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Research Article

DEVELOPMENT AND VALIDATION OF A NEW ANALYTICAL UV-VISIBLE SPECTROPHOTOMETRIC METHOD FOR THE ESTIMATION OF ALECTINIB IN API FORM AND MARKETED PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Objective: *The aim of this study is to develop three simple, specific and accurate spectrophotometric method for the determination of Alectinib in bulk and marketed pharmaceutical dosage form.* ***Methods:*** *In this method, the absorption spectrum of Alectinib is getting by 10µg/ml. In the developed method, the UV spectra were measured at 290 nm.* ***Results:*** *The proposed method was accurate, precise and selective for the determination of Alectinib in in pure form and in marketed pharmaceutical dosage form. Beer's law was obeyed in the concentration range of 10–60µg/ml in this method.* ***Conclusion:*** *The developed method was used to determine the studied drug in bulk powder, laboratory prepared mixtures and pharmaceutical dosage form with good accuracy and precision. The method was validated according to ICH guidelines and the results obtained were statistically compared to those obtained from a reported method and were found to be in good agreement.*

KEY WORDS

UV-Spectroscopy, Alectinib, Method Development, Validation, Accuracy.

INTRODUCTION

Alectinib is an organic heterotetracyclic compound that is 6,6-dimethyl-5,6-dihydro-11H-benzo[b]carbazol-11-one carrying additional cyano, 4-(morpholin-4-yl) piperidin-1-yl and ethyl substituents at positions 3, 8 and 9 respectively. Used (as the hydrochloride salt) for the treatment of patients with anaplastic lymphoma kinase-positive, metastatic non-small cell lung cancer[1]. It has a role as an EC 2.7.10.1 (receptor protein-tyrosine kinase) inhibitor and an antineoplastic agent. It is an organic heterotetracyclic compound, a member of morpholines, a member of piperidines, a nitrile and an aromatic ketone. It is a conjugate base of an Alectinib (1+). Alectinib is a second-generation oral drug that selectively inhibits the activity of anaplastic lymphoma kinase (ALK) tyrosine kinase[2]. It is specifically used in the treatment of non-small cell lung cancer (NSCLC) expressing the ALK-EML4 (echinoderm microtubule-associated protein-like 4) fusion protein that causes proliferation of NSCLC cells. Inhibition of ALK prevents phosphorylation and subsequent downstream activation of STAT3 and AKT resulting in reduced tumour cell viability. Approved under

accelerated approval in 2015, Alectinib is indicated for use in patients who have progressed on or were not tolerant of Crizotinib, which is associated with the development of resistance[3]. The IUPAC name of Alectinib is 9-ethyl-6, 6-dimethyl-8-(4-morpholin-4-yl piperidin-1-yl)-11-oxo-5H-benzo [b] carbazole-3-carbonitrile. The Chemical Structure of Alectinib is shown in follows

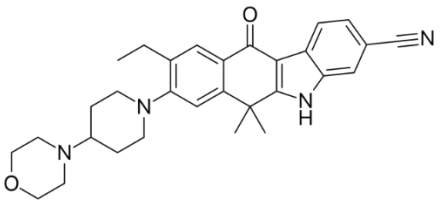

Fig-1: Chemical Structure of Alectinib

EXPERIMENTAL

List of Instruments Used:

Table 1: List of Instruments Used

Instruments/Equipments/Apparatus
ELICO SL-159 UV – Vis spectrophotometer
Electronic Balance **(SHIMADZU ATY224)**
Ultra Sonicator (**Wensar wuc-2L)**
P^H Analyzer **(ELICO)**
Triple Quartz Distillation Unit **(BOROSIL)**
Vaccum filtration Kit **(BOROSIL)**

List of Chemicals, Reagents and Standards Used:

