Original Article

Design of Experiment Mediated Development of Stability Indicating High Performance Thin Layer Chromatography Method Invoking Failure Mode Effect Analysis Based Risk Assessment in Estimation of Edoxaban Tosylate Monohydrate

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ABSTRACT

Aim: Development of stability indicating high performance thin layer chromatographic method for quantification of edoxaban tosylate monohydrate in its pharmaceutical dosage form using quality by design approach. **Methods:** Degradation was performed in acidic, alkaline, neutral, oxidative and photolytic conditions. Analytical target profile was identified, based on which failure modes were identified by brainstorming session and preliminary trials. Each failure mode was assigned a risk priority number based on its severity and detectability. Identified potential method variables were further screened by Taguchi OA design. 3^2 full factorial design was applied for optimization of critical factors. The developed analytical method was validated using the Q2R1 guideline of the International Council for Harmonization. **Results:** In acidic, alkaline, and oxidative environments, the substance was shown to be degraded. After failure mode analysis, seven factors were found potential for estimation as it shows high risk priority number (RPN). Two important method variables, the volume of modifier and migration distance, were screened using screening design from these seven components. For the estimation of edoxaban tosylate monohydrate, the response surface model created design space and a control strategy was devised. Method found to be accurate, precise, and linear, with detection limit 1.021 ng/band and quantification limit 3.095 ng/band. **Conclusion:** Using methanol-ethyl acetate-triethylamine (6:4:0.2, v/v) as mobile phase on silica gel GF_{254} plate, described method was effectively employed for estimation of edoxaban tosylate monohydrate in its tablet dosage form.

Key words: Edoxaban tosylate monohydrate, Stability indicating High Performance Thin Layer Chromatography, Failure mode effect analysis, 3^2 full factorial design, Design of experiment.

INTRODUCTION

Edoxaban tosylate monohydrate (Figure 1) acts by dose-dependent inhibition of prothrombin to thrombin conversion. It is used to treat pulmonary embolism and deep vein thrombosis.[1-6]

In six sigma quality improvement initiatives, Failure Mode Effect Analysis (FMEA) is now increasingly extensively employed in industry. In two notable objections of the traditional FMEA approach, first one, according to measurement theory, the Risk Priority Number (RPN) used to rank failure modes is an erroneous measure, and the second is, RPN does not weigh the three decision criteria used in FMEA. FMEA is a preventative measure and a systematic

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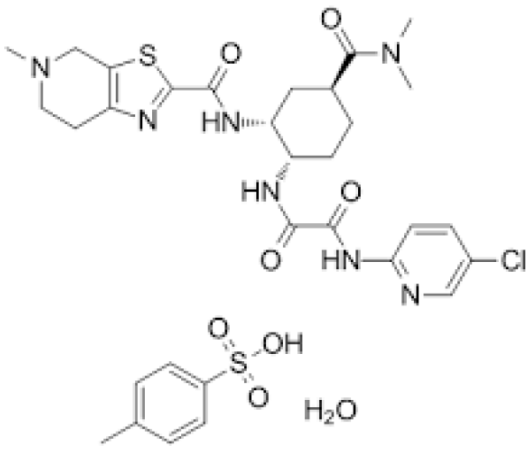

Figure 1: Chemical structure of edoxaban tosylate monohydrate.

procedure to identify process failures ahead of their occurrence, with goal of eliminating or reducing the risk associated with them. To put it another way, FMEA is proactive, methodical way to recognize potential for design to fail and its rectification.[7-11]

Design of experiments (DoE) is an important part of Quality by Design and a tried-and-true characterization method for product and process development. Recently, there has been a greater focus on applying DoE to analytical methodologies. Method development for new or improved techniques, method validation, and measurement of the influence of analytical methods on product and process acceptance are three key uses of DoE for analytical methods.[12,13]

A thorough review of the literature revealed spectrophotometric and chromatographic methods for estimating edoxaban tosylate monohydrate, although none of the degraded products were entirely separated. Few stability indicating HPLC methods were found with gradient elution technique.[14-22] From literature search it was found that no analytical method has been developed for estimation of edoxaban tosylate monohydrate using HPTLC method hence, The purpose of this study is to use a QbD approach with FMEA and DoE tools to establish a stability-indicating analytical method for estimating edoxaban tosylate.

