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A NEW WAY OF METHOD ESTABLISH AND VALIDATED OF RELATED SUBSTANCE OF GLASDEGIB BY RP-HPLC AND ITS FORCED DEGRADATION STUDY

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Keywords:

RP-HPLC, ICH guidelines, Degradation, Method validation, Glasdegib

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ABSTRACT: A novel, simple, and accurate, high-performance liquid chromatographic method has been a developed with quantitative analysis of Glasdegib using Waters X-Bridge C_{18} 150 × 4.6mm, 3.5µ column with a flow rate of 1ml/min. The buffer containing 0.1% OPA and the mixture of two components like Buffer and Acetonitrile in the ratio of 50: 50 is used as mobile phase. The detection was carried out at 250nm. The proposed method shows good linearity in the concentration range from 25µg/ml to 500µg/ml for Glasdegib. Precision and accuracy study results are in between 98-102%. In entire robustness conditions % RSD is below 2.0%. Degradation has minimum effect in stress conditions, and solutions are stable for 24hrs. Method validation is carried out according to ICH guidelines, and the parameters are precision, accuracy, specificity, stability, robustness, linearity; the limit of detection and limit of quantification are evaluated, and the values are found to be within the acceptable limit. The developed method gave good resolution between Glasdegib and its impurities with a short runtime, high efficiency, and complies with modified SST specifications of USP. The result of Glasdegib being subjected to different stress conditions led to the fact that it was stable during the thermal condition. It degraded extensively under UV, Thermal and Peroxide conditions.

INTRODUCTION: Glasdegib is an FDA[1] approved cancer drug [2] developed by Pfizer. It is a small molecule inhibitor of sonic hedgehog [3, 4], which is a protein [6] overexpressed in many types of cancer [7, 8].

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It inhibits the sonic hedgehog receptor smoothened (SMO), as do most drugs in its class. Four phases II clinical trials are in progress. One is evaluating the efficacy [9] of glasdegib in treating myelofibrosis [10, 11] in patients who were unable to control the disease with ruxolitinib [12, 13].

Another is a combination trial of glasdegib with decitabine, daunorubicin, or cytarabine for the treatment of acute myeloid leukemia [14, 15]. The third is for the treatment of myelodysplastic syndrome [17, 18] and chronic myelomonocytic leukemia [19, 20]. The fourth administers glasdegib to patients at high risk

for relapse [21, 22] after stem cell transplants in acute lymphoblastic [23, 24] or myelogenous leukemia.

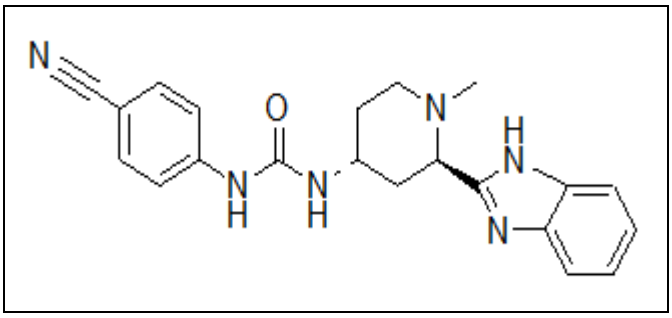

FIG. 1: STRUCTURE OF GLASDEGIB

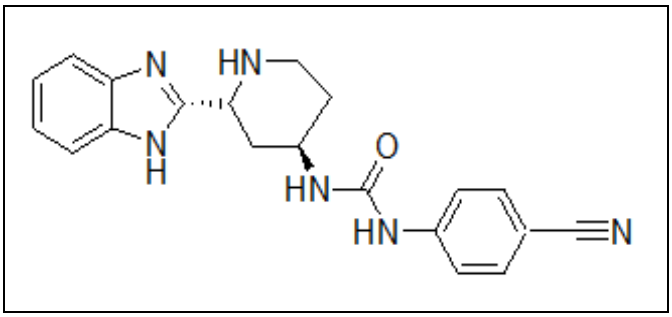

FIG. 2: STRUCTURE OF GLASDEGIB IMP-1

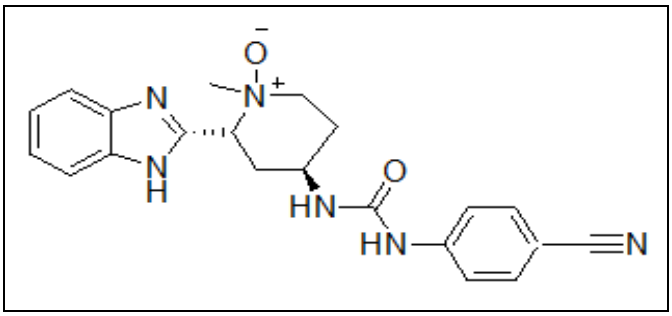

FIG. 3: STRUCTURE OF GLASDEGIB IMP-2

By the literature search, there is no article published so far for the references. The proposed method was simple and economical sensitive for the estimation of Glasdegib.