Table 2: List of Chemicals, Reagents and Standards Used

Name	**Specifications**		**Manufacturer/Supplier**
	Purity	**Grade**	
Doubled distilled water	----	**----**	**Sd fine-Chem ltd; Mumbai**
Methanol	99.9%	A.R.	**Loba Chem; Mumbai.**
Ethanol	96%	L.R.	**Sd fine-Chem ltd; Mumbai**
Chloroform	99.9%	HPLC	**Loba Chem; Mumbai.**
Hydrochloric acid	99.9	L.R.	**Sd fine-Chem ltd; Mumbai**
Sodium Hydroxide	99.9	L.R.	**Sd fine-Chem ltd; Mumbai**
Sodium nitrite	99.9	L.R.	**Sd fine-Chem ltd; Mumbai**
MBTH Reagent	99.99	L.R.	**Sd fine-Chem ltd; Mumbai**
Ferric Chloride	**99.99**	**L.R.**	**Sd fine-Chem ltd; Mumbai**

METHOD DEVELOPMENT

Instrumentation

The Spectroscopic analysis[4] was carried out using Double beam PG Instruments recording UV-Visible Spectrophotometer ELICO SL-159 with 1mm path length matched quartz cells were used for analytical purpose.

Preparation of Standard Solution:

Accurately weigh and transfer 10 mg of Alectinib working standard into a 10ml of clean dry volumetric flasks add about 7ml of Methanol and sonicate to dissolve and removal of air completely and make volume up to the mark with the same Methanol (1000 ppm).

Further pipette 1ml of the above Alectinib stock solution into a 10ml volumetric flask and dilute up to the mark with Methanol (100ppm).

Further pipette 1ml of the above Alectinib stock solution into a 10ml volumetric flask and dilute up to the mark with Methanol (10ppm).

Preparation of Sample Solution:

Take average weight of the Powder and weight 10 mg equivalent weight of Alectinib sample into a 10mL clean dry volumetric flask and add about 7mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent (1000ppm).

Further pipette 1ml of the above Alectinib stock solution into a 10ml volumetric flask and dilute up to the mark with Methanol (100ppm).

Further pipette 1ml of the above Alectinib stock solution into a 10ml volumetric flask and dilute up to the mark with Methanol (10ppm).

Procedure:

Measure the samples by checking in the UV Spectroscopy[5,6] and record the absorbance, note the conditions of proper conditions for performing validation parameters as per ICH guidelines[7,8].

RESULTS AND DISCUSSION

OPTIMIZATION OF METHOD

Optimization of Selection of Solvent

It is well known that the solvents[9] do exerts a profound effect on the quality and the shape of the peak. The choices of solvents for UV method development are: Acetonitrile, Ethanol, Chloroform, Acetone, Methanol, Dimethyl sulfoxide (DMSO), Dimethyl formamide etc. First optimize the different solvents. From that solvents Methanol satisfied the all the optimized conditions.

Selection of Wavelength:

The standard solutions are prepared by transferring the standard drug in a selected solvent and finally diluting with the same solvent. That prepared solution is scanned in the UV wavelength range of 200-400nm.This has been performed to know the maxima of Alectinib, so that the same wave number can be utilized in UV detector[10] for estimating the Alectinib. While scanning the Alectinib solution we observed the maxima at 290 nm. The UV spectrum has been recorded on ELICO SL-159 make UV – Vis spectrophotometer model UV-2450. The scanned UV spectrum is attached in the following page. The λ_{max} of the Alectinib was found to be 290 nm in methanol as solvent system.