MATERIALS AND METHODS

Chemicals and Reagents

Cadila Pharmaceuticals in Ahmedabad provided the reference standard, edoxaban tosylate monohydrate. All other chemicals and reagents were of analytical grade, and the mobile phase solvents, methanol, ethyl acetate, and triethylamine, were purchased from Rankem (Delhi, India). The sample tablet Savaysa (30 mg, Daiichi Sankyo, Inc.) was purchased from local market.

Instrumentation

The method was created utilizing an CAMAG HPTLC system (Switzerland) that included a spotting device, scanner, twin-trough chamber (10 ×10 cm) and a syringe.

Preparation of standard solutions

Edoxaban tosylate monohydrate (10 mg) was accurately weighed into a 10 mL volumetric flask, dissolved and diluted to mark with methanol. Further, one mL was transferred to 10 mL volumetric flask and diluted with methanol. Aliquot (0.4 mL) was diluted further to produce a 4 µg/mL solution.

Preparation of sample solutions

Acidic condition: To five mL aliquot of standard stock solution, 5 mL 0.2 M HCl was added. The solution was heated to 80°C for one hour. One mL aliquot of the aforementioned solution was neutralized with 0.4 M NaOH and methanol was added upto 10 mL. Further dilution was made to obtain a solution with a strength 25 µg/mL.

Alkaline condition: To five mL aliquot of standard stock solution, 5 mL 0.1 M NaOH was added. The solution was heated to 80°C for one hour. One mL aliquot of the aforementioned solution was neutralized with 0.2 M HCl and methanol was added upto 10 mL. Further dilution was made to obtain a solution with a strength 25 µg/mL.

Oxidative condition: To five mL aliquot of standard stock solution, 5 mL 6 percent H_2O_2 was added. The solution was heated to 80°C for one hour. One mL aliquot of the aforementioned solution was diluted to 10 mL with methanol. Further dilution was made to obtain a solution with a strength 25 µg/mL.

Photolytic condition: Edoxaban tosylate monohydrate, accurately weighed 10 mg, was exposed to direct sunlight for 8 hr. The sample was then transferred to a 10 mL volumetric flask, dissolved and diluted to mark with methanol. One mL aliquot of the aforementioned solution was diluted to 10 mL with methanol. Further dilution was made to obtain a solution with a strength 25 µg/mL.

Dry heat condition: Edoxaban tosylate monohydrate, accurately weighed 10 mg, was kept in oven at 100°C for four hours. The sample was then transferred to a 10 mL volumetric flask, dissolved and diluted to mark with methanol. One mL aliquot of the aforementioned solution was diluted to 10 mL with methanol. Further

dilution was made to obtain a solution with a strength 25 µg/mL.

Identification of failure modes

Various preliminary trials were carried out to identify probable failure mode in method development. Solvents in different proportions were tried to see their effect on separation between degradation product and drug, Methanol, ethyl acetate, and triethylamine were shown to be useful in improving separation and keeping the spot intact. Other methodological and instrumental failure modes, such as mobile phase volume, slit width, band width, saturation time, drying time, and so on, were also tested to see how they affected spot resolution. The identified parameters as failure modes through preliminary trials and scientific knowledge were then structured and categorized through fishbone diagram (Ishikawa diagram) for further analysis. (Figure 2).

Failure mode effect analysis

The occurrence, severity, and detectability of failure modes classified in the fishbone diagram were investigated further for method development. FMEA was carried out by multiplying each detected risk factor's score of occurrence, severity, detectability by RPN. Score for occurrence and severity was given by examining the influence on resolution and compactness of the spot at very low (2), low (4), medium (6), high (8), and very high (10) levels. Score for detectability was assigned to each factor by detection of failure very certainly (2) to very uncertainty (10) scale. According to this scale each failure mode was analyzed and a graph of failure mode versus RPN was plotted for better identification of critical factors affecting stability indicating HPTLC method development (Figure 3).