MATERIALS AND METHODS:

Materials: Acetonitrile, Ortho Phosphoric Acid (OPA), water was purchased from Merck (India) Ltd. Worli, Mumbai, India. All API's of Glasdegib as reference standards were procured from Glen mark pharmaceuticals, Mumbai.

Equipment: HPLC, make: Waters alliance e-2695 chromatographic system consisting of a quaternary pump, PDA detector-2996, and chromatographic software Empower-2.0 was used.

Chromatographic Conditions: An instrument of the HPLC system (Waters Alliance e2695 model) was used to develop the method and its validation. Empower 2.0 software was used to processing the data. The column was Waters X-Bridge C_{18} 150 × 4.6mm, 3.5µ dimensions. The main compounds and its related impurities are separated by isocratic elution. Mobile phase having 0.1% OPA, Acetonitrile in the ratio of 50: 50. The flow rate of pump was set as 1.0ml/min. The PDA detection was captured at 250nm. Injection volume fixed as 10µl and the diluent was same as the mobile phase.

Preparation of Mobile Phase:

Preparation of Buffer: 1ml of Ortho Phosphoric Acid is dissolved in 1lt of water and filtered through 0.45µ filter paper.

Preparation of Mobile Phase: Buffer: Acetonitrile (50:50)

Diluent: Mobile Phase is used as diluent.

Preparation of Solutions:

Preparation of Standard Solution: Weigh accurately 250mg of Glasdegib standard and transferred into a 100ml volumetric flask, then add 70ml of mobile phase and sonicate for 10 min. to dissolve the contents, make upto the mark with diluent. Further diluted 5ml of the above solution to 50ml with diluent.

Preparation of Sample Solution: Weigh the weight accurately equal to 250 mg equivalent weight of the formulation of the Daurismo 100mg tablet transferred to the 100ml volumetric flask, then apply 70ml of diluent and sonicate to 10min to dissolve the contents entirely and then dilute the label. 5ml of the above solution was further diluted to 50ml with diluent.

Preparation of Impurity Standard Stock Solution (10µg/ml): Weigh each 5mg of Glasdegib impurities accurately into a 100ml volumetric flask. Add 70ml of diluent, sonicated to dissolve, and makeup to the mark with diluent. Further diluted 2ml of the above solution to 10ml with diluent.

Preparation of Spiked Sample Solution: Transfer 5ml of Glasdegib sample solution into a 50ml volumetric flask, then add 30ml of diluent and also add 5ml of impurity standard stock solution and makeup to the mark with diluent. Filter through a 0.45µ syringe filter.

Wavelength Optimization: The absorption spectra of the solution of Glasdegib drug is scanned over the range of 200-400 nm by using PDA detector, and the spectra were recorded. By observing the spectrum, we can found that impurities, Glasdegib showing maximum absorbance at 250nm. Hence, 250nm is selected for method validation.

Method Validation: The analytical method was validated as per ICH Q2(R1) guidelines for the parameters like system suitability, specificity, accuracy, precision, linearity, robustness, the limit of detection (LOD), the limit of quantification (LOQ), forced degradation and stability.

System Suitability: System suitability parameters were measured to verify the system performance. The parameters including USP plate count, USP tailing, and % RSD are found to be within limits.

Accuracy: Accuracy is the closeness of the test results obtained by the method to the true value. It was assessed by the recovery studies at three different concentration levels. In each level, a minimum of three injections was given, and the amount of the drug present, percentage recovery, and related standard deviation were calculated.

Specificity: Specificity is the ability to assess the analysis unequivocally in the presence of other components (impurities, degrades, or excipients), which may be expected to be present in the sample and standard solution. It was checked by examining the chromatograms of blank samples and samples spiked with Glasdegib and Valsartan.

Precision: The precision of an analytical method is the degree of agreement among individual test results. It was studied by analysis of multiple sampling of a homogeneous sample. The precision of the present method was assessed in terms of repeatability, intra-day and inter-day variations. It was checked by analyzing the samples at different time intervals of the same day as well as on different days.

Linearity and Range: The linearity of an analytical method is its ability to obtain results directly proportional to the concentration of the analyte in the sample within a definite range. The six series of standard solutions were selected for assessing the linearity range.

The calibration curve was plotted using peak area versus concentration of the standard solution, and the regression equations were calculated. The least-squares method was used to calculate the slope, intercept, and correlation coefficient.

LOD and LOQ: LOD is the lowest amount of analyte in a sample that can be detected, while LOQ is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy. LOD and LOQ were separately determined base on the calibration curves. The LOD and LOQ for Glasdegib were determined by injecting progressively low concentrations of standard solutions using the developed RP-HPLC method. The LOD and LOQ were calculated as 3.3 s/n and 10s/n, respectively, as per ICH guidelines, where s/n indicates signal-to-noise ratio.

