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Determination of Lapatinib in Bulk and Tablet Dosage Form using Ultraviolet Spectrophotometric and RP-HPLC Analytical Methods

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ABSTRACT

Objectives: The present article involved the development of sensitive and validated Ultraviolet (UV) Spectrophotometric and reverse phase liquid chromatographic and method for the determination of lapatinib in bulk and pharmaceutical dosage form. **Materials and Methods:** The present UV method is based on measurement of absorption at maximum at 268 nm using methanol as a solvent. In the High Performance Liquid Chromatography (HPLC) method, Waters HPLC with Empower-2 Software with PDA Detector was utilised. Acetonitrile and phosphate buffer in the ratio of 65:35 (v/v) utilised as a mobile phase. **Results:** In the UV Spectrophotometric method the drug obeyed beer lambert's law in the concentration range of 2-20 µg/ml with regression coefficient 0.999. In HPLC method the linearity level was 20-200 µg/ml. The developed UV and HPLC methods have been successfully applied in the validation study. The percentage purity of the marketed dosage form of lapatinib was found 99.68 % and 99.82% for UV and HPLC method. In both methods, the percent RSD of all the validation parameters examined as recommended in the ICH guidelines was found to be less than 2. The highest degradation (19.58%) occurs in alkaline stressed environments in the force degradation analysis by HPLC technique. The degradation of lapatinib is also associated with remaining stressed conditions. **Conclusion:** The two methods developed were found to be accurate, simple and validated for estimating lapatinib in the form of bulk and tablet doses.

Key words: High Performance Liquid Chromatography, International Council for Harmonisation Guidelines, Lapatinib, Method development, Ultraviolet Spectrophotometry.

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INTRODUCTION

Lapatinib has potential antineoplastic properties and is a synthetic, orally-active quinazoline. It blocks epidermal growth factor receptor (EGFR) phosphorylation, ErbB2, and Erk-1 and-2 and AKT kinases reversibly. It also inhibits cyclin D protein levels in human tumors cell lines and xenografts.[1]

Lapatinib is a small molecule inhibitor of kinase and a 4-anilinoquinoline[2] derivative. $C_{29}H_{26}ClFN_4O_4S$ is its molecular formula, and chemically it is N-[3-chloro-4-[(3-fluorophenyl) methoxy] phenyl]-6-[5-[(2-methylsulfonylethylamino) methyl]-2-furyl] quinazolin-4-amine[3] (Figure 1). Extensive review of literature raveled that, using color, few colorimetric methods.[4] Complex formation with lapatinib has been described, but not published elsewhere, in a doctoral thesis. The literature analysis of the High Performance Liquid Chromatography (HPLC) methods[5-8] available for lapatinib shows that few methods exist. On linearity and retention time, sensitivity, all the approaches have their own weaknesses. Almost all techniques have a retention time of more than 4 min, linearity levels were very narrow, and as an organic step, more acetonitrile volume was used. The lapatinib stress degradation analysis has not been published yet.

Therefore, considering all the details, efforts have been made to eliminate the drawbacks of all the HPLC methods reported above and to develop a novel, fast, reliable and validated method for estimating lapatinib in bulk and tablet dosage form as per the ICH guidelines[9] and, similarly, the first reported method for estimating lapatinib could be the developed Ultraviolet (UV) spectrophotometric method. The existing HPLC and UV methods can therefore be effectively used for the routine study of lapatinib.

MATERIALS AND METHODS

Instruments and Chemicals

UV–Visible double beam spectrophotometer with 1 cm matched Quartz cell, ELICO SL-159, Electronic Balance from SHIMADZU-ATY224, Ultra Sonicator (Wensar wuc-2L), and Waters HPLC with Empower-2 Software with PDA Detector (Waters). Lapatinib API (Active Pharmaceutical Ingredient) has been procured from Shilpa Medicare Limited, Raichur, and Karnataka, India. Tykerb Tablets manufactured by Stickler Pharmaceuticals, Gujarat, India, collected from the local market of Raichur, Karnataka. HPLC grade methanol and acetonitrile were used procured form Loba chemicals, Mumbai, India. Dipotassium hydrogen phosphate, orthophosphoric acid, hydrochloric acid were analytical grade and from SD- fine chemicals, Mumbai. HPLC grade distilled water was used from Millipore.