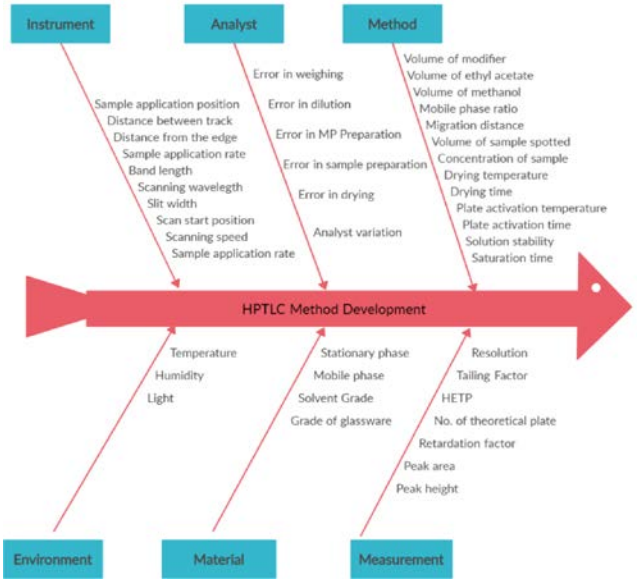

Figure 2: Fishbone diagram showing risk factors affecting HPTLC method development.

Identification of critical method parameters (CMP) and critical quality attributes (CQA) by Taguchi OA

Identified seven potential method parameters with high RPN were further taken to screening design Taguchi OA and analyzed at two levels to determine method parameters that affect the method development process critically (Table 1). In the laboratory, eight experimental runs were done in triplicate as advised by the metrics, and

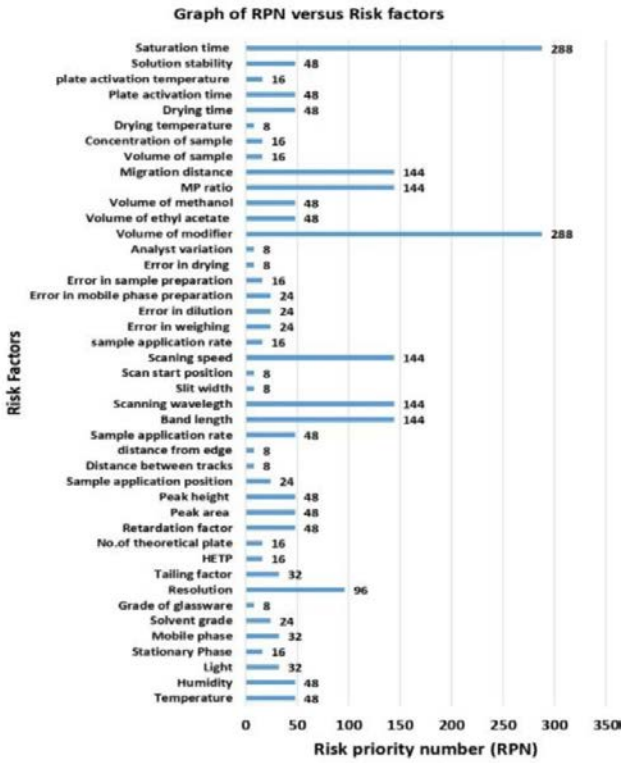

Figure 3: Graph of RPN versus risk factors for quality risk assessment.

Table 1: Potential risk factors and their levels for Taguchi OA.

Potential method parameters	Levels	
	Level-1	Level-2
Factor-A: Volume of modifier	0.1 mL	0.3 mL
Factor-B: Volume of mobile phase	8 mL	12 mL
Factor-C: Saturation time	15 min	45 min
Factors-D: Migration distance	70 mm	80 mm
Factor-E: Band length	4 mm	8 mm
Factor-F: Detection wavelength	293 nm	297 nm
Factor-G: scanning speed	10 nm/sec	20 nm/sec

Table 2: Design metrics of Taguchi OA.