Stress Degradation: Stress degradation should be no interference between the peaks obtained for the chromatogram of forced degradation preparations. Stress degradation studies were performed as per ICH guidelines Q_1A (R2). The degradation peaks should be well separated from each other, and the resolution between the peaks should be at least 1.0, and the peak purity of the principle peaks shall pass. Forced degradation studies were performed by different types of stress conditions to obtain the degradation of about 20%.

Robustness: The robustness of an analytical procedure is a measure of its ability to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness study was performed by injecting a standard solution into the HPLC system and altered chromatographic conditions such as flow rate (±0.2ml/min), wavelength (±5nm), variation in pH (±0.2), organic content in the mobile phase (±10%).

The separation factor, retention time and peak asymmetry were calculated by determining the effect of the modified parameters.

Stability: Analytical solution was prepared and injecting into the HPLC system at periodic intervals of 0 h to 24 h at 6 h intervals depending on the instrument utilization and sequence of injection.

RESULTS AND DISCUSSION:

Optimization of Method and Sample Concentration: For the first chromatographic conditions selected for the method is reversed-phase HPLC with Waters X-Bridge C_{18} 150 × 4.6mm, 3.5µ column with isocratic elution. The mobile phase is a mixture of buffer and acetonitrile (50:50). The flow rate is 1.0ml/min, and the column temperature is ambient.

All impurity peaks are well separated with greater than 2 resolutions. And there are no interference peaks observed at Glasdegib and its impurities due to the blank and other excipients which are used in the tablet formulation. The spiked sample chromatogram is shown in **Fig. 4**.

The parameters of the developed and validated HPLC method are presented in **Table 1**. Recovery data and peak sharpness depend on finalized the diluent and sample concentration, and injection volumes were finalized greater threshold than the limit of quantification (LOQ). The isocratic was optimized to get the best resolution.

TABLE 1: OPTIMIZED HPLC METHOD CONDITIONS

S. no.	Parameter	Method conditions
1	Column	Waters X-Bridge C_{18} 150 × 4.6mm, 3.5µ
2	Flow rate	1.0ml/min
3	Wavelength	250nm
4	Injection volume	10µl
5	Run time	12min
6	Mobile phase	ACN+0.1% OPA (50:50)

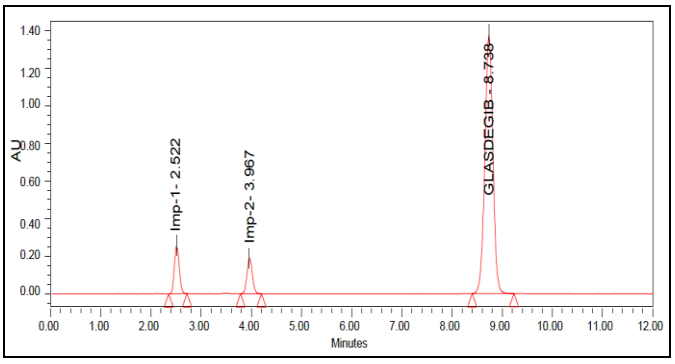

FIG. 4: TYPICAL CHROMATOGRAM OF STANDARD

System Suitability: The standard solution was introduced into HPLC system and found that system suitability parameters are within the limits. The percentage of RSD was calculated standard peak areas. The similar injections RSD percentage was observed and it is within the limit. The obtained results were presented in **Table 2** and the system suitability chromatogram was exhibited in the **Fig. 5**.

TABLE 2: SYSTEM SUITABILITY DATA FOR GLASDEGIB AND VALSARTAN

S. no.	System suitability parameter	Acceptance criteria	Drug Name Glasdegib
1	% RSD	NMT 2.0	0.23
2	USP Tailing	NMT 2.0	1.04
3	USP Plate count	NLT 3000	6105

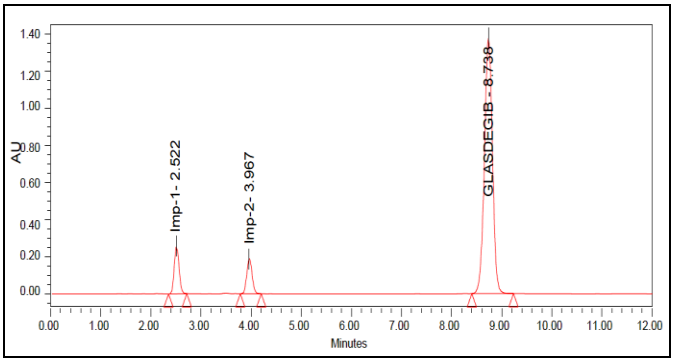

FIG. 5: TYPICAL CHROMATOGRAM OF SYSTEM SUITABILITY

Specificity: A study was conducted to establish the placebo interference. As per the test method, samples are prepared with equivalent weight of API and placebo with test concentration and then injected into HPLC system. Interference was not found for the chromatograms of placebo solution, empty cell solution, and impurities solution at the retention time of Glasdegib and its impurities.

