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A Validated Liquid Chromatographic Method for the Estimation of Imatinib Mesylate in Dosage Forms: Application to Chemometrics based Robustness Testing and Greenness Assessment

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An eco-friendly liquid chromatography method was developed for determining imatinib mesylate in pharmaceuticals. During pre-development studies, Using a greener mobile phase and a combination of qualitative and semi-quantitative green metrics techniques, the environmental sustainability of the procedure was maintained. Methanol:water (pH maintained at 3.5 using orthophosphoric acid) at 75:25%, v/v flowing at 1 mL/min was the final mobile phase used on a C-18 column. The diode array detector detected imatinib at 262 nm. Method specificity, accuracy, precision, selectivity and system suitability were tested over a linear concentration range of 5-120 µg/mL of imatinib. The limit of detection and limit of quantitation values were 1.5 and 5.0 µg/mL, respectively. In addition, the factorial design showed the procedure to be reliable with minimum testing. Finally, the method recovered the maximum (> 99%) of the analyte from the dosage form. Overall, the present method is suitable for routine applications in quality control of dosage forms of imatinib.

Keywords: Analytical eco-scale, Imatinib mesylate, Liquid chromatography, Robustness, Taguchi design.

INTRODUCTION

Imatinib mesylate (IMB) is a potent tyrosine kinase inhibitor used widely in various neoplastic conditions such as Philadelphia chromosome abnormality in chronic myeloid leukaemia and acute lymphoblastic leukaemia, gastrointestinal stromal tumours, myelodysplastic syndromes, hypereosinophilic syndrome and aggressive systemic mastocytosis [1-6]. Chemically, it is α-(4-methyl-1-piperazinyl)-32-{[4-(3-pyridyl)-2-pyrimidinyl]-amino}-*p*-toluidide methanesulfonate [7]. Since, its approval in early 2000s, this drug has been investigated using different analytical techniques such as UV spectrophotometry, infrared spectroscopy, capillary electrophoresis, gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry, *etc.* [8-15]. A special emphasis on the survey of literature based on liquid chromatography revealed that different authors had developed several methods to quantify imatinib from diverse pharmaceutical samples [16-26]. However, these methods consist of several drawbacks (Table-1). Before planning the method intent and desired performance, a valuable summary (Table-2) of the critical method validation parameters was also considered. It was quite evident from this comparison and evaluation of reported methods that none of these methods reported the green behaviour of their proposed methods. Also, none of the authors discussed the role of chemometrics in validation studies. This expands the possibilities of developing a new eco-friendly liquid chromatographic method that addresses the highlighted limitations and shines a light on the performance of method in the context of chemometrics-based designed experiments.

The chemometrics-based designed experiments utilized a Taguchi orthogonal array design. These highly fractional designs provide accurate information on the effects of method factors on the various response variables while demanding the least number of experiments. In chromatography, it is reported to screen method factors and optimize chromatography [27,28]. However, in present study, we utilized this experimental design to identify method factors that affect method robustness and

TABLE-1
A COMPARATIVE STUDY OF THE CURRENT METHODS WITH REPORTED LC METHODS

Method	Remarks	Ref.
HPLC	(1) Low sensitive linear dynamic range (2) Poor precision (3) Complex preparation of aqueous mobile phase	[16]
HPLC	(1) Highly acidic pH of mobile phase may degrade the column (2) High%RSD result for precision study	[17]
HPLC	(1) Complex preparation of mobile phase using multiple organic phases (2) Demands use of peak modifier leading to longer equilibration time	[18]
HPLC	(1) Complex preparation of mobile phase using multiple organic phases (2) Low sensitive linear dynamic range (3) Demand use of peak modifier leading to longer equilibration time	[19]
HPLC	(1) Uses higher strength of buffers	[20]
HPLC	(1) Complex preparation of mobile phase (2) Longer run time	[21]
HPLC	(1) Uses multiple organic phases (2) Demands use of peak modifier leading to longer equilibration time (3) Low sensitive linear dynamic range	[22]
HPLC	(1) Uses multiple non-green chemicals to maintain pH of mobile phase	[23]
HPLC	(1) Demands use of peak modifier leading to longer equilibration time	[25]
UPLC	(1) Complex preparation of mobile phase using multiple organic phases (2) Demands use of peak modifier leading to longer equilibration time	[26]
UFLC	(1) Sensitive linear dynamic range (2) Doesn't demand use of peak modifier (3) Avoids the use of a toxic organic solvent such as acetonitrile (4) Reliable validation study results (5) Doesn't demand temperature based separation (6) Risk assessment supported robustness study (7) SST limits establish effective method control strategy	Present study