Run	Factors							Responses in terms of resolutions		
	A	B	C	D	E	F	G	1	2	3
1	0.3	8	45	70	8	293	20	0.249	0.238	0.156
2	0.3	12	15	70	8	297	10	0.256	0.206	0.16
3	0.1	8	15	80	8	297	20	0.183	0.172	0.081
4	0.1	12	45	80	8	293	10	0.181	0.186	0.081
5	0.3	12	15	80	4	293	20	0.278	0.268	0.18
6	0.1	12	45	70	4	297	20	0.153	0.155	0.056
7	0.3	8	45	80	4	297	10	0.282	0.271	0.184
8	0.1	8	15	70	4	293	10	0.151	0.15	0.05

the findings of resolution between degradation product and drug were recorded against the corresponding experimental runs. (Table 2).

Response surface modelling by 3^2 full factorial design

Modifier volume and migration distance were recognized as critical risk factor in the screening design, while resolution-3 was indicated as a critical method attribute. To establish relationship between CMP and CMA, 3^2 complete factorial design was utilized, in which two critical method parameters were examined at three levels to determine their impact on critical method attributes. (Table 3). Thirteen experimental runs were done in triplicate in the laboratory as advised by the design metrics, and the findings were placed against the appropriate experimental runs and analyzed for relationships. (Table 4).

Table 3: Critical risk factors and their levels for 3^2 full factorial design.

Factors	Levels		
	+1	0	-1
Volume of modifier	0.1 mL	0.2 mL	0.3 mL
Migration distance	70 mm	75 mm	80 mm

Table 4: Design metrics of 3^2 full factorial design.

Run	Volume of modifier (mL)	Migration distance (mm)	Resolution-3
1	0.2	75	1.383
2	0.3	80	2.104
3	0.1	80	1.323
4	0.1	75	0.704
5	0.2	70	0.938
6	0.2	75	1.331
7	0.1	70	0.563
8	0.2	75	1.366
9	0.2	75	1.484
10	0.3	75	1.546
11	0.3	70	1.046
12	0.2	75	1.419
13	0.2	80	1.864

Validation of response surface model

Five solutions were chosen from a variety of recommended solutions by the design expert program with desirability 1 and tested. By comparing actual response value to anticipated values, the model was validated.

Optimized chromatographic condition

On silica gel $60F_{254}$ plate, chromatographic separation was done. The Linomat V semi-automatic spotter was used to spot samples on plates at 15 mm above the base with 6 mm band width and 0.1 µl/s application rate. The plate was developed in a twin trough chamber at 25 ± 2°C and relative humidity 35±5%, with methanol-ethyl acetate-triethylamine (6:4:0.2, v/v/v) as the mobile phase, chamber saturation time 30 min, and migration distance 80 mm. TLC Scanner IV and winCAT software were used to scan and analyze the TLC plate, with the following parameters: slit dimension 4 × 0.45 mm; scanning speed 20 mm/sec.

Preparation of calibration curve

Aliquot of 5, 10, 15, 20, and 25 µL of edoxaban tosylate monohydrate working standard solution (4 µg/mL) were spotted to get concentration of 20, 40, 60, 80, and 100 ng/band, respectively. According to chromatographic conditions, the plate was created, dried, and analyzed. Peak area vs relative concentrations of edoxaban tosylate monohydrate were plotted to generate the calibration curve.

Analysis of forced degraded sample

Volume of 30 µL was applied to the plate from each forcibly deteriorated sample solution. As specified under chromatographic conditions, the plate was developed and analyzed at 295 nm.

Method validation

The method's specificity, linearity, recovery, precision, sample application and measurement repeatability were all tested. Limits of detection (LOD) and quantitation (LOQ) were also established. The method's specificity was determined by examining standard drug and commercial formulations. By comparing R*f* and UV spectra of sample and standard, the band for edoxaban tosylate monohydrate in the sample was confirmed. Linearity was ascertained by regression analysis over the range 20 to 100 ng/band. On a single plate, repeatability of the spotter and scanner was tested with a concentration of 60 ng/band and results were expressed as a percentage RSD. Precision was established over the calibration range by examining the solutions three times on the same day and on different days. Spiking the standard edoxaban tosylate monohydrate with a pre-analysed sample at a level of 80, 100 and 120 percent in triplicates was used to test the method's recovery. The method's LOD and LOQ were established using equations.[23]