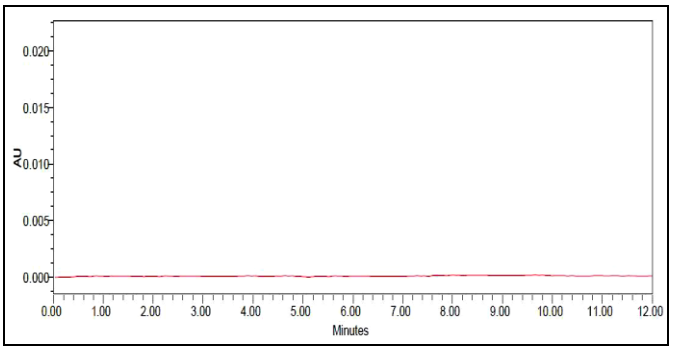

FIG. 6: CHROMATOGRAM FOR BLANK

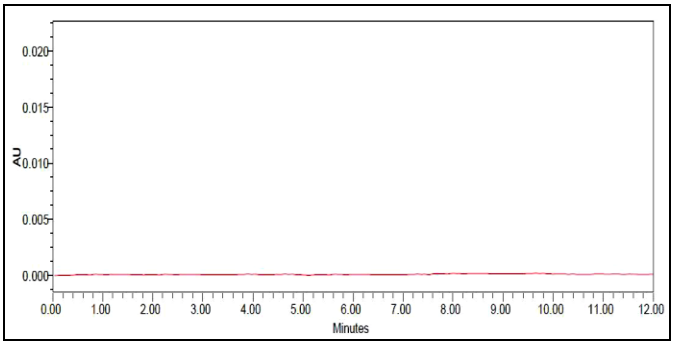

FIG. 7: CHROMATOGRAM FOR PLACEBO

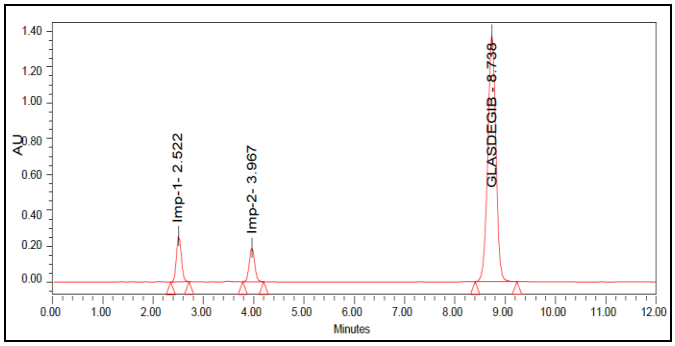

FIG. 8: CHROMATOGRAM OF STANDARD SOLUTION

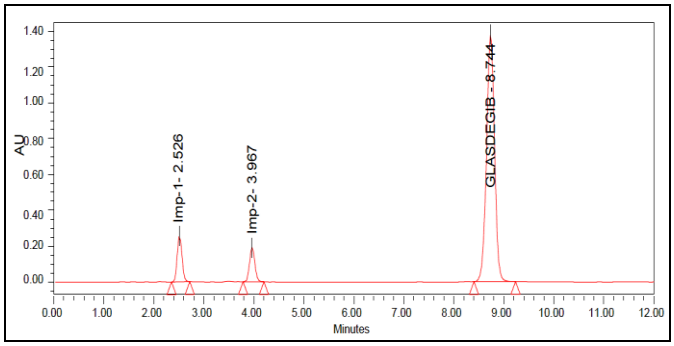

FIG. 9: CHROMATOGRAM OF SAMPLE

The typical chromatograms of specificity were shown in **Fig. 6, 7, 8,** and **9**. Interference was not found for the chromatograms of placebo solution, blank solution, and impurities solution at the retention time of Glasdegib and its impurities.

Linearity: Glasdegib linearity concentration was prepared in the range of 25µg/ml to 500µg/ml. The regression equation was found to be Y= 56253x+419330 and correlation coefficient is 0.99955. Impurity-1 concentration range from 0.1µg/ml to 2.0µg/ml, regression equation is Y= 1330061x+11521 and correlation coefficient was found to be 0.99955. Impurity-2 concentration range from 0.1µg/ml to 2.0µg/ml, regression equation is Y= 1091061x+32113 and correlation coefficient was obtained 0.99922.