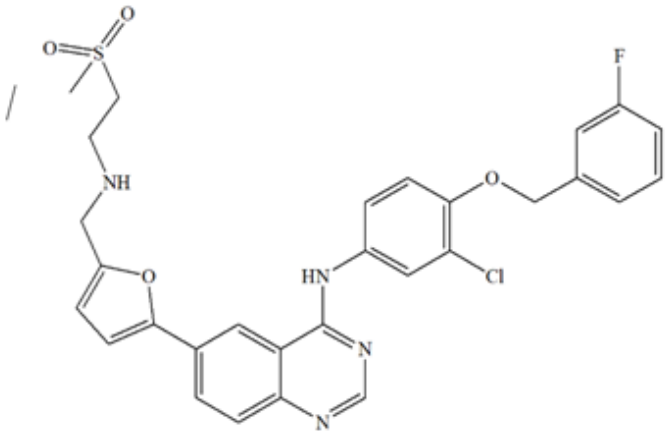

Figure 1: Chemical structure of the Lapatinib.

UV spectrophotometric method development and validation

Preparation of standard and working solution of lapatinib in methanol

Weighed accurately 100 mg of lapatinib, transferred into 100 ml Standard flask, dissolved and made up to the volume-using methanol. This solution had a concentration of 1 mg per ml of lapatinib. Accurately pipette out 10ml of above solution separately into 100 ml standard flask and the volume was made up to 100 ml using methanol. The resulting solution had a concentration of 100 µg/ml of lapatinib. Accurately pipette out 2 ml of solution from the standard stock solution separately into 10 ml standard flask and the volume was made up to 10 ml using methanol. The resulting solution had a concentration of 20 µg/ml of lapatinib.

Study of spectral characteristic of lapatinib

After enabling the initial adjustments and blank correction-using methanol the solution was scanned separately in the UV region ranging from 200 nm to 350 nm. A broad band of Absorption spectrum was observed with maximum absorption at 268 nm for lapatinib.

Preparation of calibration curve and study the linearity of lapatinib

For the preparation of calibration curve to investigate the linearity, a range of sample solution has been prepared in the range of 2-20 µg/mL. Accurately pipette out 0.5 ml to 5 ml solution from the standard solution separately into ten 10 ml standard flask, volumes were made up to 10 ml using methanol to achieve the concentrations. The absorbance of each solution was measured at 268 nm. The absorbance of the prepared solutions has been measured at 258 nm wavelength. The calibration curve was constructed by plotting the concentrations in X-axis and absorbance in Y-axis. The regression coefficient was also calculated.

Estimation of lapatinib in Pharmaceutical dosage forms

Twenty tablets containing each of 250 mg lapatinib was accurately weighed and finely powdered in a glass mortar. A weight equivalent to 250 mg lapatinib was accurately weighed and transferred to a 100 ml standard flask. 40 ml of methanol was added and swirled gently for a period of 10 min. The clear supernatant solution was then transferred to 100 ml standard flask through a Whatman No 1 filter paper. The residue was further extracted twice with 20 ml each of methanol and passed through the same filter paper and the volume was made up to 100 ml with methanol. The resulting solution had a concentration of 1mg/ml (solution A). Accurately pipette out 1 ml of the above solution into a 50 ml standard flask and made up to volume with methanol. The final solution had a concentration of 100 µg/ ml lapatinib (solution B). Accurately pipette out 1ml of solution B into 10 ml standard flask and the volume was mad up using methanol to obtain concentration of 10 µg/ml of lapatinib. The absorbance of this solution was measured at 268 nm.

Validation parameters

Accuracy

Accuracy of the proposed method was determined by performing recovery studies. A fixed amount of drug from dosage form was taken and pure standard drug at different concentrations levels i.e., 80 %, 100 % and 120 % was added. The total concentration was found by the proposed method. The determination with each concentration was repeated three times and average percent recovery of the added standard was calculated.

Precision

The precision of analytical method is considered the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of homogeneous samples. The intra and inter day precision was determined by analysing the lapatinib standard solution for six times on same day (intra-day study) and repeated on the second day (inter-day study). The result of the precision was expressed as standard deviation or relative standard deviation (coefficient of variance).