TABLE-2
COMPARISON OF KEY VALIDATION PARAMETERS RESULTS OF CURRENT METHODS WITH REPORTED METHODS

Method	Linearity (µg/mL)	Accuracy (%)	Precision (%, RSD)	Ref.
HPLC	300-800	96.2-101.4	1.7-2.6	[16]
HPLC	10-50	100.3-101.3	1.422	[17]
HPLC	0.05-50	99.84-100.01	0.128-0.168	[18]
HPLC	19.815-29.722	100.3-101.2	0.4	[19]
HPLC	2-10	99.85	0.833-0.877	[20]
HPLC	0.5-1.2	99.6-101.3	0.2	[21]
HPLC	40-160	100.41-100.84	0.6	[22]
HPLC	10-60	99.83-101.57	0.13-1.63	[23]
HPLC	1-16	98.9-101.4	0.987-1.863	[24]
HPLC	50-150	99.79	0.74	[25]
UPLC	4-24	96.73-97.21	0.195-1.83	[26]
UFLC	5-120	99.29-100.13	0.5-0.95	Present study

derived control strategies based on the limits of system suitability parameters.

The fundamental principles of green analytical chemistry govern all types of green procedures and serve as basic guidelines [29-31]. With time, researchers have shifted their focus on developing green and eco-friendly analytical methods that are economical, safe and guard the environment. For developing such eco-friendly methods, green metric tools play a significant role. Some of such measurement approaches include National Environmental Methods Index (NEMI), analytical eco-scale (AES), Green Analytical Procedure Index (GAPI), *etc.* NEMI and AES were integrated to devise a scientifically sound analytical method in the present perspective [32-34]. Based on the above scope and the method intent, an attempt is made to develop a green reversed-phase liquid chromatographic method for quantifying imatinib mesylate (IMB) in pharmaceutical dosage forms. Afterward, the developed method was validated chemometrically as per the requirements of ICH guidance [35].

EXPERIMENTAL

The standard drug of imatinib mesylate (IMB) (purity > 99.8% w/w) was a generous gift from Dr. Reddy's Laboratories Pvt. Ltd., Hyderabad, India. The commercial formulation containing 100 mg of drug was purchased from the local chemist shop. Chromatographic grade methanol was from Merck Ltd., Mumbai, India and purified water was obtained using the TKA GenPure water Purifier from Thermo, Germany. Hydrochloric acid, sodium hydroxide, orthophosphoric acid and hydrogen peroxide were purchased from S.D. Fine Chem Ltd., India.

Chromatographic instrumentation and separation conditions: For chromatographic separation, binary gradient UFLC (Ultrafast liquid chromatography) pumps (Prominence Series, Shimadzu, Japan) equipped with a photo diode array detector (DAD) and manual injection port of capacity 20 µL was employed. A Shim-Pack C-18 column (250 mm × 4.6 mm i.d., 5 µm) was used. A pH meter (Eutech, India), ultrasonicator (GT-Sonics, China) and TKA HPLC water unit (Thermo Fisher, Germany) were also used during the study. Design Expert (Stat-Ease, Inc, Minneapolis, USA) software was used for chemometrics based designed experiment modeling and optimization data analysis.