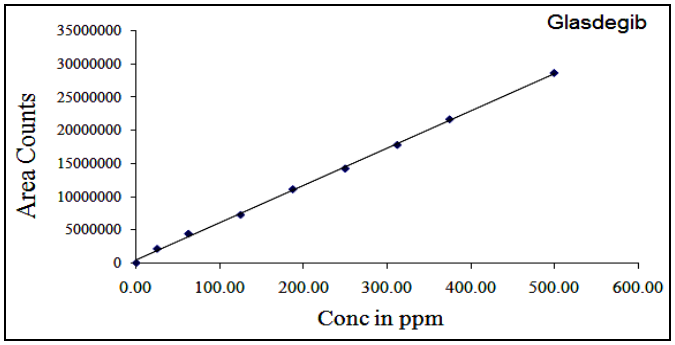

FIG. 10: LINEARITY PLOT FOR GLASDEGIB

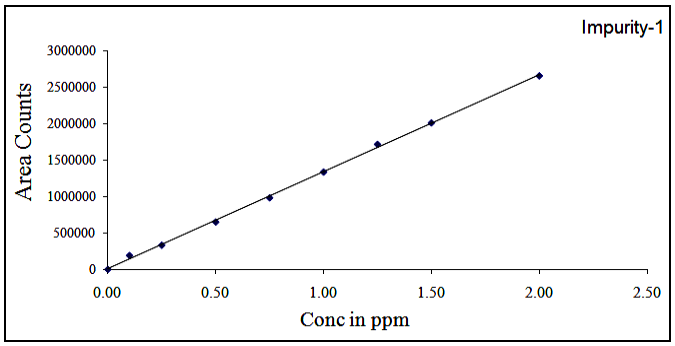

FIG. 11: LINEARITY PLOT FOR GLASDEGIB IMP-1

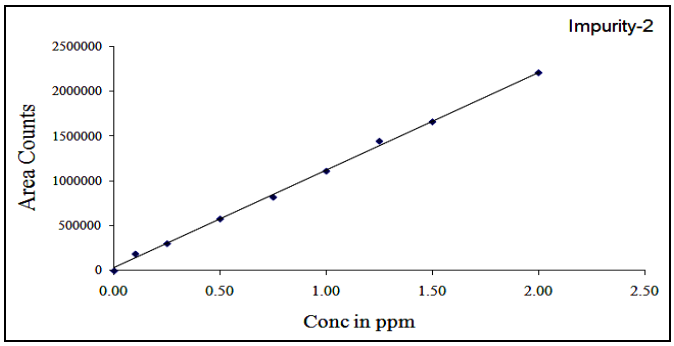

FIG. 12: LINEARITY PLOT FOR GLASDEGIB IMP-2

TABLE 3: ROBUSTNESS DATA

S. no.	Parameter name	% RSD for purity Glasdegib
1	Flow (0.8ml/min)	0.35
2	Flow (1.2ml/min)	0.29
3	Organic solvent (+10%)	0.57
4	Organic solvent (-10%)	0.48

Robustness: In Robustness, there is a small deviation in flow rate (±0.2ml) and organic solvent (±10%) in their chromatographic condition there is no significant change in RSD (%). The obtained results were presented in **Table 3**.

TABLE 4: SOLUTION STABILITY RESULTS

S. no.	Stability	Purity of Glasdegib in RT	Purity of Glasdegib in 2-8°C
1	Initial	99.5	99.8
2	6 h	99.2	99.7
3	12 h	99.1	99.3
4	18 h	98.7	98.6
5	24 h	98.4	98.3

Stability: Stability of Glasdegib was determined in sample solution was studying initial to 24 h at different time intervals at room temperature and 2-8 °C. There is no significant deviation of purity. The obtained results were listed in **Table 4.**

Precision: The method's accuracy was established by injection test preparation and tested from sample preparation to the final result through the complete experimental process. Repeatability assessed using a minimum of 6 determinations and calculated % relative standard deviation of impurities. The obtained results are tabulated in **Table 5**.

TABLE 5: PRECISION RESULTS FOR GLASDEGIB

Sample no.	% of Related Substances		
	Spiked Impurities	Total Impurities	% Purity (100-Total Imp)
1	4.89	4.89	95.11
2	4.92	4.92	95.08
3	4.97	4.97	95.03
4	4.96	4.96	95.04
5	4.98	4.98	95.05
6	4.95	4.95	95.05
Average	4.95	4.95	95.06
% RSD	0.69	0.69	0.03

Intermediate Precision: Six replicates of a sample solution were analyzed on a different day, different analysts, and different instruments. Peak areas were calculated, which were used to calculate mean, % RSD values. The obtained results were presented in **Table 6**.

TABLE 6: INTERMEDIATE PRECISION RESULTS FOR GLASDEGIB

Sample no.	% of related substances		
	Spiked Impurities	Total Impurities	% Purity (100-Total Imp)
1	4.98	4.98	95.02
2	4.95	4.95	95.05
3	4.94	4.94	95.06
4	4.99	4.99	95.01
5	5.00	5.00	95.00
6	4.98	4.98	95.02
Average	4.97	4.97	95.03
% RSD	0.47	0.47	0.03

Limit of Detection and Quantification (LOD & LOQ): LOD and LOQ were determined by the calibration curve method. LOD and LOQ of the compound were determined by injecting progressively lower concentrations of standard solutions using developed RP-HPLC method. The slope method was used for estimation of LOD and LOQ, and the equation used is LOQ= 10xσ/S and LOD= 3.3xσ/S, where S is the calibration curve slope, and σ is the standard deviation of the response. The LOD and LOQ concentrations for Glasdegib are 0.25µg/ml and 2.5µg/ml. The typical chromatogram of LOD and LOQ was shown in **Fig. 13** and **14**.

