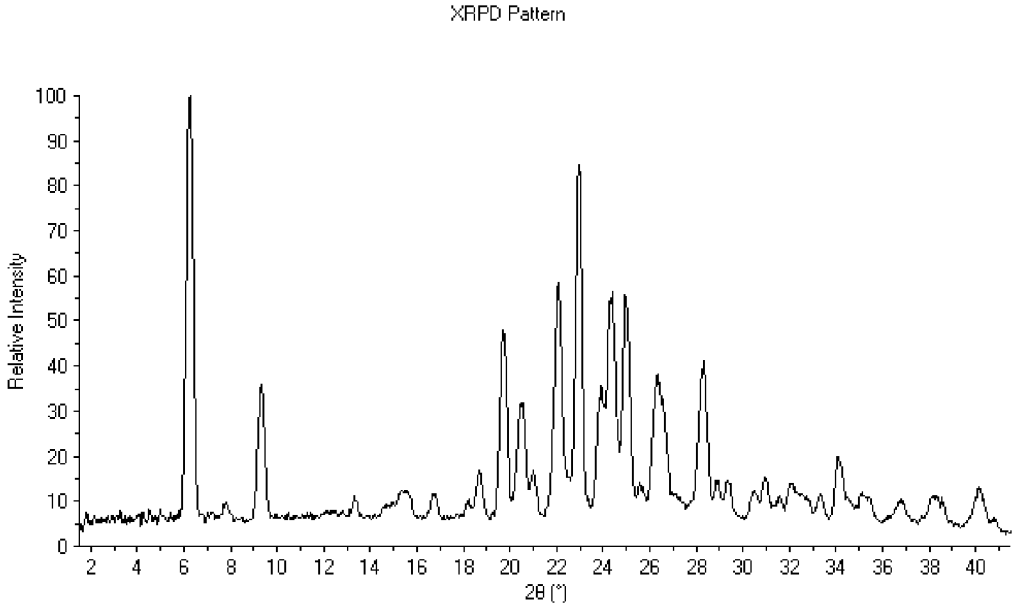
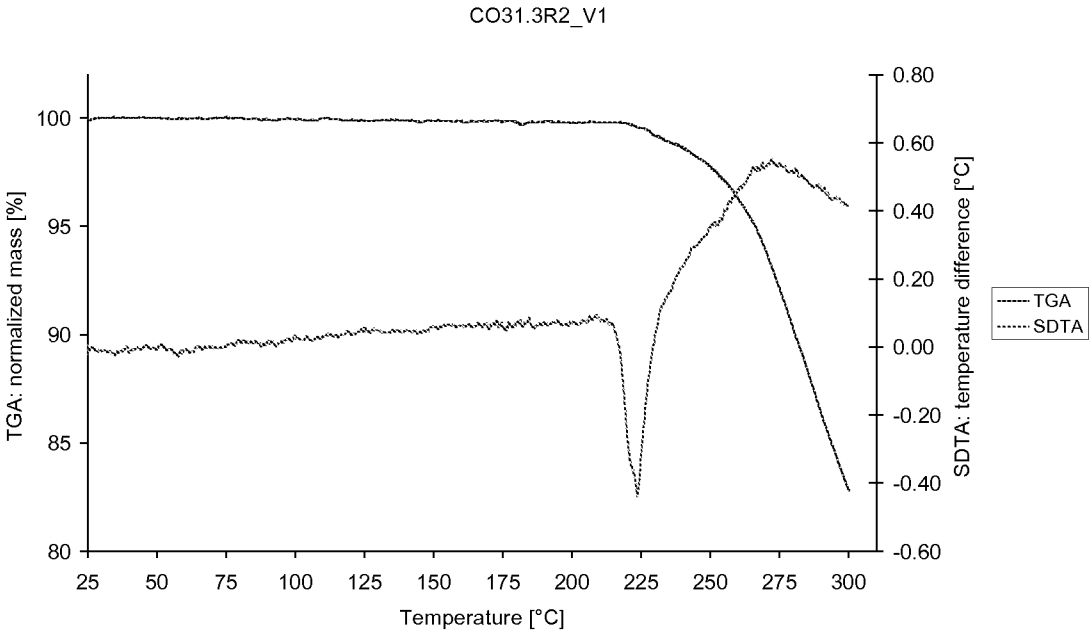