Preparation of standard solutions: Exactly measured, 10 mg of imatinib mesylate (IMB) present in 10 mL volumetric flask was dissolved in 5 mL of methanol and shaken well prior to final volume makeup. The resultant solution concentration was found to be 1000 µg/mL. This stock solution was further used to prepare calibration solution in the range of 5-20 µg/mL of IMB. The mobile phase was used as the diluent for all the calibration dilution. The prepared solution was stored under 2-8 ºC till 72 h and its stability was assessed.

Preparation of sample solutions: Tablet samples containing 100 mg of IMB were size reduced manually and then brought to a fine state by triturating. Then, an equivalent amount of tablet powder to that of standard drug was transferred to 10 mL volumetric flask containing 5 mL of diluents and then ultrasonicated for about 45 min. Afterward, the final volume was made up and the solution was filtered through a filter (0.45 µm) and was used further to prepare the test solution within the study concentration range.

Greenness assessment: A dual approach: This specific study utilized an integrative dual assessment tool approach to investigate the method's greenness profile. Based on principles of green analytical chemistry, NEMI is a qualitative approach that assigns green shadings to a pictogram that has four separate quadrants for persistent, bioaccumulative, toxic (PBT), hazardous (H), corrosive (C) and waste (W) generating reagents and chemicals. Afterward, the use of AES ensures a vital greenness score based on penalty points (PPs) awarded for a method. A typical score of 75 and above ensures excellent green behaviour of the method [33]. The real advantage of combining two greenness assessment tools is acquiring reliable information on method eco-friendly behaviour and performance of the same over method lifecycle.

Validation protocol: Specificity depicts the capability of a method to separate analyte peaks from other possible co-eluting peaks that are either sourced from impurities or degradation products. For present study, suitable aliquots of IMB to finally produce a concentration of 40 µg/mL were exposed to degradation conditions *viz.* acid (HCl), alkali (NaOH), peroxide (H_2O_2), thermal (80 ºC) and UV radiation (365 nm) were used for a specific time to observe if any degradation products are generated and assess method specificity in the presence of them.

A series of calibrations standards were prepared in the range of 5 to 120 µg/mL of IMB and analyzed to determine the Beer's range. Also, the method sensitivity was assessed visually to establish the lowest concentrations of IMB that can produce a signal-to-noise (S/N) ratio of 3:1 for the limit of detection (LOD) and 10:1 for the limit of quantitation (LOQ), respectively.

For accuracy and precision studies, 20 µg/mL concentration of IMB was selected and studied. For checking the accuracy, 80-120% of standard drugs were added to the selected analyte concentration and their recovery was found at different concentration levels. The precision study comprised intra and inter-day investigations at the mentioned concentration levels. The relative standard deviations (RSD) were calculated for each investigation.

Robustness-cum-ruggedness and system suitability limits testing: Method robustness was studied using a 3 factor 2 level factorial design with minimal 8 runs. The three factors, methanol%, pH and flow rate, were identified using a risk estimation matrix. The half-normal plots and Pareto charts, were assessed along with the three-dimensional response surface to determine the effect of these factors on overall method robustness. Further, the system suitability results obtained during this study were utilized to derive system suitability test (SST) limits.

The SST-limit tests were performed for different system suitability parameters like retention time and plate number. A detailed discussion on the same is available elsewhere [36]. Eqn. 1 was used to derive such limits.

$$\left\{\bar{Z} - t\alpha, n-1.\left(\frac{s}{\sqrt{n}}\right)\right\} \quad (1)$$

where, $\bar{Z}$ is the average of three observations $t\alpha$, $n-1 = t_{(critical)(0.05,\ n-1\ =\ degrees\ of\ freedom)}$, s = standard deviation of three observations and n the square root of number of observations.