Assay of marketed formulation

Tablet powder of edoxaban tosylate monohydrate, equivalent to 10 mg was accurately weighed and transferred to a 10 mL volumetric flask, which was filled with few mL of methanol, sonicated for ten minutes, diluted to the mark with methanol and filtered. One mL aliquot of aforementioned solution was diluted to 10 mL with methanol. Further, aliquot 0.4 mL was diluted to 10 mL with methanol. The resultant solution was applied in triplicate in a volume of 15 µL on the TLC plate, followed by development and scanning under optimal chromatographic conditions. The amount of edoxaban tosylate monohydrate present in sample solution was calculated using regression line equation.

RESULTS AND DISCUSSION

Analytical target profile (ATP) and critical quality attributes (CQA)

The analytical target profile for estimating edoxaban tosylate monohydrate was set with a resolution of more than 1.5 across all degradation products and drug. Resolution between degradation product and drug was selected as critical quality attributes for development of robust analytical method.

Preliminary trials for failure mode identification

From the preliminary trials and scientific knowledge more than thirty risk factors were assorted in different categories like material, instrument, environment, method and analyst which can affect the resolution between drug and different degradation products. All the risk factors are depicted in a fishbone diagram for further analysis of risk factors.

Failure mode effect analysis

Failure mode effect analysis was performed by allotting RPN to each risk factor. Each factor was scored for its occurrence, severity and detectability. RPN was decided by multiplying the score of occurrence, severity and detectability. Graph of RPN versus failure mode was also plotted for better understanding. Risk factors having RPN more than 60 were identified as potential for robust method development. RPN greater than 60 was identified in seven risk parameters, including modifier volume, mobile phase volume, saturation time, migration distance, band length, detection wavelength, and scanning speed. The impact of the seven risk variables identified on important quality attributes was investigated further.

Output of screening design by Taguchi OA

Screening was performed using potential risk factors found during FMEA. The primary effects of all seven risk factors on essential quality parameters were investigated using the Taguchi OA screening design. At two separate levels, volume of the modifier, volume of the mobile phase, saturation time, migration distance, band length, detection wavelength, and scanning speed were all examined. After analysis by Taguchi OA the design shows model F values 1347.27, 45.83 and 1343.45 for resolution-1 (between drug and oxidative degradation product), resolution-2 (between drug and acid degradation product) and resolution-3 (between drug and alkaline degradation product) respectively. The model p-values less than 0.05 indicates that the model is significant for all three responses. *P*-values of volume of modifier and migration distance below 0.05 indicates that these two risk factors significantly affect the resolutions. Other risk factors; volume of mobile phase, saturation time, band length, detection wavelength and scanning speed were not found critical as the p-value for these factors is above 0.05 (Table 5). The Pareto chart for each response also shows that volume of modifier and migration distance are significant model terms as bars of these two factors are

Table 5: ANOVA table of Taguchi OA.						
Source	**Sum of Squares**	**df**	**Mean Square**	***F* Value**	***p*-value Prob > F**	
ANOVA for Resolution-1 (between drug and acid degradation product)						
Model	0.021	2	0.011	1347.27	< 0.0001	significant
A-Volume of Modifier	0.020	1	0.020	2485.95	< 0.0001	
D-Migration Distance	1.65×10^{-3}	1	1.65×10^{-3}	208.60	< 0.0001	
Residual	3.96×10^{-5}	5	7.92×10^{-6}			
Cor Total	0.021	7				
ANOVA for resolution-2 (between drug and oxidative degradation product)						
Model	0.016	2	7.76×10^{-3}	45.83	0.0006	significant
A-Volume of Modifier	0.013	1	0.013	75.52	0.0003	
D-Migration Distance	2.73×10^{-3}	1	2.73×10^{-3}	16.15	0.0101	
Residual	8.47×10^{-3}	5	1.69×10^{-4}			
Cor Total	0.016	7				
ANOVA for resolution-3 (between drug and alkaline degradation product)						
Model	0.023	2	0.011	1343.45	< 0.0001	significant
A-Volume of Modifier	0.021	1	0.021	2525.95	< 0.0001	
D-Migration Distance	1.35×10^{-3}	1	1.35×10^{-3}	160.95	< 0.0001	
Residual	4.20×10^{-5}	5	8.40×10^{-6}			
Cor Total	0.023	7				

above the line of significance (Figure 4, 5 and 6). The results of each experimental run shows that resolution-1 and resolution-2 were above 1.5 in each experimental run while resolution-3 shows values below 1.5. Hence, resolution-3 was found critical for stability indicating method development and selected as critical quality attribute for further analysis.