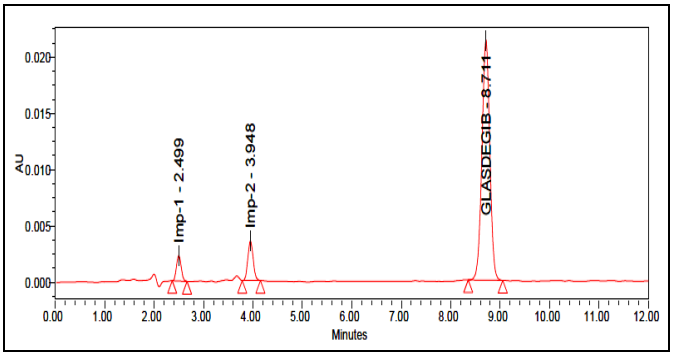

FIG. 13: CHROMATOGRAM OF LOD

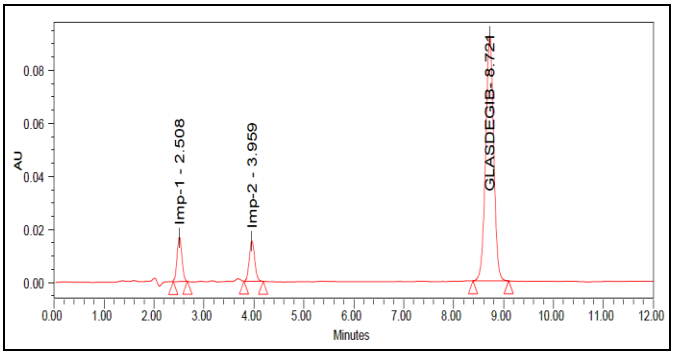

FIG. 14: CHROMATOGRAM OF LOQ

Accuracy: The accuracy of the related substances test procedure was determined by spiking of Glasdegib impurity stock solution to test the sample. So that the concentration of the impurity would be 1.0% of the test concentration as per the test method. Injecting samples in triplicate at 50%, 100% and 150% of the target concentration. The recovery results should be NLT 95% and NMT 105%. The obtained results were presented in **Table 7, 8, 9** and chromatograms were shown in the **Fig. 15, 16** and **17**.

TABLE 7: ACCURACY RESULTS FOR GLASDEGIB

S. no.	% Level	% Recovery	Ave % Recovery
1	50	98.65	98.88
2		99.12	
3		98.87	
4	100	99.89	98.79
5		99.12	
6		97.36	
7	150	99.14	98.71
8		98.63	
9		98.35	

TABLE 8: ACCURACY RESULTS OF GLASDEGIB IMP-1

S. no.	% Level	% Recovery	Ave % Recovery
1	50	98.35	98.65
2		98.47	
3		99.12	
4	100	99.35	99.12
5		99.14	
6		98.87	
7	150	99.17	99.15
8		99.54	
9		98.74	

TABLE 9: ACCURACY RESULTS OF GLASDEGIB IMP-2

S. no.	% Level	% Recovery	Ave % Recovery
1	50	99.66	99.06
2		98.78	
3		98.75	
4	100	97.65	97.27
5		97.84	
6		96.33	
7	150	98.12	98.29
8		98.42	
9		98.33	