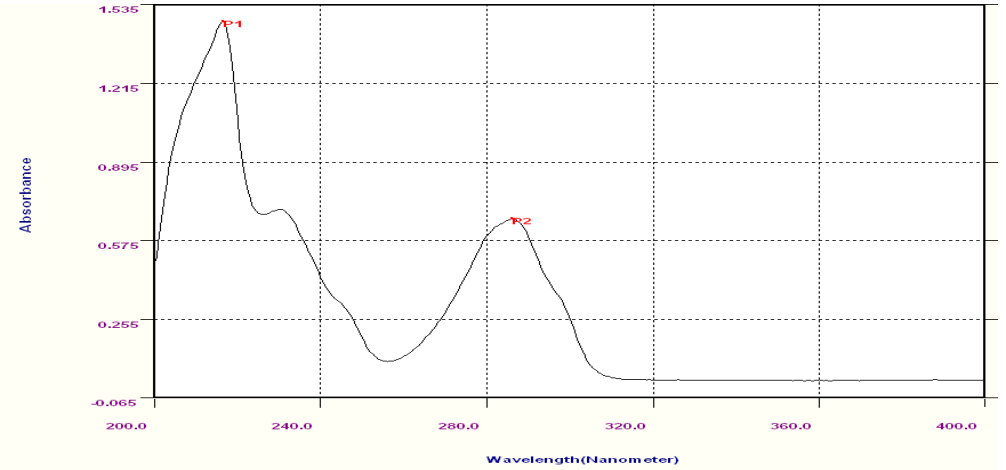

Fig 2: UV Spectrum of Alectinib at 290nm

Preparation of Calibration Curve for Alectinib

Standard solutions of Alectinib in the concentration range of 10 µg/ml to 60 µg/ml were obtained by transferring (1,2,3,4 and 5,6, ml) of Alectinib stock solution (100 ppm) to the series of clean and dry 10 ml volumetric flasks. The volumes in each volumetric flask were made up with the solvent system and mixed.

The absorbencies of the solutions were measured at 290 nm against the solvent system as blank and calibration curve is plotted. The Lambert-Beer's Law[11] is linear in concentration range of 10 to 60 µg/ml at 290 nm for Alectinib. The results are shown in Table no.3.

Table 3: Results of Calibration Curve

Concentration (µg/ml)	Absorbance (n=6)
0	0
10	0.221
20	0.425
30	0.635
40	0.836
50	1.043
60	1.238

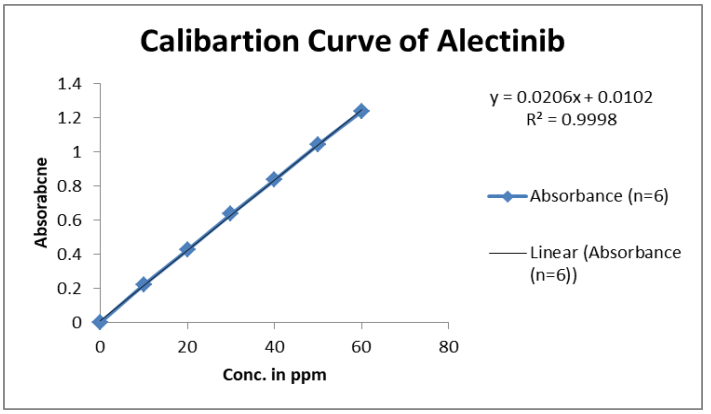

Fig 3: Calibration Curve for Alectinib at 290 nm.

RESULT AND DISCUSSION:

For Alectinib the Beer- Lambert's law is obeyed in concentration range of 10 to 60 µg/ml at 290nm. Moreover, in the linearity study at consecutive wavelength, the linear regression equation[12] for Alectinib, calibration curve at 290nm was calculated by y = 0.0206x + 0.0102 (R^2 = 0.9998).

METHOD VALIDATION

Validation of the Developed Method According to I.C.H guidelines

Following parameters were taken into consideration for validation[13-16] of proposed method:

Linearity

Method: As per Test Assessed under Above Linearity (Plotting a Calibration Curve)

Preparation of Dilutions of Alectinib for Linearity Study

Standard solutions of Alectinib in the concentration range of 10 µg/ml to 60 µg/ml were obtained by transferring (1,2,3 and 4,5,6, ml) of Alectinib stock solution (100ppm) to the series of clean & dry 10 ml volumetric flasks. The volumes in each volumetric flask were made up with the solvent system and mixed.