LOD and LOQ

For the study of LOD and LOQ, calibration curve was prepared for 5 times at 268 nm using 5 µg/mL and SD of the intercept was calculated for the drug. The LOD are calculated using the formula LOD = 3.3 x σ/ slope. Whereas for LOQ the (σ/ slope) was multiplied with 10.

Method Development by High Performance Liquid Chromatography

Standard preparation for the analysis

25 mg of lapatinib standard was transferred into 25 ml volumetric flask, dissolved and make up to volume with mobile phase. Further dilution was done by transferring 0.2 ml of the above solution into a 10 ml volumetric flask and make up to volume with mobile phase to achieve the final concentrations of 20 µg/ml.

Preparation of 0.05M phosphate buffer solution

About 6.8043 g of Potassium dihydrogen orthophosphate was weighed and transferred into a 1000 ml beaker, dissolved and diluted to 1000 ml with HPLC water. The pH was adjusted to 2.60 with orthophosphoric acid.

Preparation of mobile phase

The mobile phase used in this analysis consists of a mixture of Buffer (pH adjusted to 2.6 with ortho phosphoric acid and Acetonitrile in a ratio of 35:65. 650ml (65%) of acetonitrile and 350 ml (35%) of above prepared phosphate buffer were mixed well and degassed in ultrasonic water bath for 15 min. The solution was filtered through 0.45 µm filter under vacuum filtration.

Assay of marketed lapatinib formulation

Twenty Tykerb tablets (each of 250 mg lapatinib) was accurately weighed and finely powdered in a glass mortar. A weight equivalent to 250 mg lapatinib was accurately weighed and transferred to a 100 ml standard flask. 10 ml of acetonitrile to dissolve completely and swirled gently for a period of 10 min. The clear supernatant solution was then transferred to 100 ml standard flask through a Whatmann No 1 filter paper. The residue was further extracted twice with 20 ml mobile phase (acetonitrile: phosphate buffer in the volume ratio of 65 and 35) and passed through the same filter paper and the volume was made up to 100 ml with mobile phase. Accurately pipette out 1 ml from the resulting 1mg/ml solution into a 100 ml standard flask and made up to volume

with mobile phase. The final solution had a concentration of 100 µg/ml lapatinib. Accurately pipette out 2 ml of solution into 10ml standard flask and the volume were made up to the mark. The final solution was injected to the chromatographic system. The observed chromatogram was recorded.

Method validation

System suitability

It was evaluated to verify whether the analytical system is working properly and can able to give accurate and precise results. This study was performed by using the solution of 40 µg/ml solution of lapatinib injected six times. Average tailing factor for the peaks due to lapatinib in Standard solution should not be more than 2.0. Average theoretical plates for the lapatinib peaks in standard solution should not be less than 2000.

Accuracy

To justify the accuracy of the developed method recovery study was conducted at various levels (80%, 100%, and 120%) of pure lapatinib. The various amounts of standard lapatinib were added to a fixed concentration to lapatinib tablet sample solution to achieve the various levels. This study was carried out three times and the percentage recovery as well as percentage means recovery was calculated.

Precision

The precision of the method was studied by determining the 100% concentration lapatinib solution. It was evaluated by analysing the six lapatinib sample solutions in triplicate (n=6) intraday and inter day precision was determined by analysing for six times in three different concentrations i.e., 20 µg/ml, 40 µg/ml and 60 µg/ml. The chromatograms were recorded. The peak area and retention time of lapatinib was determined and relative standard deviation (RSD) was calculated. The % RSD for the area of six standard injections results should not be more than 2%.

Linearity

To carry out the linearity standard solution of lapatinib were prepared as describe earlier, aliquot from these solutions was diluted with mobile phase in five different concentrations to 20-200 µg/ml of lapatinib. Calibration curve plotted for the drug under study considering concentration versus peak area, obtained data was subjected to regression analysis. The relationship between the concentration and peak area should be linear in the specified range and the correlation coefficient should not be less than 0.99.