Figure 9A illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-3



CO31.3R2
TGA (10 ºC/min)
No weight loss for T<150 ºC

Figure 9B illustrates the TGA thermogram of Erlotinib bromide ERBR ULT-3

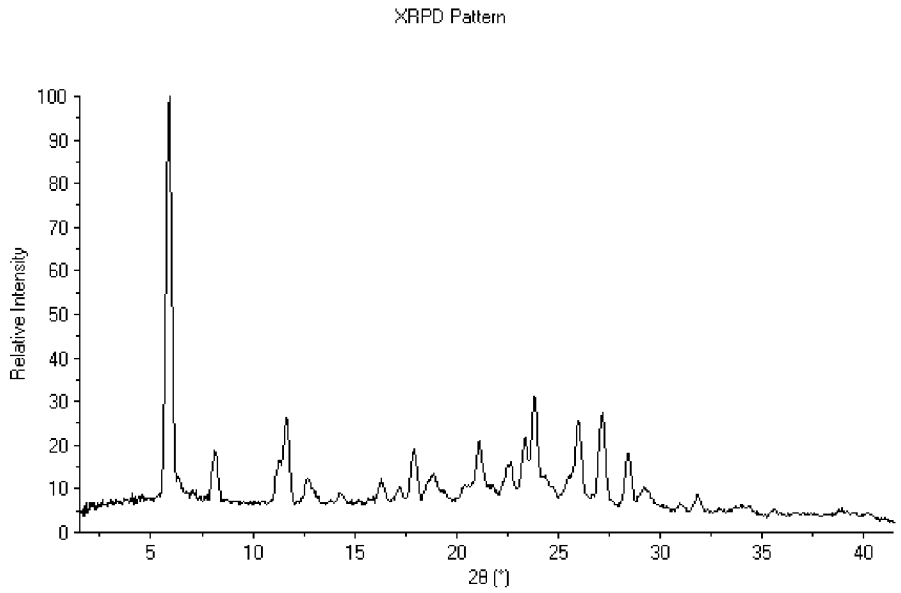


Figure 10 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-4

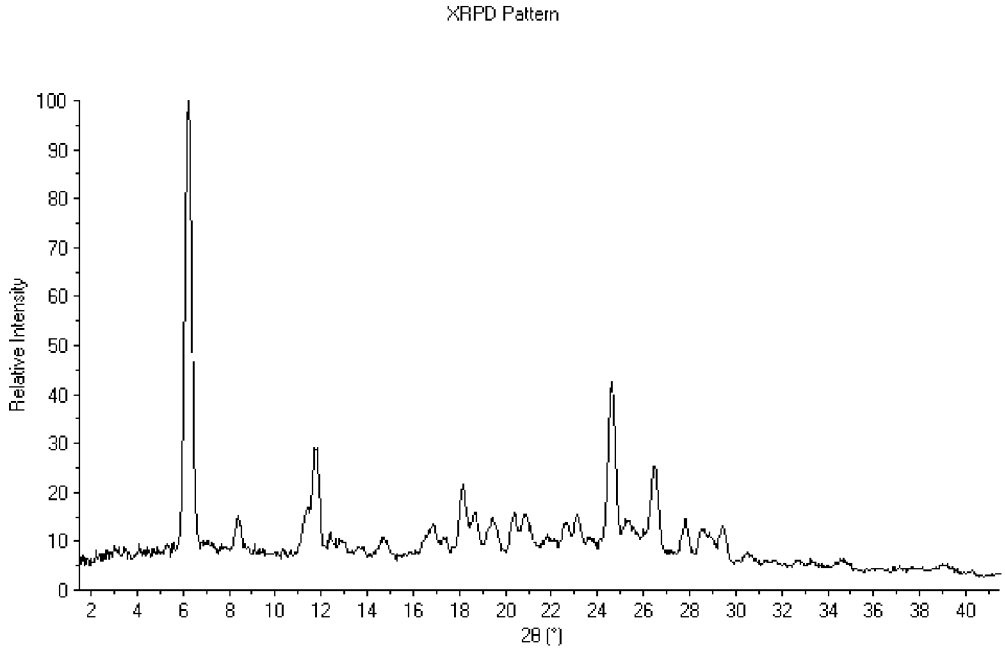


Figure 11 illustrates the X-Ray Powder Diffraction pattern of Erlotinib bromide ERBR ULT-5

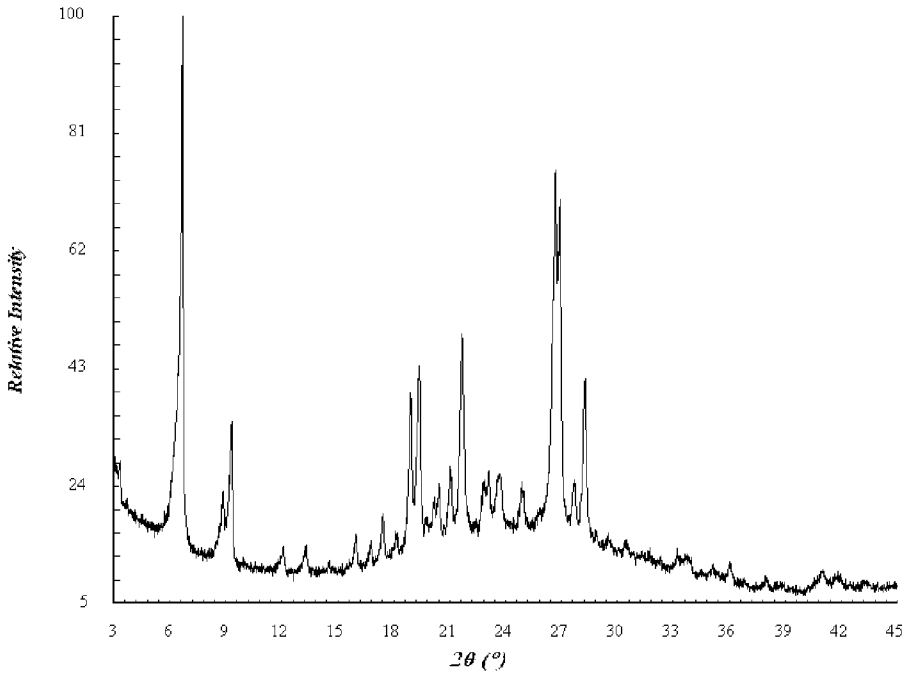
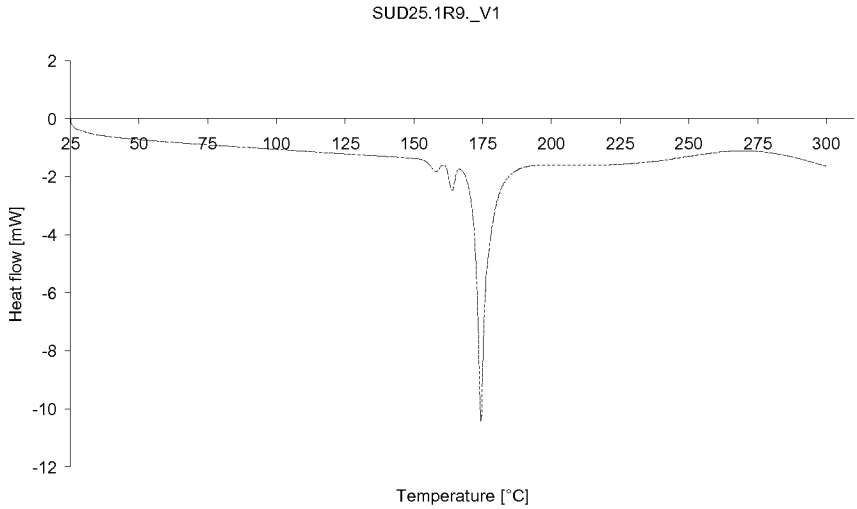
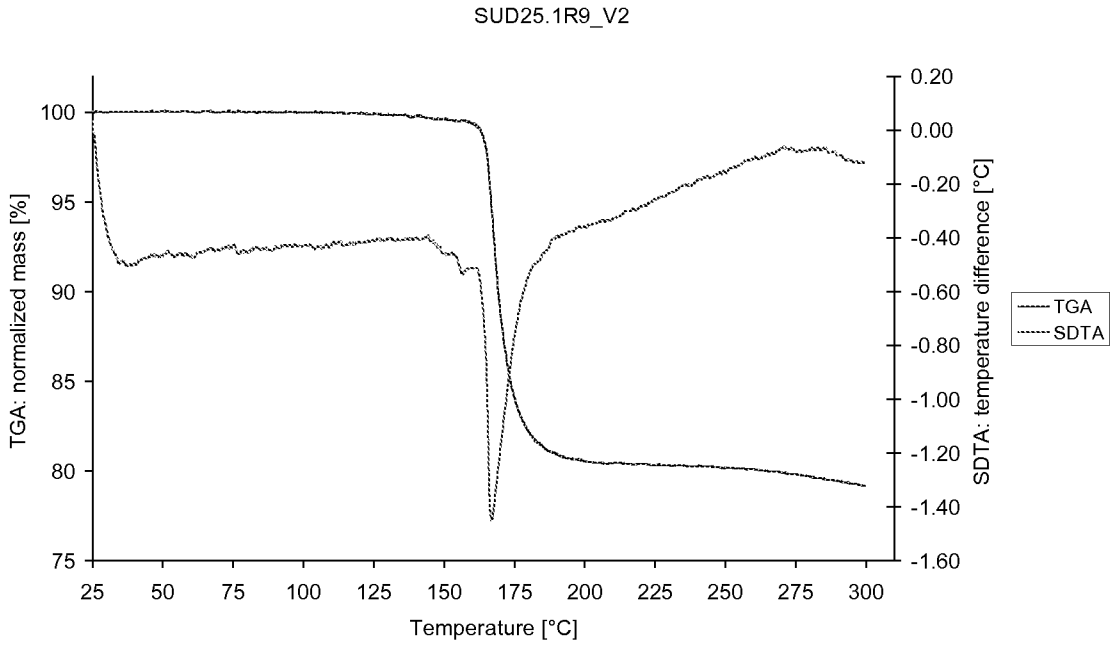


Figure 12A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib malonate ERMO ULT-1