The absorbances of the solutions were measured at 290 nm against the solvent system as blank and calibration curve is plotted. The Lambert-Beer's Law is linear[17] in concentration range of 10 to 60 µg/ml at 290 nm for Alectinib. The results are shown in Table no.4.

Table 4: Results of Linear Curve

Concentration (µg/ml)	Absorbance (n=6)
0	0
10	0.221
20	0.425
30	0.635
40	0.836
50	1.043
60	1.238

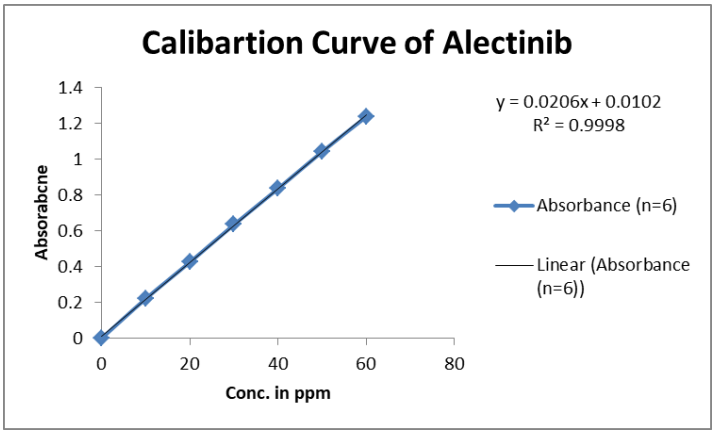

Fig 4: Calibration Curve for Alectinib at 290 nm.

RESULT AND DISCUSSION:

Linearity range[18] was found to be 10-60 µg/ml for Alectinib at 290 nm. The correlation coefficient was found to be 0.9998, which shows good linearity between above range. The slope was found to be 0.0206 and intercept was found to be 0.0102 which was close to zero intercept.

Range

Range[19] of an analytical method is the interval between the upper and lower levels (including these levels) that have been demonstrated to be determined with precision, accuracy and linearity using the method as written. It includes working range, linearity range and target range and 100% concentration or test concentration. The range my developed method concentrations are 10-60 µg/ml.

Accuracy

The accuracy[20-23] is nothing but the comparison of obtained value with the standard value. After completion of analysis of Alectinib containing 3 group 3 replicates with the bulk and marketed pharmaceutical dosage form.

Method: The accuracy of the developed method can be studied by preparing the solutions of various concentrations i.e. 80%, 100% and 120%. In these concentrations the amount of marketed pharmaceutical dosage form was kept as constant and the quantity of pure drug (API) is varied. The prepared solutions in triplicates and here determined is percentage recovery of pure drug. The results obtained from the accuracy studies are shown in Table-5.

In nine different 10 ml volumetric flasks, 1 ml of the pre-analysed tablet solution (10 µg/ml) was taken and added 1, 2, 3 ml of standard solution of bulk (API) mixture (100µg/ml) and the volume was made up to 10 ml with methanol.

The results are shown in Table no.5.

Table 5: Data of Recovery Studies

Level of Recovery	Sample Conc. (µg/ml)	Standard Conc. Added (µg/ml)	Total Conc. (µg/ml)	Amount Recovered (µg/ml)	% Recovery	Mean % Recovery ± SD	% RSD
80%	8	10	18	17.896	99.422	99.85533 ± 0.415352	0.415954
80%	8	10	18	18.045	100.25		
80%	8	10	18	17.981	99.894		
100%	10	10	20	19.968	99.840	100.1683 ± 0.300597	0.300091
100%	10	10	20	20.086	100.430		
100%	10	10	20	20.047	100.235		
120%	12	10	22	21.879	99.45	99.766333 ± 0.4753759	0.476489
120%	12	10	22	22.069	100.313		
120%	12	10	22	21.898	99.536		

Result & Discussion:

The results obtained for the accuracy study (recovery method) from three sample studies (n = 3) for each level indicated that the mean of the % recovery was 99.85533% and 100.1683% and 99.7663% and %R.S. D was found to be 0.415954%, 0.300091% and 0.476489% for Alectinib in mixture (Alectinib- 10 µg/ml). Here the mean % recovery[24] is in between 98-102 % thus showing that the analytical technique has a good recovery study.