Limit of Detection (LOD)

The study was performed by transferring a quantity of tablet powder equivalent to 50 mg of drugs in to 50 ml volumetric flask, and 15 ml of mobile phase was added than sonicated for 15 min, there after volume was made up to 25 ml with same solvent. Then 0.5 ml of the above solution was diluted to 10 ml with mobile phase. From the above solution 0.5 ml was withdrawn, and made the volume up to 10 ml to achieve dilute concentrations of 2.5 µg/ml. From this solution further 0.5 ml was withdrawn and volume was made up to 10 ml to achieve the final concentration of 0.125 µg/ml. The prepared solution was filtered and injected in to the chromatographic system. Signal to noise (S/N Ratio) value shall be 3 for LOD solution. The LOD solutions was prepared injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Limit of quantitation (LOQ)

For the study of limit of quantitation, a quantity of lapatinib tablet powder equivalent to 25 mg of drugs were transferred to 25 ml volumetric flask, and 15 ml of mobile phase was added than sonicated for 15 min, there after volume was made up to 25 ml with same solvent. Then 0.5 ml of the above solution was diluted to 10 ml with mobile phase. From the above solution 0.5 ml was withdrawn and made the volume up to 10 ml. From the above solution further 1 ml aliquot was transferred to 10 ml flask and volume was made to achieve dilute concentrations of 0.25 µg/ml. The prepared solution was filtered and injected into the chromatographic system. Signal to noise (S/N Ratio) value shall be 10 for LOQ solution. The LOQ solutions was prepared injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Robustness

This parameter is used to measure the capacity of the developed method to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness was performed by injecting the lapatinib standard solution in to the HPLC by altering the flow rate, detection wavelength and also by changing the composition of the organic solvent from the normal chromatographic conditions.

Force degradation study of lapatinib

Stress study was carried out in environmental test chamber (Acamus Technologies, India) at 60°C and 75% relative humidity, as per ICH prescribed stress condition such as acidic, basic, oxidative, thermal and photolytic stresses. The procedure[10] for carrying out the study was described in earlier section. The results are summarized in the table and chromatograms of all degradation conditions were shown as below.

Acid hydrolysis

Forced degradation in acidic media was performed by adding 1 ml of 1M HCl to 1 ml of stock solution and the mixture is heated at 80°C for approximately 2 hr and the solution is neutralized by addition of 1M NaOH and kept side for 24 hr and injected.

Alkaline hydrolysis

Forced degradation in basic media was performed by adding 1 ml 1M NaOH to 1mL of stock solution and the mixture is heated at 80°C for approximately 2 hr and the solution is neutralized by addition of 1M HCl and kept side for 24hr. The prepared solution is injected, and chromatograms were recorded.

Oxidative Degradation

To study the effect of oxidising conditions, an aliquot of stock solution was added to 1 ml 6 % H_2O_2 solution and kept side for 24 hr. The prepared solution was injected, and chromatograms were recorded.

Photolytic degradation

To study the effect of temperature an aliquot of stock solution was kept at 80°C for 2 hr and kept side for 24 hr. The resulting solution was injected into HPLC system and chromatograms were recorded.

Thermal Degradation

To study the effect of temperature an aliquot of stock solution was kept at 80°C for 2 hr and kept side for 24 hr. The resulting solution was injected into HPLC and chromatograms were recorded.

RESULTS

UV Spectrophotometric method optimization and validation study

To optimize the solvent system for the ideal and linear UV spectrum of lapatinib, a range of solvents and mixture of solvents with buffer systems with different volume ratio were tested. Finally, the solvent methanol was

selected. With this solvent UV spectrum was obtained linear at the λ_{max} 258 nm as shown in optimized UV spectrum in Figure 2. The solvent methanol was used for the subsequent validation studies and the assay of lapatinib marketed dosage form.

Method validation study results by UV spectrophotometer

The percentage of assay of the lapatinib marketed dosage form "Tykerb", (each tablet contains 250 mg of lapatinib.) was found 99.84% which is found within the limit i.e. 90-102%. The details of the result shown in Table 1. In the study of linearity, the developed method was found linear in the range of 2-20 µg/ml, with a regression coefficient (R^2) of 0.999. The recovery study was performed to justify the accuracy of the developed the average percentage recovery of lapatinib was found 98.34±0.319, as Table 2. The average %RSD for the intraday precision study was found 0.54 and found 0.64 for the interday precision. In the study of LOD, the detection limit was found 0.2524 µg/ml, and quantitation limit was found 0.764 µg/ml. The details are shown in summary of validation parameters as Table 2. In the robustness study of the developed UV method where measured absorbance at different wavelengths were considered, the % RSD value was found 0.36.