Response surface modeling by 3^2 full factorial design

Risk factors found critical in screening design were further taken to optimization design to check its relationship and effect on resolution-3. 3^2 full factorial design was used for response surface modeling as it provides metrics with least number of experimental runs and provides maximum information for a given number of critical method parameters at three levels. The ANOVA table shows model *F*-value 74.92 and *p*-value less than 0.05 which indicates that quadratic model is significant. Both main effects and one square effect were found significant as p-value is less than 0.05 (Table 6). The model shows following mathematical model in terms of actual factors.

Resolution-3 = +10.28 + 0.69 * Volume of Modifier - 0.340 * Migration Distance + 0.14 * Volume of Modifier

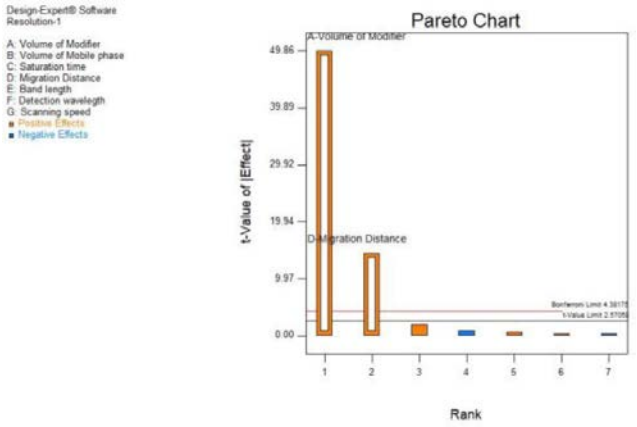

Figure 4: Pareto chart for screening design of resolution-1.

* Migration Distance - 20.90 * Volume of Modifier^2 + 2.68×10^{-3} * Migration Distance^2

The mathematical model that was finally employed for optimization after ignoring insignificant model terms is shown below.

Resolution-3 = - 6.89 + 10.85 * Volume of Modifier + 0.09 * Migration Distance - 18.35 * Volume of Modifier^2

The model lack of fit *F*-value 3.06 implies that the lack of fit is insignificant and there is only 11.95% chance that this much large value could occur due to noise. The

results predicted by the model is in good agreement with actual values as the predicted R squared 0.900 and the adjusted R squared 0.954 are in reasonable agreement and the difference is below 0.2. Contour plot of volume of modifier and migration distance is shown in Figure 7.

Validation of response surface model

The proposed model is robust, since modest variations in factors within the design space reflect that resolution is similar to that of anticipated values, indicating a stronger

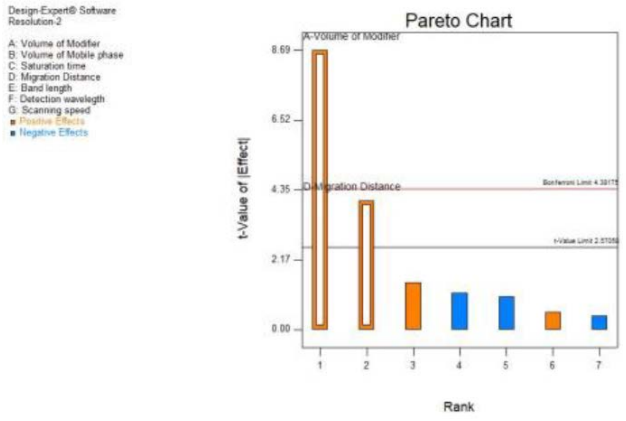

Figure 5: Pareto chart for screening design of resolution-2.