SUD25.1R9_V1
DSC (10 ºC/min)
Onset: 171.89 ºC
Peak: 174.31ºC

Figure 12B illustrates the DSC thermogram of Erlotinib malonate ERMO ULT-1



SUD25.1R7_V1
TGA (10 ºC/min)
Mass loss ~0.5% for T<170 ºC

Figure 12C illustrates the TGA thermogram of Erlotinib malonate ERMO ULT-1

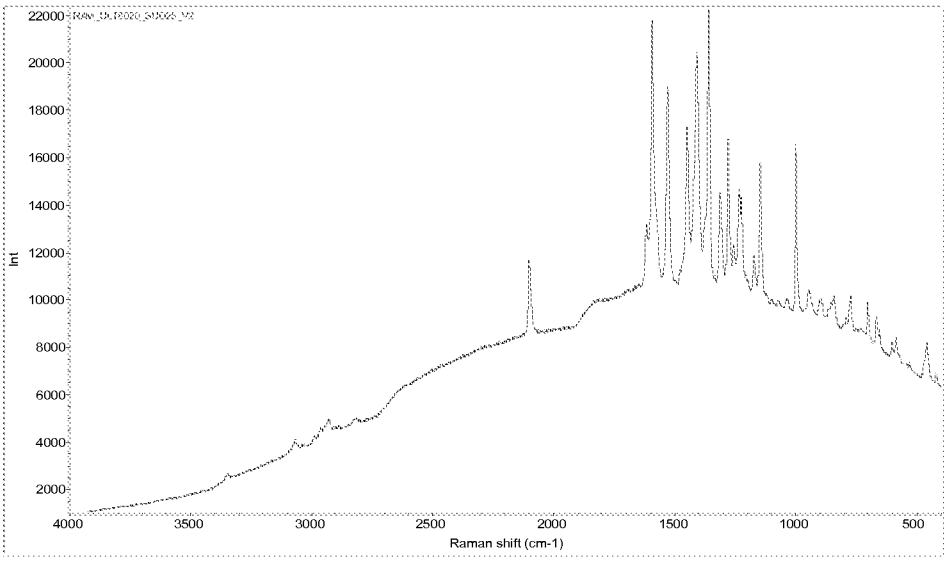


Figure 12D illustrates the Raman spectrogram of Erlotinib malonate ERMO ULT-1
Table 12A. Characteristic Raman peaks of Erlotinib malonate ERMO ULT-1

Wavenumber (cm^{-1})	Intensity	H>20000>M>10000>L
458.9	8147.705	L
586.3	8354.759	L
666.6	9312.834	L
702.3	9859.756	L
773	10100.338	M
842.1	10111.687	M
945.4	10412.782	M
999.6	16496.973	M
1146.7	15723.957	M
1172.7	11825.752	M
1234.5	14594.386	M
1257.4	12322.608	M
1278.9	16747.904	M
1312.3	14478.837	M
1360.9	22315.775	H
1408.5	20408.787	H
1449.1	17271.182	M
1529.2	19022.09	M
1592.9	21731.154	H
2102	11702.666	M

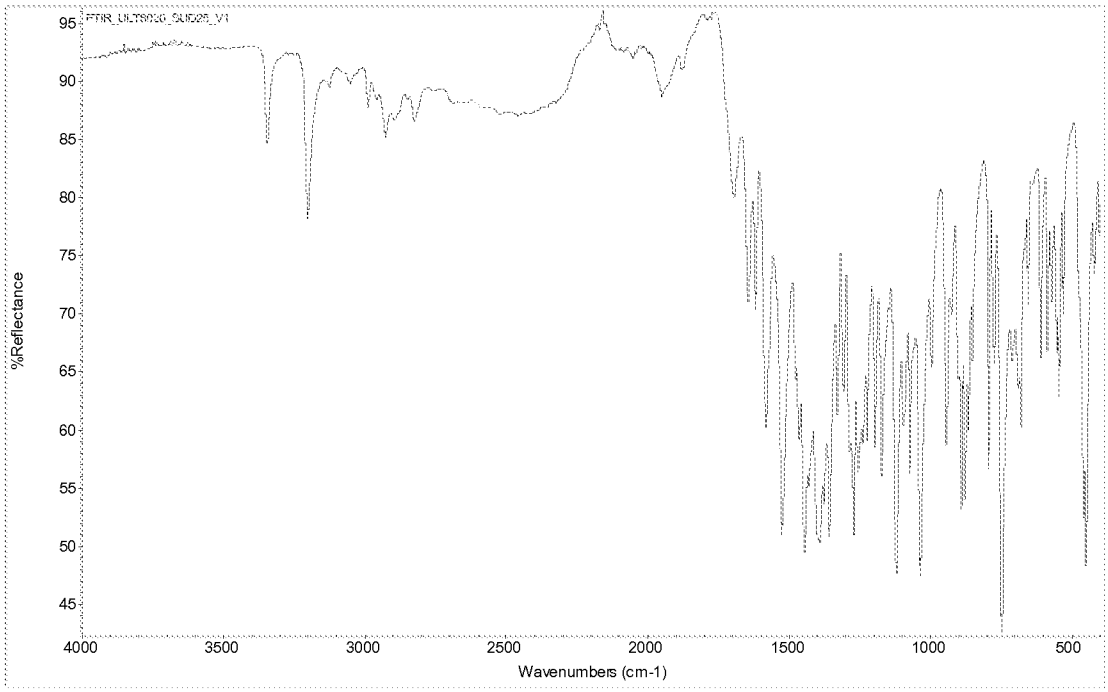


Figure 12E illustrates the FT-IR spectrogram of Erlotinib malonate ERMO ULT-1

Table 12B. Characteristic FT-IR peaks of Erlotinib malonate ERMO ULT-1

Wavenumber	%reflectance	L>70>M>60>H	Wavenumber	%reflectance	L>70>M>60>H
401.1	76.588	L	1195.1	58.209	H
420.2	73.176	L	1222.4	58.923	H
448.4	47.688	H	1254.6	56.031	H
457.2	52.312	H	1269.6	50.589	H
528.6	69.847	M	1306.9	63.094	M
543.7	62.643	M	1329.1	61.199	M
569.6	70.716	L	1357.9	50.544	H
584.4	66.598	M	1391.5	50.04	H
608.2	65.817	M	1444.9	49.307	H
653.8	70.505	L	1462.7	58.936	H
679.4	59.852	H	1524.6	50.589	H
710.2	65.762	M	1580.4	59.916	H
746.4	42.299	H	1617.8	70.268	L
773.4	65.603	M	1644.1	70.694	L
792.1	56.036	H	1692.5	79.841	L
849.9	65.685	M	2458.1	86.906	L
864.7	59.537	H	2825.3	86.515	L
876.6	53.369	H	2927.8	85.095	L
890.2	52.674	H	3202.6	78.012	L
942.4	58.409	H	3346.4	84.451	L
994.7	65.204	M			
1033.9	46.998	H			
1071.6	55.882	H			
1096.2	60.184	M			
1119.6	47.188	H			
1171.1	55.663	H			