Precision

The precision of developed analytical method said to be the closeness of agreement between a series of measurement obtained from the multiple sampling of the homogenous sample solution under the prescribed experimental conditions. The precision[25-27] of the developed method can be analysed by the 5 or 6 different homogenous solutions and the respective are noted down. The results are shown in the precision is % RSD. The results obtained from the precision studies are shown in the Table-5.

The precision can be divided into following types. 1. Repeatability and 2. Intermediate precision. In this first one is Repeatability or Intra-day precision was determined on six replicates of same sample solutions on the same day. Inter-day precision was estimated by analyzing newly prepared sample solutions in triplicate over the 3 consecutive days. Both inter day and intraday precision was expressed as % RSD[28]. The % RSD values for intraday precision for Method A was found to be within the limits. The % RSD for inter day precision for Method A found to be within the limits. The results were summarized in Table-5. The low value of % RSD for the method indicates the high precision of the method.

Repeatability

Repeatability[29] was assessed using:

Six-time repetition of target concentration 100 % that is (10µg/ml).

Intermediate precision can be assessed by intra-day and inter day analysis.

Method: In the study of the repeatability precision which was conducted on the solution which has the concentration value 100 % of the target concentration (n = 6). The results are shown in Table-6.

Table 6: Data of Repeatability of Absorbances

Conc. (µg/ml)	Wavelength (nm)	Absorbance
10	290	0.221
10	290	0.225
10	290	0.226
10	290	0.224
10	290	0.229
10	290	0.223
0	**0**	**0.224667**
0	**0**	**0.002733**
0	**0**	**1.216255**

Result & Discussion:

Repeatability study showed a R.S.D of 1.216255% for Alectinib. Thus, it is concluded that the analytical technique has a good repeatability precision as R.S.D for the drug were less than 2 %.

Intermediate Precision:

Intra-Day & Inter-Day:

The intra & inter day variation[30] of the method was carried out & the high values of mean assay & low values of standard deviation & % RSD (% RSD < 2%) within a day & day to day variations for Alectinib revealed that the proposed method is precise.

Table 7: Intra-Day and Inter-Day Precision for Method

Con. taken (µg/mL)	Observed Conc. of Alectinib (µg/ml) by the proposed method			
	Intra-Day		Inter-Day	
	Con. found (µg/mL)	% RSD	Con. found (µg/mL)	% RSD
8	8.065	0.862	7.968	0.726
10	10.015	0.748	9.896	0.863
12	11.968	0.639	12.054	0.634

Robustness

Robustness[31] of the method was determined by carrying out the analysis under different temperature condition i.e. at 23°C, 25°C and at 28°C. The respective absorbances of 10µg/ml were noted and the result was indicated as % RSD (Table no.8).

Table 8: Results Showing Robustness for Alectinib

Temperature-23°C

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.221	Mean = 0.224667 SD = 0.002582 % RSD = 1.149253
10	0.228	
10	0.223	
10	0.224	
10	0.225	
10	0.227	

Temperature-25°C

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.236	Mean = 0.236167 SD = 0.001722 % RSD = 0.729316
10	0.237	
10	0.239	
10	0.236	
10	0.235	
10	0.234	

Temperature-28°C

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.246	Mean = 0.246333 SD = 0.00216 % RSD = 0.876961
10	0.248	
10	0.249	
10	0.247	
10	0.245	
10	0.243	

Ruggedness

In the ruggedness study, the influence of small, deliberate variations of the analytical parameters on the absorbance of the drug was examined. The factor selected was a change in the analyst. The Ruggedness[32] of the method was determined by carrying out the analysis by different analyst and the respective absorbance of 10µg/ml was noted. The result was indicated as %RSD (Table No-9).