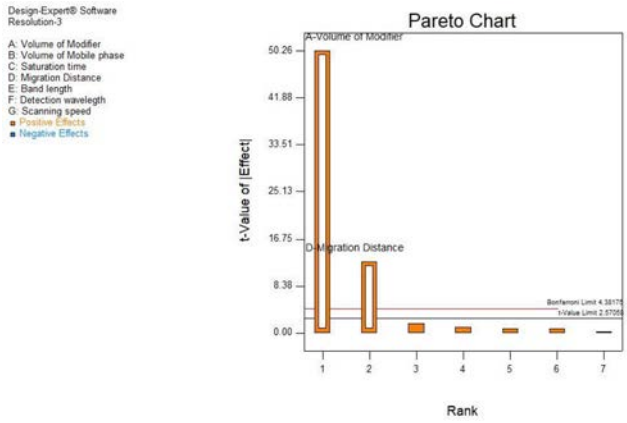

Figure 6: Pareto chart for screening design of resolution-3.

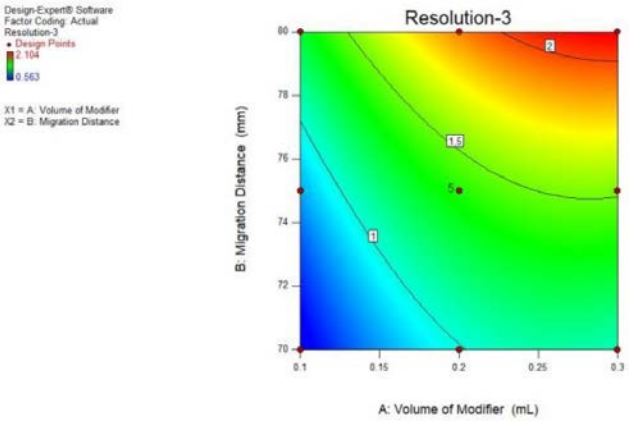

Figure 7: Contour plot of volume of modifier and migration distance.

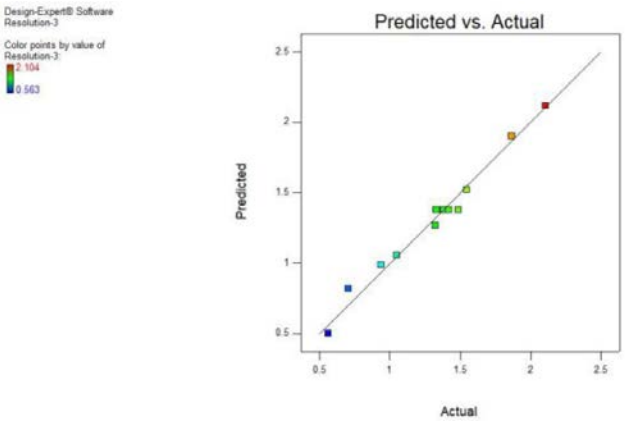

Figure 8: Graph showing predicted versus actual resolution.

Table 6: ANOVA table for 3^2 full factorial design.

Source	Sum of Squares	df	Mean Square	*F* Value	*p*-value Prob > F	
Model	2.14	5	0.43	74.92	< 0.0001	significant
A-Volume of Modifier	0.74	1	0.74	129.54	< 0.0001	
B-Migration Distance	1.25	1	1.25	219.91	< 0.0001	
AB	0.022	1	0.022	3.89	0.0892	
A^2	0.12	1	0.12	21.15	0.0025	
B^2	0.012	1	0.012	2.17	0.1842	
Residual	0.040	7	5.70×10^{-3}			
Lack of Fit	0.026	3	8.79×10^{-3}	2.59	0.1899	not significant
Pure Error	0.014	4	3.39×10^{-3}			
Cor Total	2.18	12				

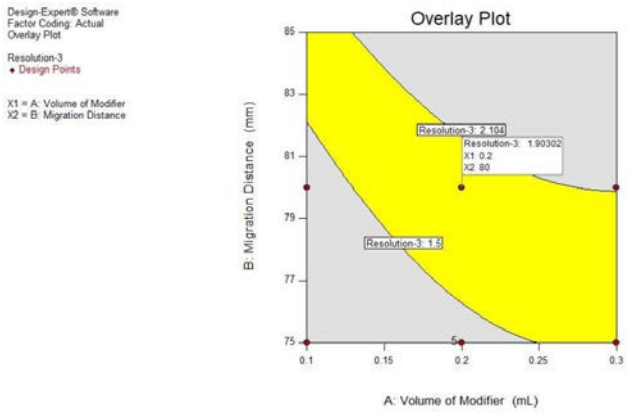

Figure 9: Design space for resolution 1.5 as per analytical target profile.