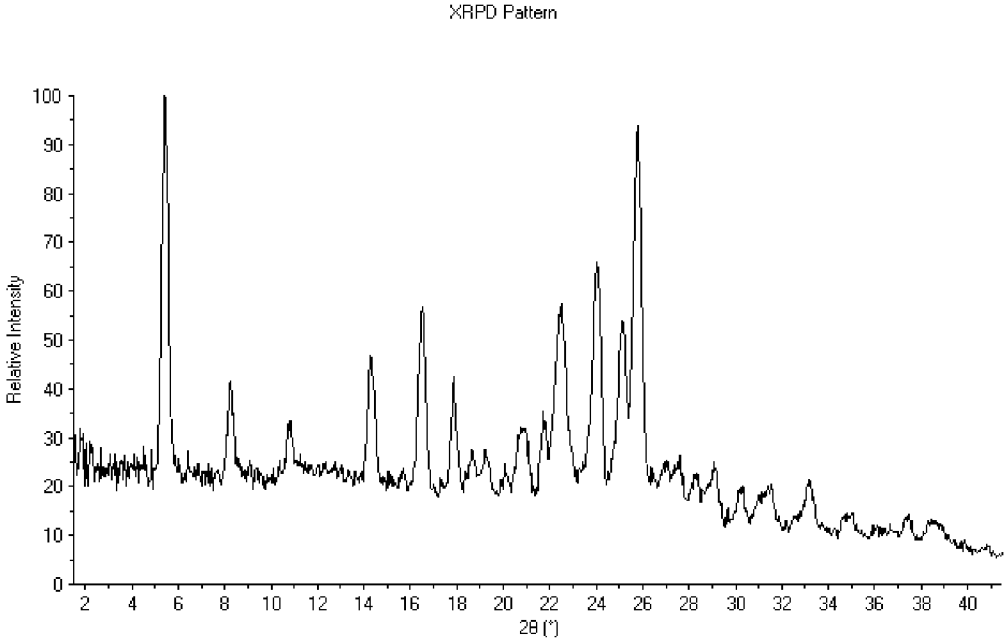


Figure 13 illustrates the X-Ray Powder Diffraction pattern of Erlotinib malonate ERMO ULT-2

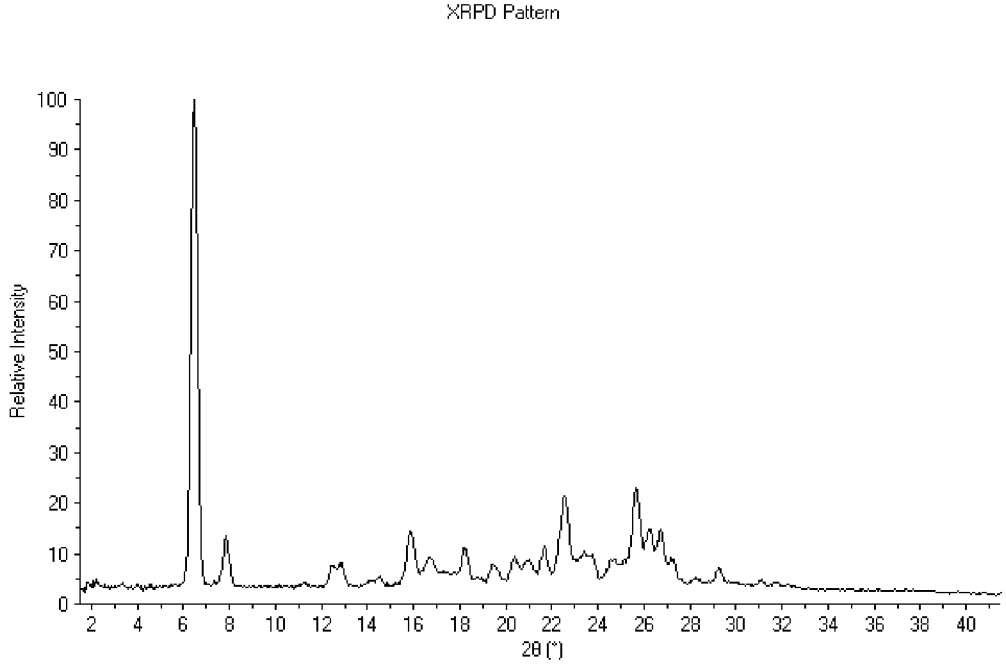


Figure 14 illustrates the X-Ray Powder Diffraction pattern of Erlotinib L-lactate ERLA ULT-1

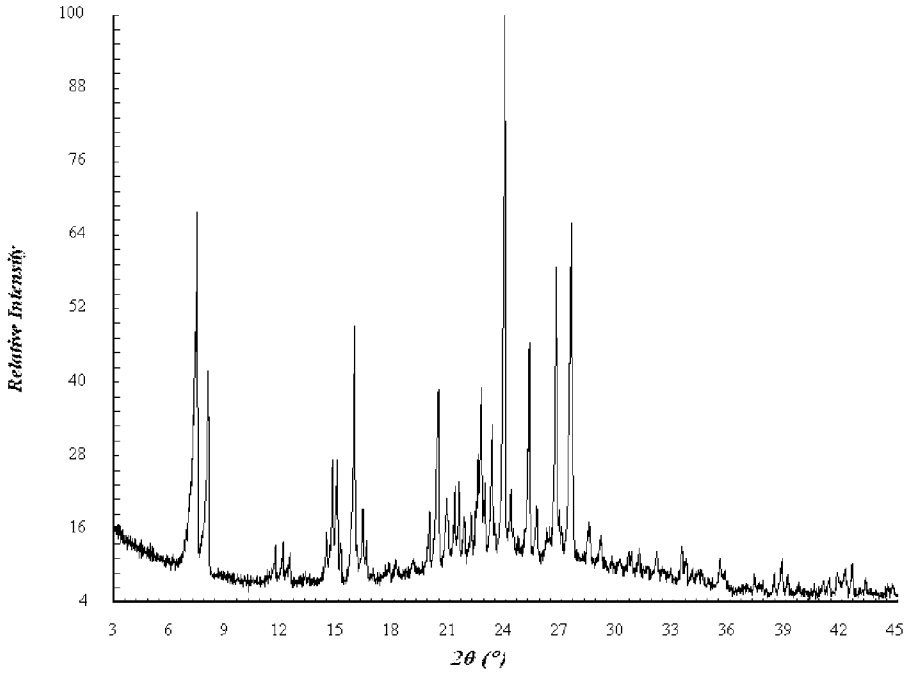
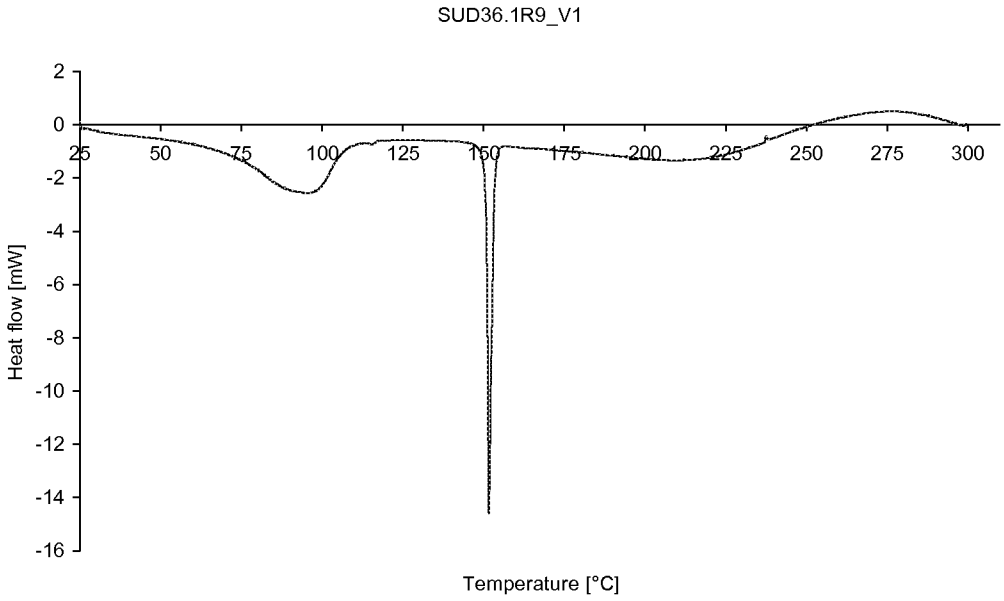
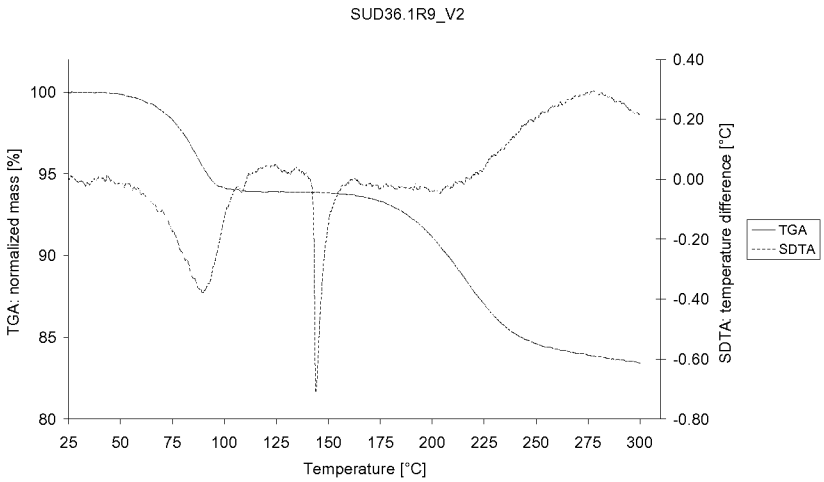