RESULTS AND DISCUSSION

Preliminary method development studies and greenness assessment: The pre-method development preliminary studies included confirming the solubility of analytes in different solvents, which concluded that imatinib mesylate (IMB) was soluble in methanol. Though ethanol is the first choice for green solvent for many analytical operations, factors such as its higher UV cutoff, high viscosity and production of abnormally high pressure make it less suitable for routine applications [37]. Instead, methanol was found as a greener option for reversed-phase chromatographic analysis of pharmaceuticals due to its advantages over the reported drawbacks of ethanol. Additionally, a pH 3.5 aqueous buffer phase is found to be suitable for reversed phase separation after taking into account the chemistry of analyte. The analyte possessed satisfactory system suitability values at a nominal flow rate of 1 mL/min and diode array detection at 262 nm. At a retention time of 3.591 min the drug possessed 2800 theoretical plates and a minimal peak tailing of 1.296 while the overall run time at 6 min was fixed. However, the dual qualitative and quantitative green metrics tools known as NEMI and AES were employed before further validation studies. The former approach qualitatively indicated adequate greenness by covering three quadrants of pictogram with a green shade (Fig. 1). In complement to the above, the

TABLE-3
PENALTY POINTS (PPs) FOR THE CURRENT LC METHOD

Reagents	Amount	Amount PP	Hazard	Hazard PP	Total PP[a]
(1) Methanol	< 10 mL	1	Yes	6	6
(2) Phosphate buffer	< 10 mL	1	None	4	4
Instrument		Energy			
(1) UFLC		< 0.1 kWh per sample			0
(2) Ultrasonicator		< 0.1 kWh per sample			0
(3) Vaccum filter		< 0.1 kWh per sample			0
(4) Occupational hazards		Process hermetization			0
(5) Waste		< 10 mL			3
Overall PPs: 13					
Greenness score[b]: 100-13= 87					
Remark: Excellent greenness					

[a]Total PP = Amount PP × Hazard PP; [b]Greenness score = 100 – Overall PPs.

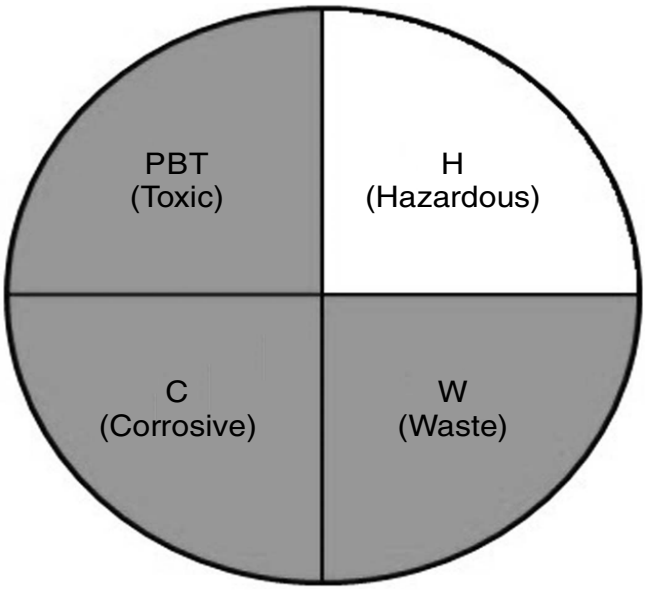

Fig. 1. NEMI oriented pictogram depicting qualitative greenness of the present method

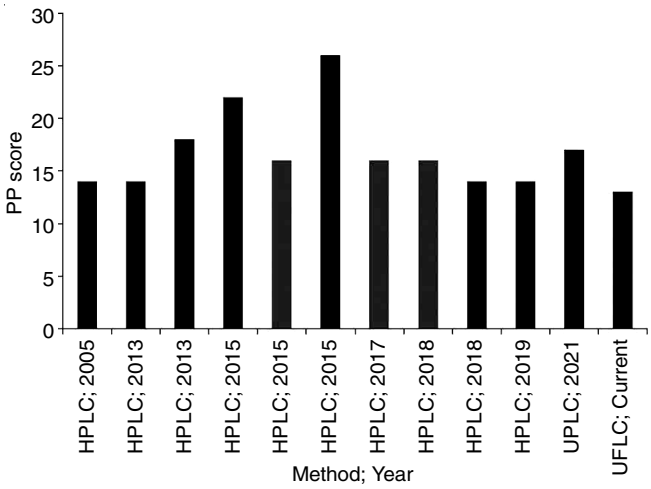

Fig. 2. A comparative assessment of penalty points scored by reported and current method