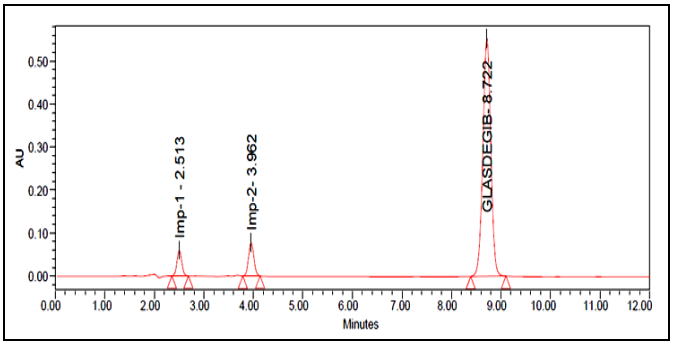

FIG. 15: CHROMATOGRAM OF ACCURACY 50%

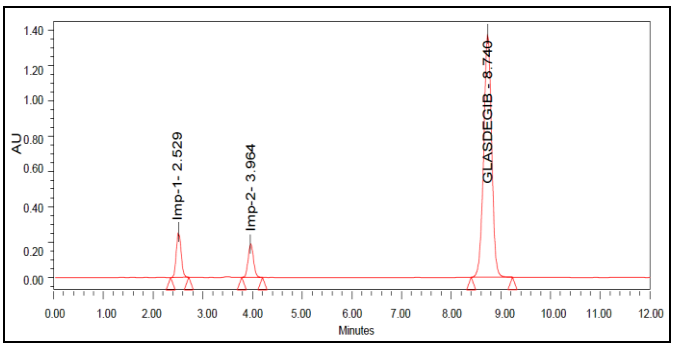

FIG. 16: CHROMATOGRAM OF ACCURACY 100%

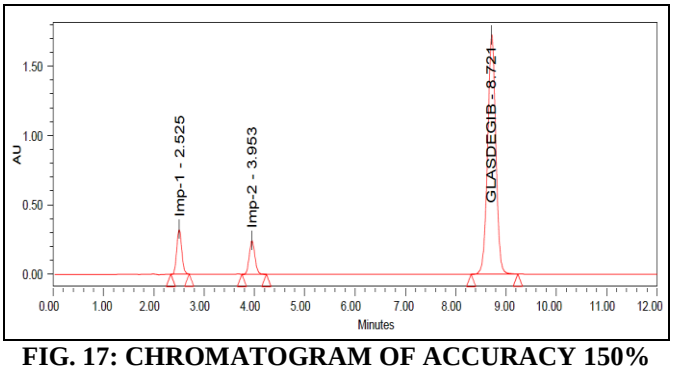

FIG. 17: CHROMATOGRAM OF ACCURACY 150%

Forced Degradation: The Glasdegib sample was subjected into various forced degradation conditions to effect partial degradation of the drug. Forced degradation studies were performed to show the method is suitable for degraded products. Moreover, the studies provide information about the conditions in which the drug is unstable so that measures can be taken during formulation to avoid potential instabilities.

Acid Degradation: 5ml of sample stock and 5ml of impurity stock solution was transferred into a 50 ml volumetric flask; add 5ml of 1N HCl heat for 15 min at 60 ºC after that, add 5 ml of 1N NaOH then makeup to mark with diluent. Then the solution is filtered through a 0.45µ nylon syringe filter.

Alkali Degradation: 5ml of sample stock and 5ml of impurity stock solution was transferred into a 50ml volumetric flask add 5ml of 1N NaOH heat for 15 min at 60 ºC; after that, add 5ml of 1N HCl then make up to the mark with diluent. Then the solution is filter through 0.45µ nylon syringe filter.

Peroxide Degradation: 5 ml of sample stock and 5ml of impurity stock solution was transferred into a 50ml volumetric flask add 5ml of 10% H_2O_2 heat for 30 min at 60 ºC, then cool to makeup with diluent. Filter the solution with a 0.45µ nylon syringe filter.

Reduction Degradation: 5ml of sample stock and 5ml of impurity stock solution was transferred into a 50 ml volumetric flask; add 5ml of 10% sodium bicarbonate solution heat for 15 min at 60 ºC then cool to makeup with diluent. Filter the solution with a 0.45µ nylon syringe filter.

Thermal Degradation: The impurity spiked sample drug solution was placed in an oven at 105 ºC for 6 h. The resultant solution was injected into the HPLC system.

UV Degradation: The impurity spiked sample solution was exposed to the sunlight for 6 h. The sample was injected into the HPLC system.

TABLE 10: RESULTS FOR FORCED DEGRADATION

Degradation Condition	% of Purity (Glasdegib)
Acid Degradation	89.4
Alkali Degradation	88.1
Peroxide Degradation	85
Reduction Degradation	82.3
Thermal Degradation	85.8
UV Degradation	84.2