Figure 15A illustrates the high resolution X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-1



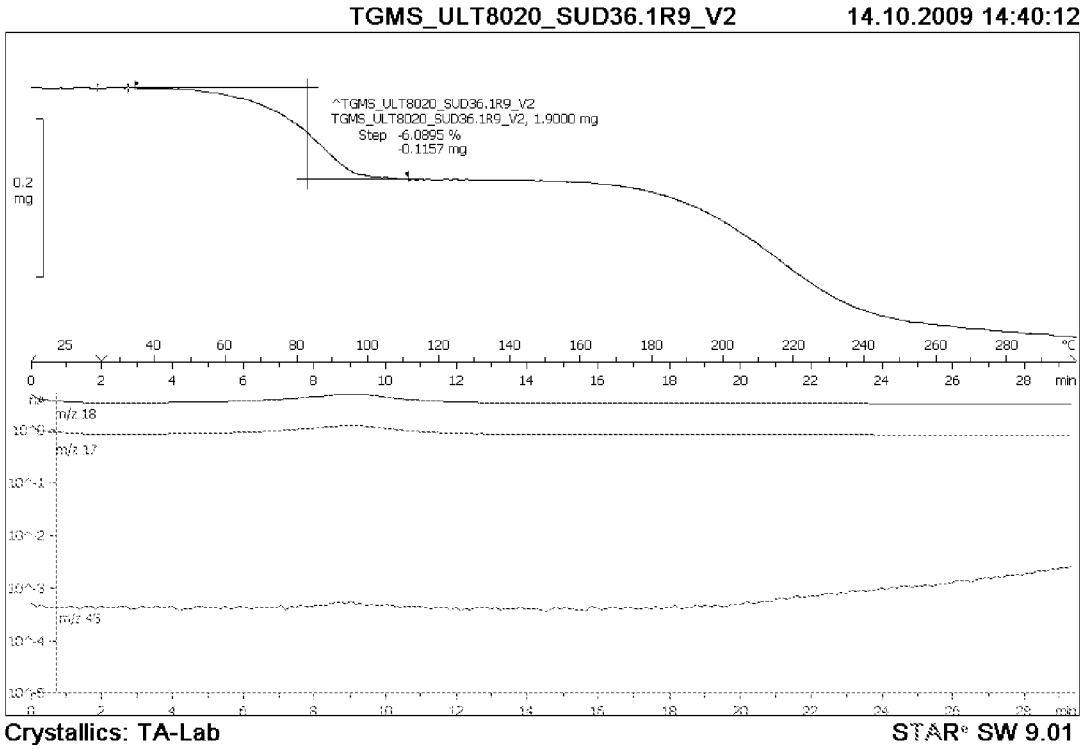
SUD36.1R9_V1
DSC (10 ºC/min)
Onset: 150.69 ºC
peak: 151.62ºC

Figure 15B illustrates the DSC thermogram of Erlotinib succinate ERSC ULT-1



SUD36.1R9_V1
TGA (10 ºC/min)
Mass loss ~6.08% for T<150 ºC

Figure 15C illustrates the TGA thermogram of Erlotinib succinate ERSC ULT-1



SUD36.1R9_V1
TGA (10 ºC/min)
Mass loss ~6.08% for T<150 ºC
Solvents detected: Water

Figure 15D illustrates the TGA thermogram (top) and MS spectrum (bottom) of Erlotinib succinate ERSC ULT-1