semi-quantitative AES approach assigned penalty points (PPs) to the several method reagents and instruments that may be hazardous and potentially generate larger waste proportions (Table-3). The overall greenness score (87) was above the excellent greenness level of 75 (Fig. 2). This advocated optimum method greenness compared to the reported methods (Table-4). Hence, with these satisfactory results of method greenness, the optimized chromato-graphic conditions (Table-5) were proceeded for the validation studies.

Validation studies: The results of forced degradation of IMB, revealed that the drugs degraded (Fig. 3) in all stress studies (Table-6) except exposure to UV light, where the drug was found to be relatively stable. This suggests the specificity of the developed method for the quantification of IMB. In addition, one must choose the best way to store the drug such that the analyte remains stable during administration.

The present method's linearity was found in the range of 5 to 120 µg/mL of IMB with sensitive LOD and LOQ values of 1.5 and 5.0 µg/mL, respectively. The linearity of the procedure has been justified as appropriate on the basis of regression analysis (Table-7).

TABLE-4
COMPARISON OF PENALTY POINTS (PPs) OF REPORTED LC AND CURRENT LC METHOD

Reagents PP	Instruments PP	Total PP	Chemometrics oriented validation	Ref.
13	1	14	No	[16]
13	1	14	No	[17]
17	1	18	No	[18]
21	1	22	No	[19]
15	1	16	No	[20]
25	1	26	No	[21]
15	1	16	No	[22]
15	1	16	No	[23]
13	1	14	No	[24]
17	1	18	No	[25]
17	0	17	No	[26]
13	0	13	Yes	Present study

The recovery of added standard analyte was found optimum, with average recoveries ranging between 99 to 100% (Table-7) without interference from the formulation excipients. The % RSD values were also found in agreement with the ICH guidance of values less than 2%. The lower values% RSD (Table-7) confirmed excellent method reproducibility and repeatability.

The risk estimation matrix (Table-8) identified three robustness study factors: methanol %, pH and flow rate, which were

TABLE-5
OPTIMIZED CHROMATOGRAPHIC CONDITIONS FOR BOTH THE LC METHODS

Parameter	Optimized LC conditions
Mobile phase (v/v)	Methanol: buffer (75:25)
pH	3.5
Mode of separation	Isocratic
Stationary phase	Reversed phase
Flow rate (mL/min)	1.0
Sample injection volume (µL)	20
Detection wavelength (nm)	262
Column backpressure (kgf)	168
Retention time (min)	3.5

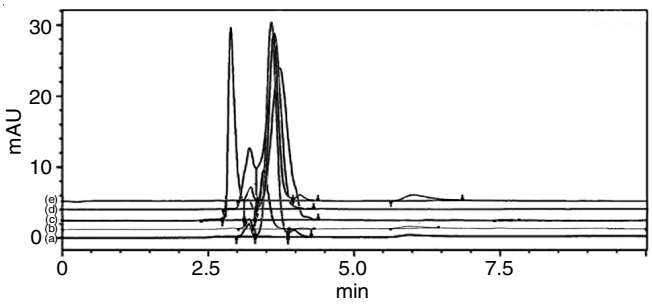

Fig. 3. Overlaid chromatograms of imatinib mesylate (IMB) treated with (a) acid, (b) alkali, (c) peroxide, (d) heat and (e) photolysis

TABLE-6
FORCED DEGRADATION DATA OF IMATINIB MESYLATE

Degradation condition/ exposure time (min)	Retention time (min)	Degradation (%)	Peak purity
0.1 N HCl/30 min	3.568	3.5	0.99987
0.1 N NaOH/30 min	3.455	8	0.99999
3% H_2O_2/30 min	3.713	4.13	0.99990
80 °C/30 min	3.629	7.56	0.99909
UV light (365 nm)/60 min	3.616	ND[c]	1.00000

[c]ND = No degradation.