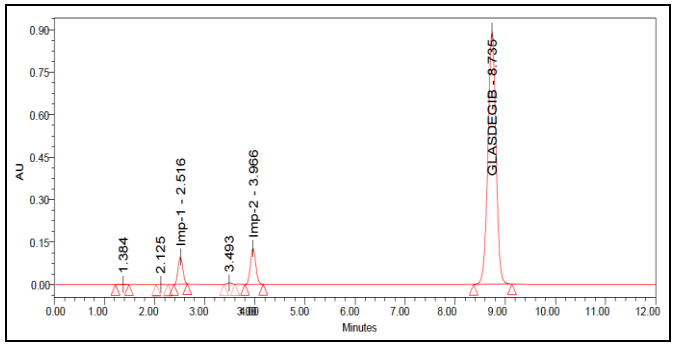

FIG. 18: CHROMATOGRAM FOR ACID DEGRADATION

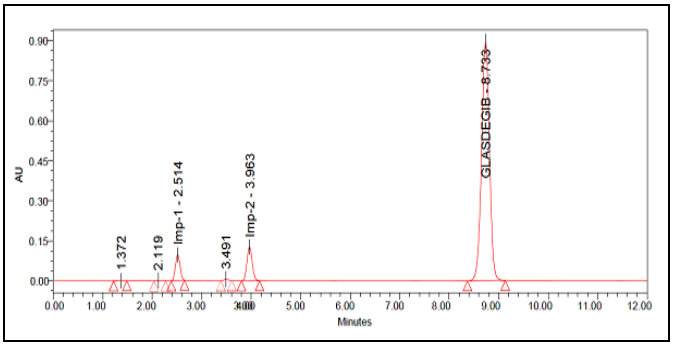

FIG. 19: CHROMATOGRAM FOR ALKALI DEGRADATION

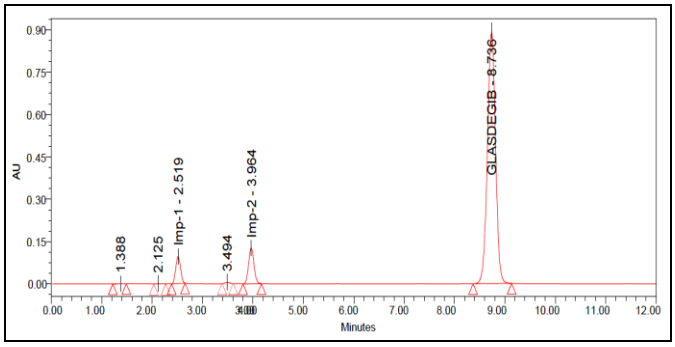

FIG. 20: CHROMATOGRAM FOR PEROXIDE DEGRADATION

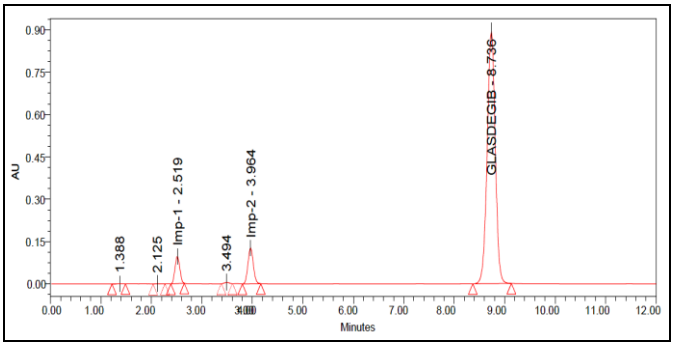

FIG. 21: CHROMATOGRAM FOR REDUCTION DEGRADATION

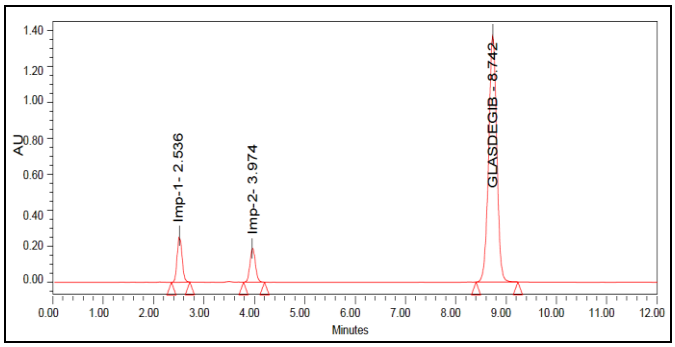

FIG. 22: CHROMATOGRAM FOR THERMAL DEGRADATION

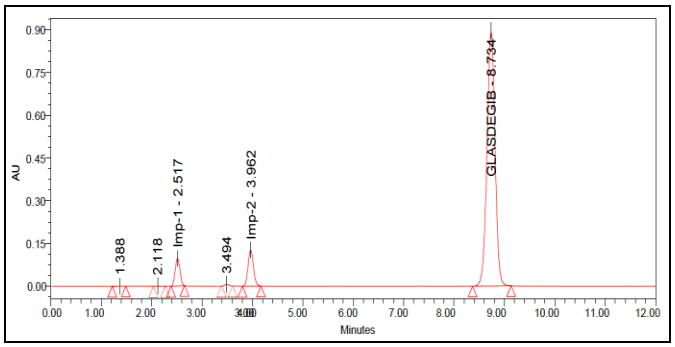

FIG. 23: CHROMATOGRAM FOR UV DEGRADATION

CONCLUSION: The developed method gave good resolution between Glasdegib and its impurities with a short runtime, high efficiency and complies with modified SST specifications of USP.

The proposed method was found to be simple, precise, accurate, linear, robust, and rapid for simultaneous determination and quantification of Glasdegib. The result of Glasdegib being subjected to different stress conditions led to the fact that it was stable during thermal condition. It degraded extensively under UV, Thermal, and Peroxide conditions. Obtained stability studies, degradation studies useful for a better understanding of Glasdegib during storage and stable formulations and contribute to the safety of Glasdegib being manufactured in pharmaceutical laboratories.

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