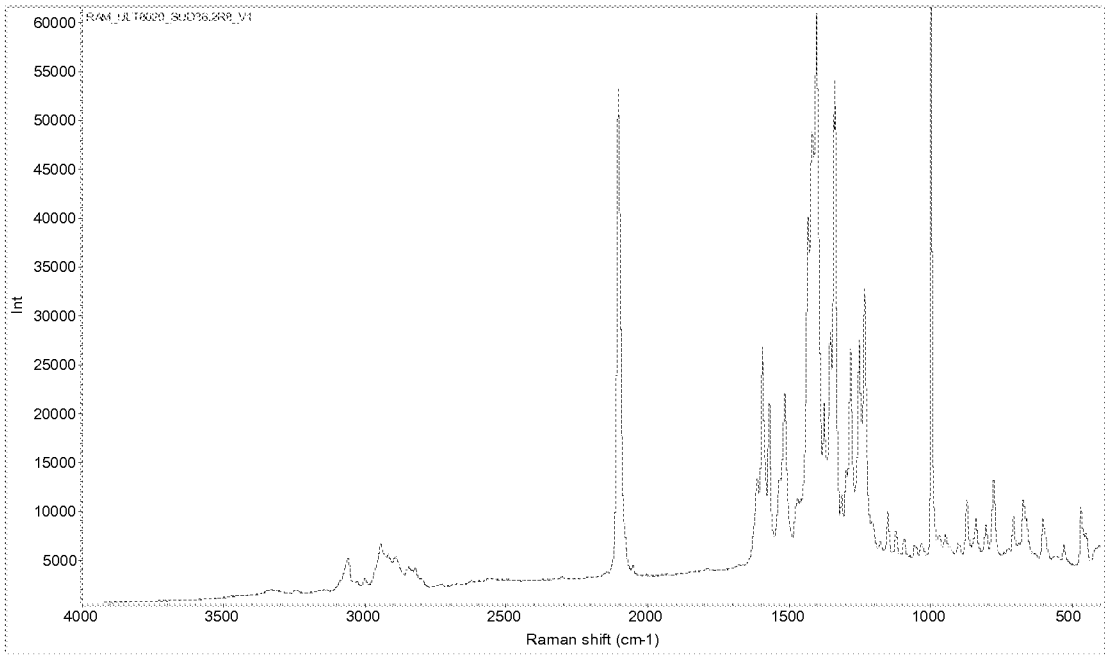


Figure 15D illustrates the Raman spectrogram of Erlotinib succinate ERSC ULT-1

Table 15A. Characteristic Raman peaks of Erlotinib succinate ERSC ULT-1

Wavenumber (cm^{-1})	Intensity	H>30000>M>20000>L
468.1	10232.676	L
602	9226.509	L
671.1	10988.576	L
707.3	9261.651	L
777.1	13005.018	L
803.8	8400.065	L
839.5	9235.695	L
871.8	10897.597	L
997.9	61634.344	H
1122.7	7798.456	L
1151.4	9932.27	L
1233.5	32581.459	H
1252.9	27379.826	M
1283.3	26465.463	M
1315	11609.112	L
1339.3	54142.121	H
1355.1	28140.057	M
1376.3	20919.793	M
1402.9	60889.281	H
1420.3	48647.059	H
1433.2	39934.93	H
1515.7	21822.254	M
1571.2	21103.1	M
1595.7	26675.984	M
2105.6	53220.914	H
2945.5	6512.958	L
3061.4	4957.257	L

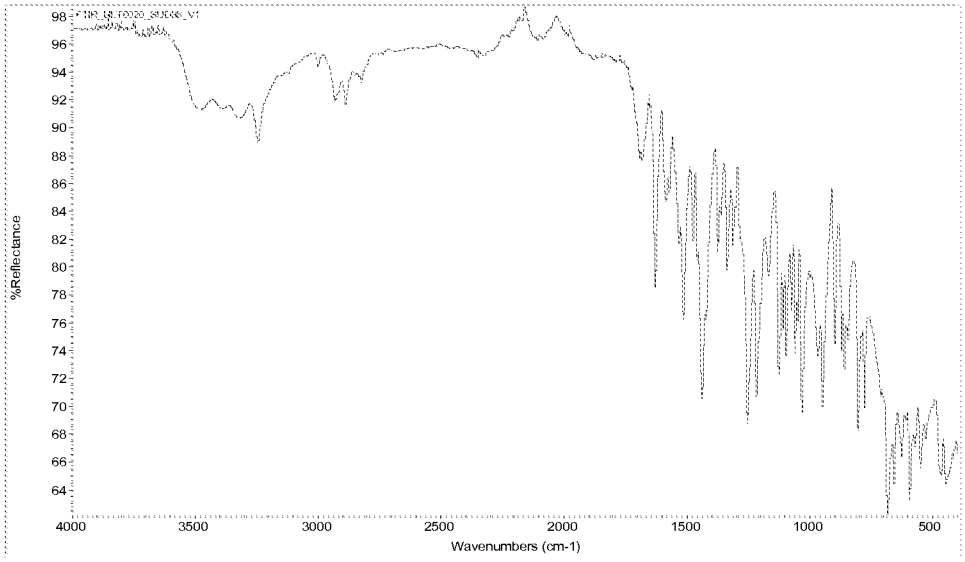


Figure 15E illustrates the FT-IR spectrogram of Erlotinib succinate ERSC ULT-1

Table 15B: Characteristic FT-IR peaks of Erlotinib succinate ERSC ULT-1

Wavenumber (cm	%reflectance	L>70>M>60>H	Wavenumber	%reflectance	L>70>M>60>H
445.3	64.297	M	1216.2	70.418	L
463.3	64.935	M	1251.5	68.639	M
547.4	65.461	M	1312.5	81.341	L
590.3	63.071	M	1335	79.682	L
623.6	66.098	M	1372.9	80.935	L
656.7	64.122	M	1435.6	70.346	L
683	62.076	M	1472.1	81.758	L
775.9	69.688	M	1511.8	76.123	L
800.9	68.084	M	1583.9	84.603	L
859.2	72.23	L	1626.6	78.287	L
869.2	73.821	L	1680.3	87.551	L
895.3	74.137	L	2889.6	91.618	L
947.4	69.805	M	2930.8	91.806	L
965.9	73.484	L	3244.2	88.872	L
1028.8	69.317	M			
1048.1	75.761	L			
1057.1	73.668	L			
1072.6	76.693	L			
1094.5	73.25	L			
1107.2	75.391	L			
1124	72.004	L			
1166.1	79.265	L			