TABLE-7
SUMMARY OF ANALYTICAL VALIDATION DATA

Parameter	Results obtained
Beer's range (µg/mL)	5-120
Regression equation (Y= ax + b)[d]	29064x + 60424
Correlation coefficient (R^2)	0.999
Accuracy (% recovery[e] ± S.D.)	
80%	99.6 ± 0.13
100%[f]	100.13 ± 0.32
120%	99.29 ± 0.32
Precision (% RSD[g])	
Intra-day	0.51
Inter-day	0.95
System	0.5
LOD (µg/mL)	1.5
LOQ (µg/mL)	5
Analysis of tablets (Mean[h] ± S.D.)	99.94 ± 0.06
Solution stability at 2-8 °C for 72 h (Mean[h] ± S.D.)	98.64 ± 0.41

[d]Y = ax + b; where 'Y' is response while 'a' and 'b' are slope and intercept of the line and 'x' is unknown concentration in µg/mL.
[e]Recovery of added standard from sample solution.
[f]100% level is 20 µg/mL of IMB.
[g]Mean of three determinations.
[h]n = 3.

TABLE-8
RISK ESTIMATION MATRIX WITH LEVELS OF RISK FOR VARIOUS METHOD VARIABLES

Method variables	Retention time	Theoretical plate count	Tailing factor
Methanol (%)	High	High	High
pH	High	High	High
Flow rate (mL/min)	High	High	High
Detection	High	Med	Low
Column	Med	Low	Low
Solvents	Low	Low	Med
Reagents	Med	Med	Med
Sample purity	Med	Low	Med
Calculation error	Low	Low	Low
Integration of peaks	Low	Med	Med
Error in dilution	Low	Low	Med
Error in glassware	Low	Low	Low

slightly varied to a high and a low level (Table-9). A study of diagnostics plots (Fig. 4a-b) revealed that pH and flow rate interacted, out of which flow rate contributed the maximum effect on analyte retention. Furthermore, the three-dimensional response (Fig. 5a) obtained depicted a gradual decrease in retention behaviour of IMB with increasing flow rates. In case of plate number count for IMB, the diagnostics (Fig. 4c-d) show the interaction between methanol% and pH while a typical "saddle" shaped response surface (Fig. 5b) derives the same conclusion. Further, SST limits were derived (Table-10) using eqn. 1 and helped to establish the control limits for the studied factors.

TABLE-9
RESULTS OF ROBUSTNESS STUDY USING TWO-LEVEL FACTORIAL DESIGN FOR THE DEVELOPED LC METHOD

A: Methanol (%)	B: pH	C: Flow rate (mL/min)	X1: Retention time (min)	X2: Plate number
73	3.3	0.9	4.068	2210.87
73	3.7	0.9	4.121	2473.88
73	3.3	1.1	3.58	2220.12
77	3.3	1.1	3.159	2754.14
77	3.7	0.9	4.092	2406.62
73	3.7	1.1	3.461	2658.19
77	3.3	0.9	3.462	2388.92
77	3.7	1.1	3.354	2201.56

TABLE-10
SYSTEM SUITABILITY TEST RESULTS OBTAINED FOR IMB

S. No.	Retention time (min)	Plate number
Mean	3.923	2301.623
(n)	3	3
S.D.	0.29	149.25
Obtained value[i]	3.420	2050

[i]Utilizes eqn. 1 as described under results and discussion

The assay method efficiently separated the analyte from the sample matrix with a % recovery of more than 99% (Table-5). The chromatogram of sample (Fig. 6b) solution was well in agreement with that of the standard drug (Fig. 6a). Higher recovery of analyte in the presence of excipient matrix revealed the method selectivity and aptness for routine application.