HPLC Method optimization

In the HPLC method development approach, prior the selection of the optimised condition, several preliminary trials has been conducted by utilising different solvent combinations, various buffers, pH, temperature, flow rate, and columns in order to rationalize the retention time, peak shape, and other chromatographic parameters. The mobile phases were prepared by incorporating various buffer systems with organic solvents. Numerous solvents (methanol, acetonitrile), buffers (ammonium acetate pH 5 and 7, orthophosphoric acid pH 2, 8, potassium dihydrogen orthophosphate pH 5, 6.8) used in the different volume ratio. Various analytical columns were tested with U.V detection at 268 nm. Finally a selected mobile phase consisting of acetonitrile and phosphate buffer in the ratio of 65:35(v/v) using Waters C_{18}, 250mm x 4.6mm .i.d., 5 µm Particle size, analytical column was found optimum condition with the isocratic elution at 268 nm PDA detection and at the flow rate of 1 ml/min, In this chromatographic conditions lapatinib was fully separated at 3.008 min retention time with an improved sensitivity and excellent peak shape, Figure 3.

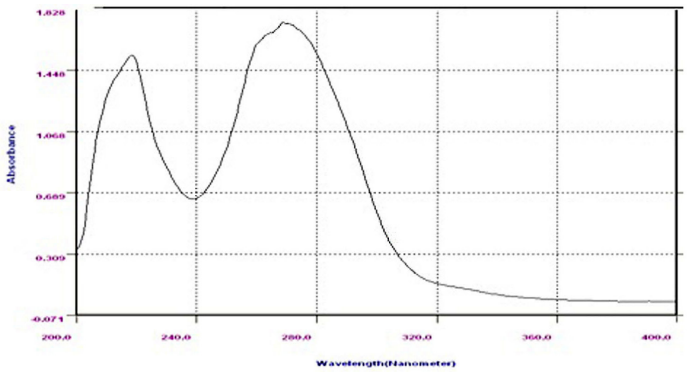

Figure 2: Optimized UV spectrum of Lapatinib.

Table 1: Assay of marketed dosage from by the UV-Visible spectroscopy.

Formulation	Label Claim in mg	*Absorbance at 268.0nm	Amt of Drug found mg	% Label Claim
Tykerb	250	0.868	249.65	99.68

Table 2: Summary of Validation Parameters by UV methods.

Parameters	Lapatinib
Beer's law limit in mg/ml	2 to 20
Co-relation co-efficient	0.999
LOD µg/ml	0.2524
LOQ µg/ml	0.764
Intraday Precision (% RSD)	1.87
Inter day Precision (% RSD)	1.73
Accuray (% recovery)	98.34

Method Validation by developed HPLC method

The developed and optimized chromatographic condition was utilized for the following validation study and force degradation study as per the ICH guidelines. System Suitability is a test to check that the equipment used for analytical measurements is working adequately. Parameters such as tailing factor, peak area, retention time and theoretical plates were considered. The %RSD of area, tailing factors, theoretical plates and retention time were 0.05, 1.10, 0.46 and 0.36 respectively. No corresponding peak was observed at the retention time of the analyte in the analysis of specificity. The assay of marketed dosage form using developed HPLC method was conducted and the amount of drug in Tkerb tablets (marketed formulation) was found 249.65 mg and % assay was 99.82%. The details were given in Table 3 and chromatogram was shown in Figure 4. The calibration curve showed linearity in the range of 20-200 µg/ml, for lapatinib (API) with correlation coefficient (r^2) of 0.995. The linearity overlay chromatogram was shown in Figure 5. The Minimum concentration level at which the analyte can be detected (LOD) and quantified (LOQ) were found to be 0.05 and 0.25 µg/ml respectively. In the study of intra and interday precision, the %RSD was found 1.44 and 0.94. The accuracy of the developed method was proved by conducted the recovery study. The average recovery of the lapatinib using HPLC method was 100.06%. The results of all validation parameters was summarised in Table 4. The method was robust with the change in flow rates for ±0.1 ml/min, the mobile phase acetonitrile and phosphate buffer ratios (63:37 and 67:33) and detection wavelength (266