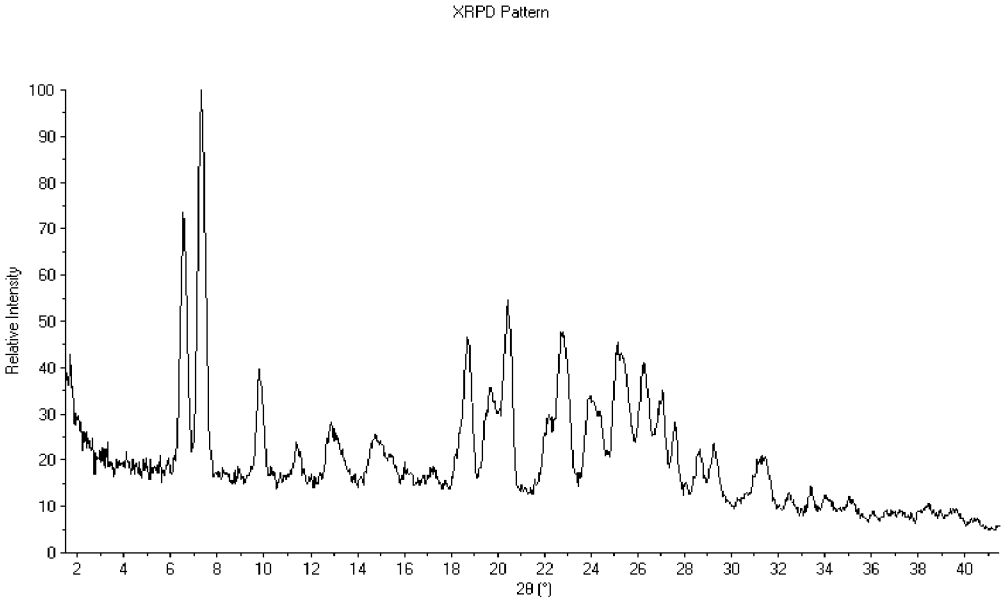


Figure 16 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-2

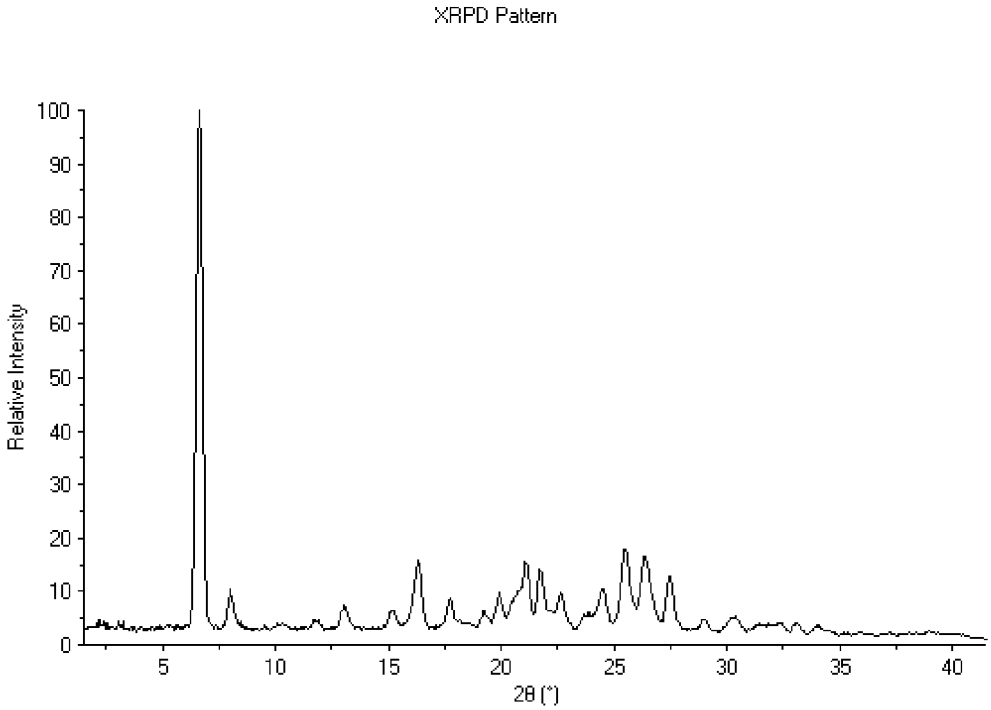


Figure 17 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-3

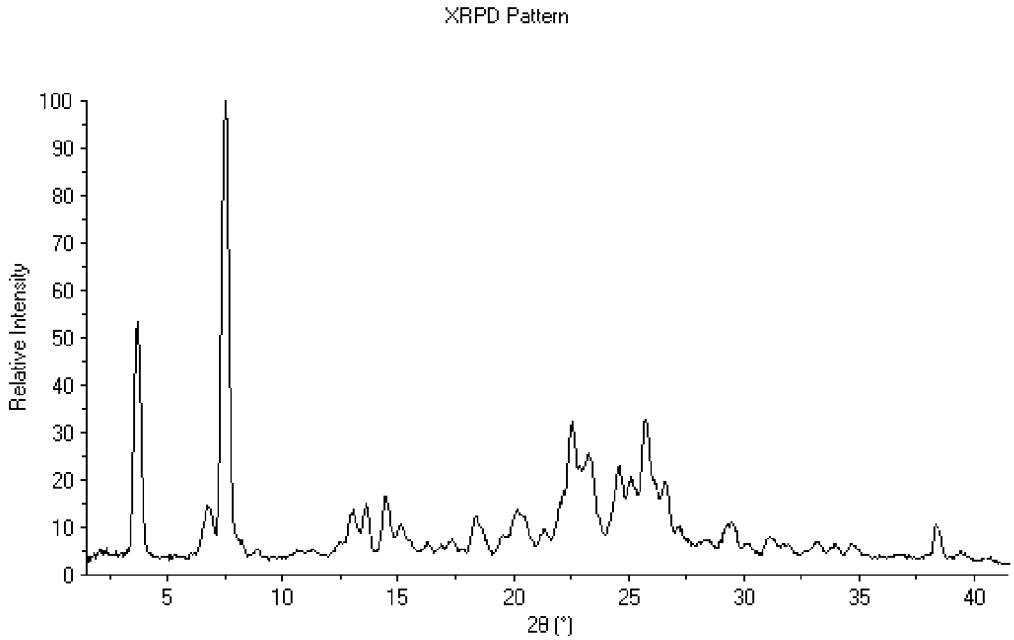


Figure 18 illustrates the X-Ray Powder Diffraction pattern of Erlotinib succinate ERSC ULT-4

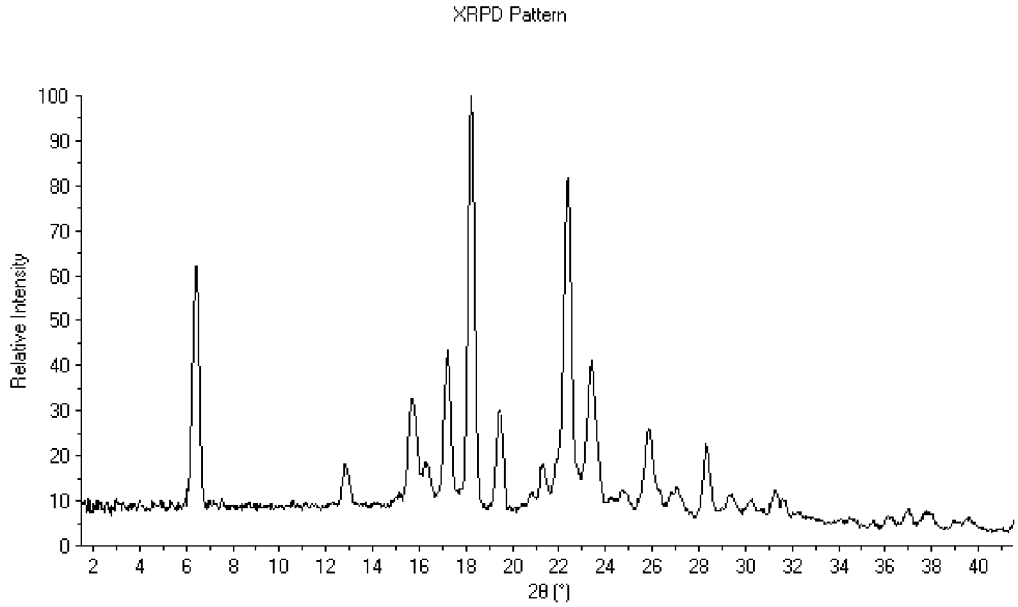
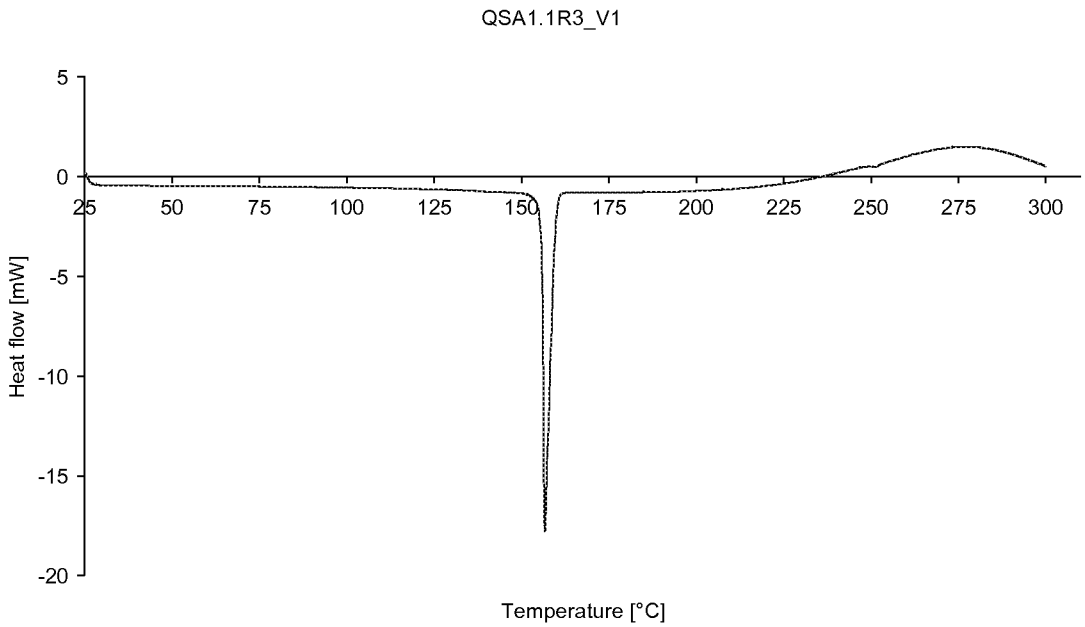
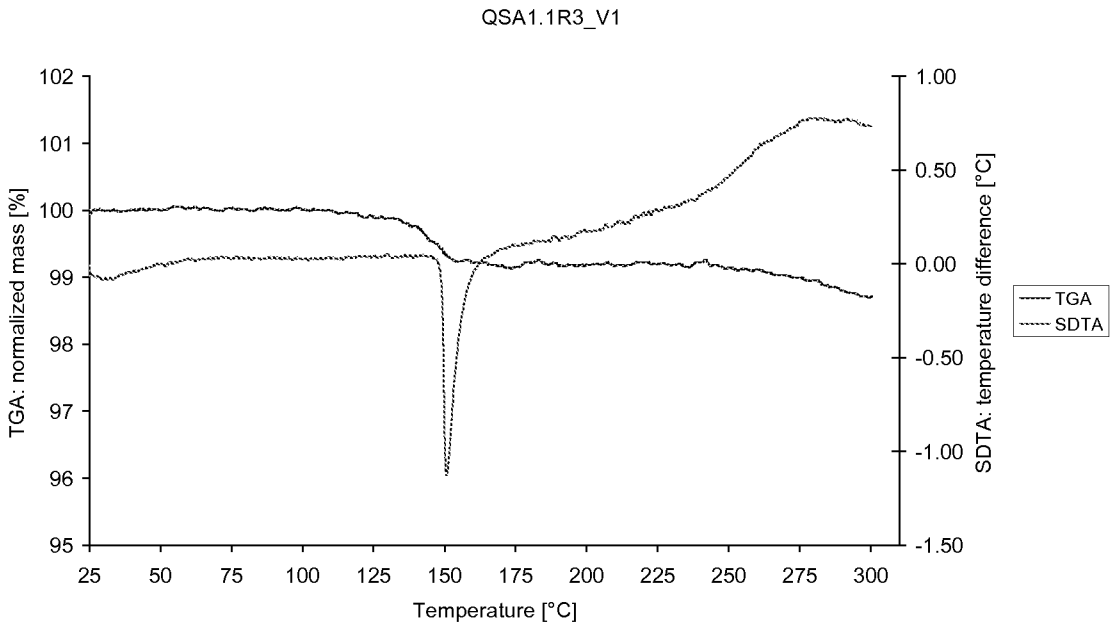