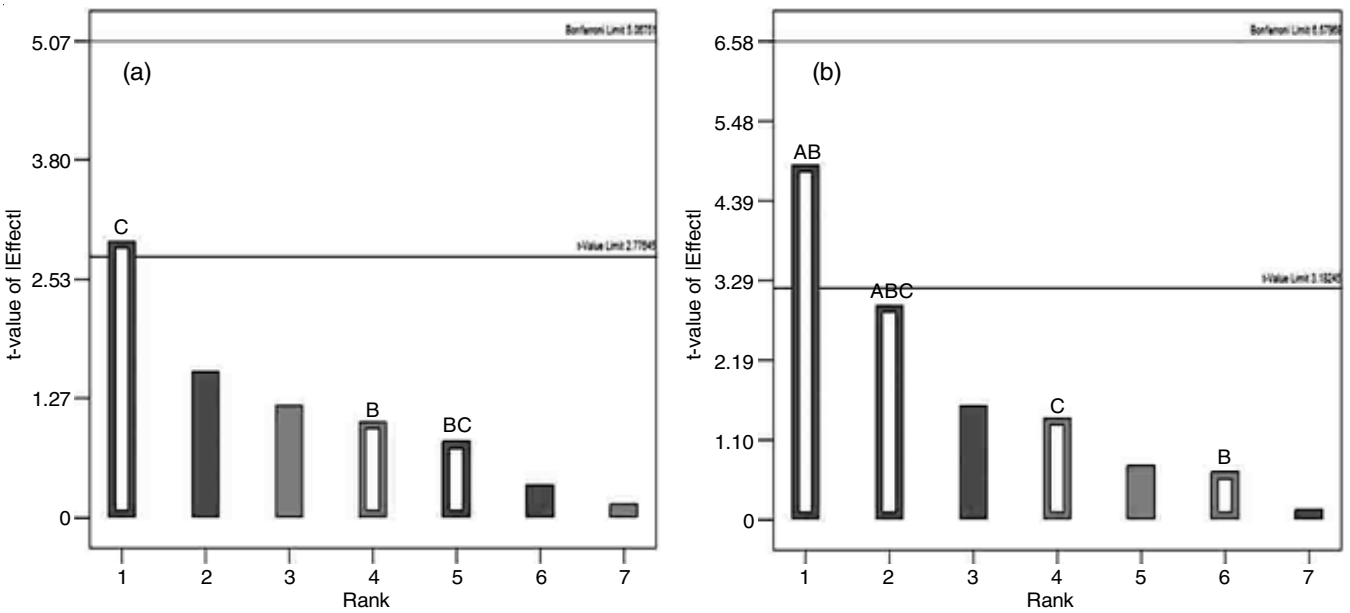

Fig. 4. Pareto charts depicting effect of method factors on method robustness attributes like (a) retention time and (b) plate number