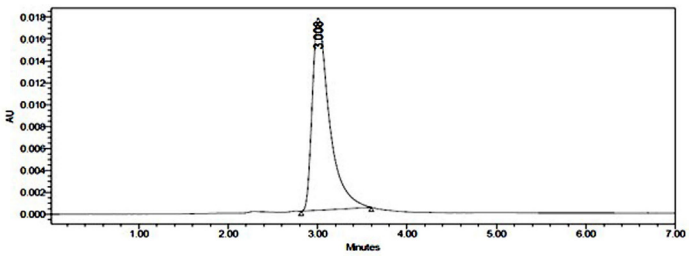

Figure 3: Optimized HPLC chromatogram of Lapatinib.

Table 3: Assay of marketed dosage form by the HPLC method.

Brand name of tablet	Labelled amount of Drug (mg)	Mean (±SD) (*n*=6) of the obtained amount	Mean (± SD) Assay (*n*=6)
Tykerb Tablets (Stickler Pharmaceuticals)	250	249.86 (±0.06)	99.82 (±0.48)

nm and 270 nm). The tailing factor was considered for every changed condition. The calculated percentage RSD for robustness study were found 0.5 and 0.46 for increased and decreased flow rate, %RSD value 0.34 to 0.79 for the decreased and increased mobile phase ratio the results are shown in Table 5. The study on stress degradation was performed in a variety of stressed environments and the percentage of degradation was determined. It was noted that 19.58% and 10.44% degradation took place in alkaline and UV light degradation studies. The percent degradation was 18.87% and 8.44% in the case of oxidative and acid degradation. In Table 6, the details were given and degradation chromatograms were cited in Figure 6.

DISCUSSION

The solvent methanol was considered acceptable for optimising the UV spectrum of lapatinib at 268 nm in the UV spectrophotometric process. The results of the UV Visible spectrophotometric method validation study were found within the limit and verified the method's validity. Similarly, the mobile phase acetonitrile and phosphate buffer at 65:35(v/v) ratio using Waters C_{18}, 250 mm x 4.6 mm. i.d., 5 m particle size, analytical column, at 268 nm PDA detection, under optimised chromatographic conditions in the HPLC method. The 1 ml/min flow rate was found to be optimum. Within the retention time of 3,008 min, Lapatinib was separated with better sensitivity and excellent peak shape. The regression coefficient value of 0,995-0,999, which is very close to 1, was found in the linearity analysis for both the UV and HPLC methods, indicating the linearity of the methods developed. For the precision analysis using the UV and HPLC process, the percentage of RSD was found to be less than 2, which suggested that the UV and HPLC methods developed were found to be accurate. The average percentage recovery results of 98.34 percent for the UV method and 100.06 percent for the HPLC method showed the accuracy of the methods produced since the values are within the acceptance limit. The results of the LOD and LOQ studies showed that both the methods developed for lapatinib were found to have been sensitive and easily quantifiable. It was found to be substantially acceptable in the assay of the marketed dosage form using both the UV and HPLC process, since 99.82 percent for HPLC

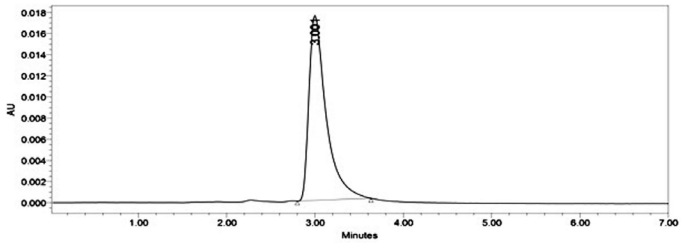

Figure 4: Chromatogram of Lapatinib in the assay of marketed dosage form.