Table 9: Results showing Ruggedness for Alectinib

Analyst-1

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.228	Mean = 0.2265 SD = 0.001871 % RSD = 0.825973
10	0.229	
10	0.227	
10	0.226	
10	0.224	
10	0.225	

Analyst-2

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.246	Mean = 0.244667 SD = 0.003141 % RSD = 1.283839
10	0.241	
10	0.249	
10	0.242	
10	0.247	
10	0.243	

Analyst-3

Concentration(µg/ml)	Absorbance	Statistical Analysis
10	0.252	Mean = 0.254833 SD = 0.003061 % RSD = 1.200981
10	0.257	
10	0.256	
10	0.251	
10	0.259	
10	0.254	

Specificity

The presence of excipients in formulation does not interfere with the drug absorbances. Therefore, the proposed method was found specific[33] and selective for the drug.

Limit of Detection and Limit of Quantification

The limit of detection (LOD) and the limit of quantification limit (LOQ) are measured by using the following equations:

L.O.D. = 3.3 (SD/S).
L.O.Q. = 10 (SD/S)

Where, SD = Standard deviation of the response
S = Slope of the calibration curve
The slope S and the SD may be estimated from the calibration curve of the analyte/sample.

Result & Discussion

The LOD[34] was found to be 2.08 µg/ml and LOQ was found to be 6.303 µg/ml for Alectinib respectively which represents that sensitivity of the method is high.

Analysis of Marketed Formulation

Twenty tablets/Capsules were weighed accurately and finely powdered. Tablet powder equivalent to 10 mg of Alectinib was accurately weighed and transferred to a 10 ml volumetric flask. A few ml of diluent was added and sonicated for 15 min. Volume was made upto the mark with methanol. An aliquot of 1ml was transferred to a 10ml volumetric flask and the volume was made up to the mark to obtain 10µg/ml of Alectinib. The solution was filtered using 0.45µ Millipore PVDF filter. This solution was prepared six times and the absorbance of each solution was determined at 290 nm and the concentration of drug in sample solution was determined from calibration curve.

Table 10: Assay Results of Pharmaceutical Dosage Form

Formulation	Actual Amount (mg)	Amount Found ± SD (mg)	% of Drug Found ± SD
ALECensa 150mg Capsule (Roche Products India Pvt Ltd)	150	149.486 ± 0.798	99.685 ± 0.475

SUMMARY

The standard solutions of Alectinib in Methanol (10µg/ml) subjected to a scan individually at the series of wavelengths of 200 nm to 400 nm. Absorption maximum of Alectinib was found to be at 290 nm. Therefore, 290nm was selected as λ_{max} of Alectinib for the present study. The calibration curve of Alectinib was found to be linear in the range of 10-60 µg/ml at 290 nm. Therefore, it was clear that Alectinib can be determined without interference of any irrelevant substance in single component pharmaceutical products. The used technique was initially attempted on bulk drugs in their synthetic sample and concentrations were estimated.

The % recovery was carried out at 3 levels, 80%, 100% and 120% of Alectinib standard concentration. Three samples

were prepared for each recovery level. The solutions were then analysed, and the percentage recoveries were found to be satisfactory within the acceptable limits as per the content of the label claim for marketed tablet dosage form. The newly developed method was validated according to the ICH guidelines and the method validation parameters.

The developed method was subjected to do the various method validation parameters such as specificity, accuracy, precision, linearity and range, limit of detection and limit of quantification, robustness and ruggedness etc.

CONCLUSION

From the experimental studies it can be concluded that first the method is developed for Alectinib in marketed pharmaceutical dosage form. The developed method for the drug (Alectinib) was found to be accurate and precise.

The great features of spectrophotometric methods are their simplicity, economical and rapidity. The results of method validation showing that the developed analytical procedure is suitable for its intended purpose and meets the Guidelines given by the ICH. The developed method was successfully applied for the routine analysis of Alectinib in bulk and marketed pharmaceutical dosage form in the future.

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