Figure 19A illustrates the X-Ray Powder Diffraction pattern of Erlotinib free base



QSA1.1R3_V1
DSC (10 °C/min)
Onset: 155.72 °C
Peak: 156.82 °C

Figure 19B illustrates the DSC thermogram of Erlotinib free base



QSA1.1R3_V1

TGA (10 ºC/min)
Mass loss ~0.86% for T<175 ºC

Figure 19C illustrates the TGA thermogram of Erlotinib free base

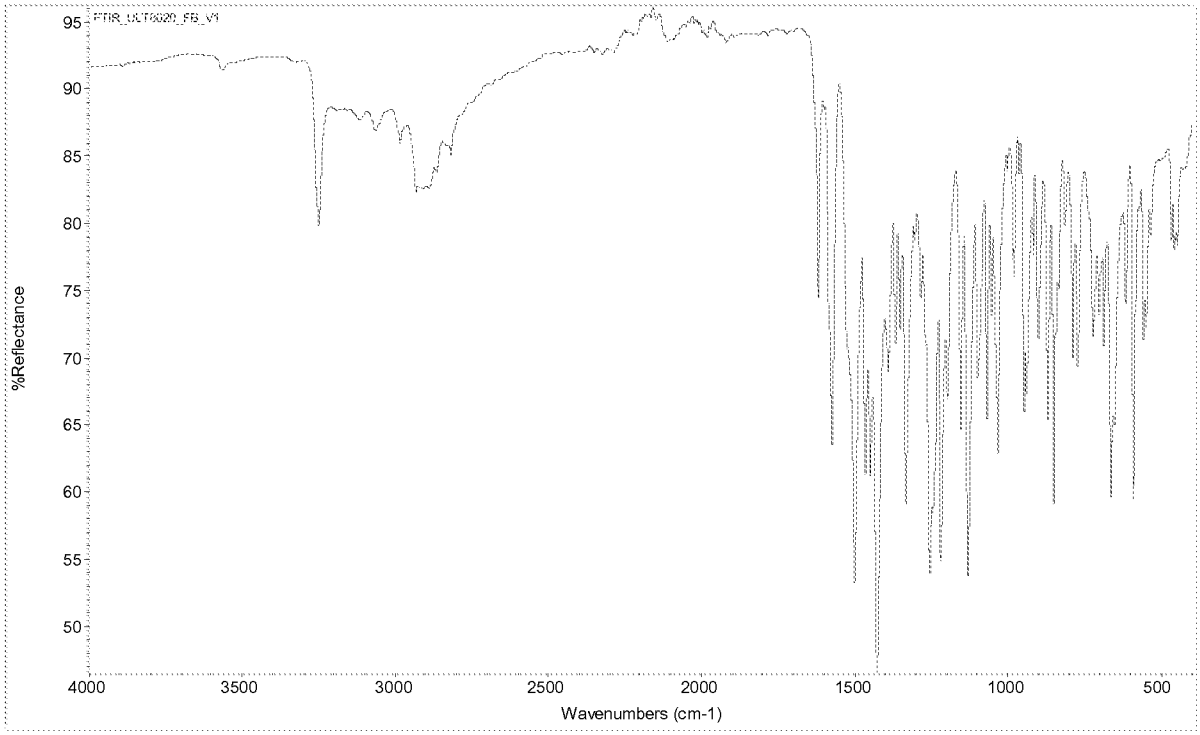


Figure 19D illustrates the FT-IR spectrogram of Erlotinib free base

Table 19A Characterirstic FT-IR peaks of Erlotinib free base

Wavenumber (cm^{-1})	%reflectance	L>75>M>60>H	Wavenumber (cm^{-1})	%reflectance	L>75>M>60>H
455.8	77.776	L	1051.4	72.936	M
466	78.37	L	1067.2	64.968	M
533	78.857	L	1098.5	68.206	M
547.8	72.18	M	1129.7	53.531	H
556.5	70.714	M	1153.8	64.356	M
589.5	58.87	H	1197.2	66.816	M
613.8	73.759	M	1217.3	54.678	H
663.6	59.492	H	1254.6	53.473	H
685.7	70.372	M	1283.1	74.24	M
702.8	72.944	M	1332.8	58.989	H
720.9	71.452	M	1352.5	71.845	M
770.5	68.989	M	1366.4	70.8	M
787	69.873	M	1390	68.819	M
812.6	79.624	L	1427	46.466	H
850.4	58.997	H	1447.6	60.889	M
870.3	65.029	M	1464	61.154	M
900.7	71.288	M	1498.7	53.079	H
917.6	77.467	L	1574.1	63.363	M
938.2	66.882	M	1618.3	74.265	M
947.2	65.793	M	2932.5	82.131	L
962.4	83.625	L	3249.1	79.692	L
979.9	75.845	L			
1032	62.672	M			