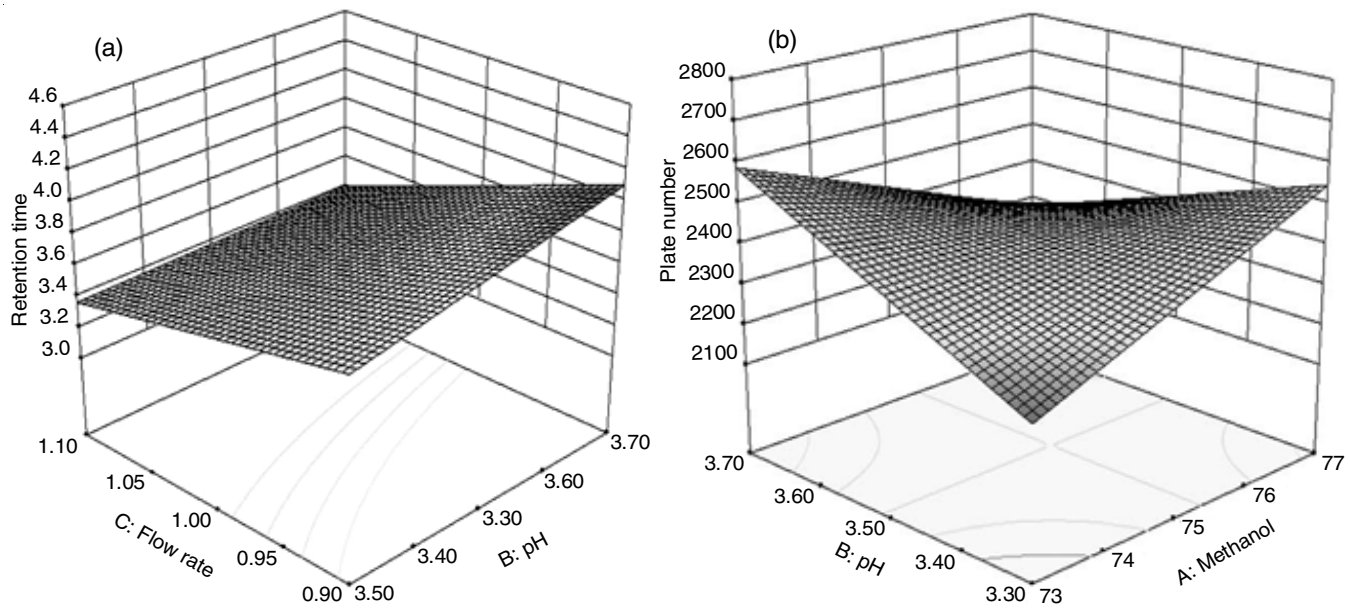

Fig. 5. Three-dimensional response surface plots obtained for (a) retention time and (b) plate number of imatinib mesylate (IMB)

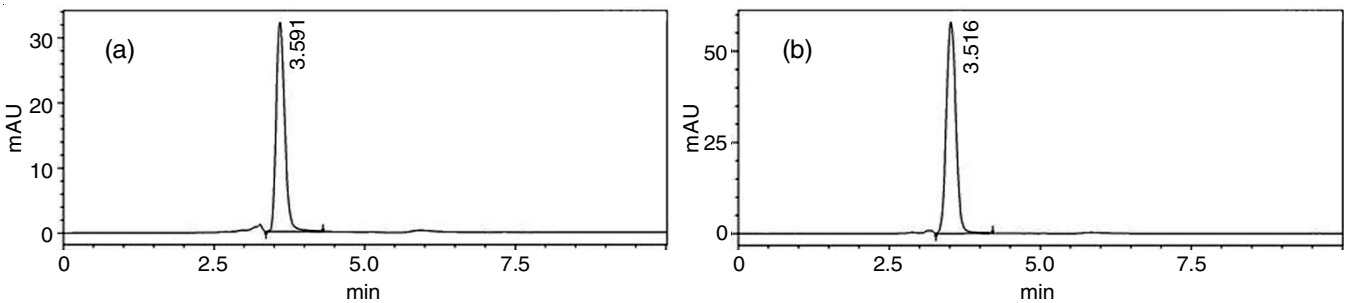

Fig. 6. Typical chromatograms of (a) standard imatinib mesylate (IMB), (b) sample solution containing imatinib mesylate (IMB)

Conclusion

A stability-indicating green liquid chromatographic method was developed and validated as per the ICH requirement for quantifying imatinib mesylate (IMB) from the commercial dosage form. The developed method was ecofriendly, with high greenness scores than earlier reported methods. Furthermore,

the forced degradation results revealed the stability feature and the specific nature of the proposed method. The designed experiment-based rapid robustness study disseminated valuable information on the method's response to deliberate factorial changes. Also the method efficiently recovered IMB from the commercial dosage form. In short, it is concluded that the developed chromatographic method is more advantageous than the reported methods and can be routinely used for quality control of pharmaceutical dosage forms of IMB.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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