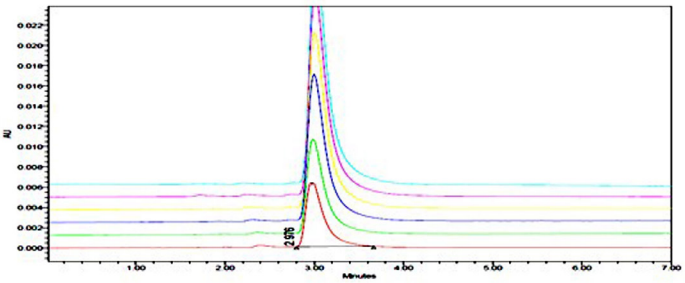

Figure 5: Linearity overlay chromatogram of lapatinib in HPLC method.

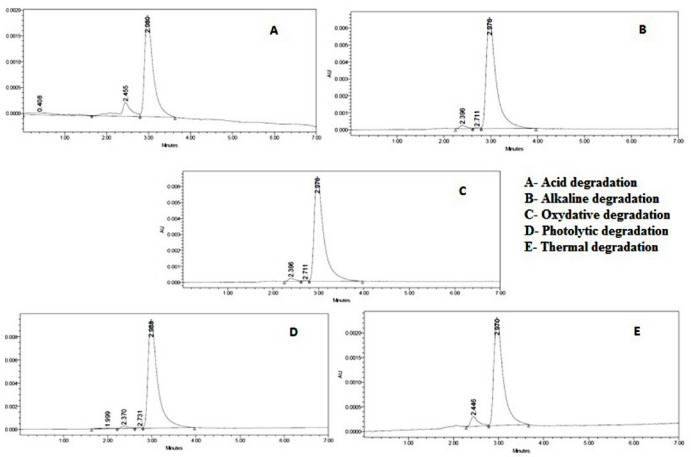

Figure 6: Stressed degradation chromatograms of lapatinib.

Table 4: Summary of Validation Parameters by HPLC methods.

Parameters	Lapatinib
Beer's law limit in µg/ml	20-200
Co-relation co-efficient	0.995
LOD µg/ml	0.05
LOQ µg/ml	0.25
Intra day Precision (% RSD)	1.44
Inter day Precision (% RSD)	0.94
Accuray (% recovery)	100.06

Table 5: Robustness study of the Lapatinib by HPLC method.

Change in parameter	%RSD of tailing factor* (*n*=3)
Flow (1.1 ml/min)	0.54
Flow (0.9 ml/min)	0.46
Less Organic	0.34
More Organic	0.79
Wavelength of Detection (254 nm)	0.98
Wavelength of detection (258 nm)	0.48

Table 6: Force degradation study of Lapatinib.

Stress condition	Time	Assay of active substance	Assay of degraded products	Mass Balance (%)
Acid Hydrolysis (0.1N HCl)	24hrs.	91.56	8.44	100.0
Basic Hydrolysis (0.IN NaOH)	24hrs.	80.42	19.58	100.0
Thermal Degradation (60 ˚C)	24hrs.	92.34	7.66	100.0
UV (254nm)	24hrs.	89.56	10.44	100.0
3 % Hydrogen peroxide	24hrs.	81.13	18.87	100.0

and 99.68 percent for the UV process. The outcome of the robustness analysis shows that there are no major changes in the outcome of minor deliberate changes in the mobile phase ratio, column temperature and mobile phase flow rate, which suggest that the method developed is robust. The results of the force degradation analysis showed that in most of the decomposition conditions there is a very narrow degradation stage. Alkaline and oxidation have induced further decomposition of lapatinib relative to acidic, thermal and photolytic degradation. The obtained result indicates that the drug is resistant to the above degradation conditions, as the percentage of degradations in each stressed condition was found to be within the ICH guideline limit,[11] indicating that the developed method is stable.

CONCLUSION

The results of the pharmaceutical dosage form analysis suggested that the spectrophotometric and RP-HPLC method produced is highly reliable, accurate and robust and is in good agreement with the drug's labelled claim and the results of the assay obtained. For both the established approach, the empirical evidence from the validation studies showed that the findings are within the acceptance criteria and considered validated according to ICH guidelines. In addition, the authors should indicate that the suggested methods of UV and RP-HPLC have excellent sensitivity, accuracy and reproducibility.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HPLC: High performance liquid chromatography; **ICH:** International conference on harmonization; **PDA:** Photo diode array; **LOD:** Limit of detection; **LOQ:** Limit of quantitation; **SD:** Standard deviation; **RSD:** Relative standard deviation.

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