Table 7: Control strategy.	
Method variables	**Operating range**
Volume of modifier	0.2 mL
Migration distance	80 mm
Saturation time	30 min
Band length	6 mm
Detection wavelength	295
Scanning speed	20 nm/sec
Volume of mobile phase	10 mL

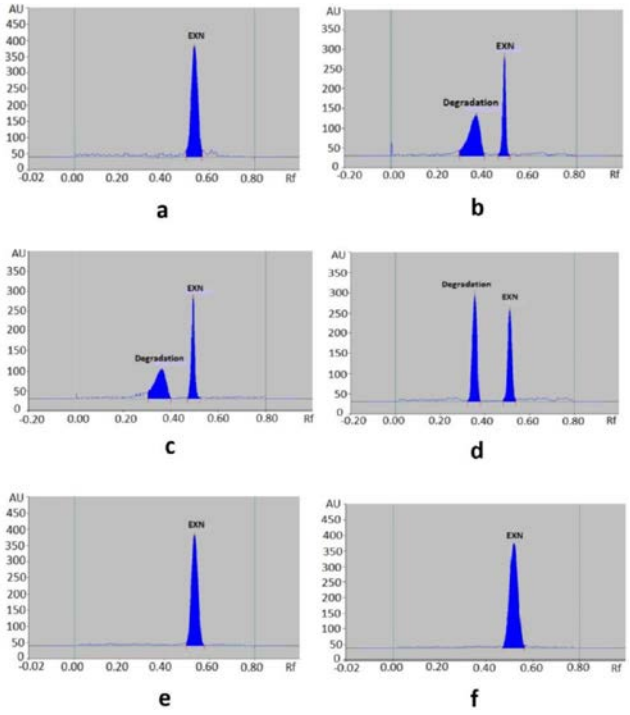

Figure 10: Densitogram of a) Standard edoxaban tosylate monohydrate b) edoxaban tosylate monohydrate acid degradation c) edoxaban tosylate monohydrate alkaline degradation d) edoxaban tosylate monohydrate oxidative degradation e) edoxaban tosylate monohydrate photolytic degradation f) edoxaban tosylate monohydrate dry heat degradation.

correlation between predicted and experimental values. (Figure 8).

Design space and control strategy

Design space has been developed after validating the model (Figure 9). Working in this design space will always give resolution above 1.5. Control strategy has been developed by deciding optimized chromatographic conditions to get resolution above 1.5 between drug and alkaline degradation products and to get reproducible results (Table 7).

Analysis of forced degraded sample

The drug was tested under various stress conditions and found unstable in acidic, alkaline, and oxidative degradation conditions, producing one degradation product in each with R_f of 0.37, 0.37, and 0.42, respectively. In dry heat, photolytic degradation conditions, the drug was shown to be stable. As no additional peak of degradation product is observed in these conditions without decrease in peak area of drug (Figure 10). The purity of corresponding spots is confirmed by peak purity of the dry heat, photolytic degradation sample. Table 8 displays the percentage degradation data.

Method validation

When chromatograms of standard and test samples of edoxaban tosylate monohydrate were compared, R*f* values of 0.53±0.02 (*n*=3) were found to be equal. Excipients and other components in the synthetic mixture had no effect on edoxaban tosylate monohydrate separation. The UV absorbance spectra of individual spots edoxaban tosylate monohydrate scanned at peak start (s), peak apex (m), and peak end (e) positions exhibited high degree of correlation, verifying the purity of the relevant spots. The method was linear in the range of 20 to 100 ng/band with regression coefficient of 0.9984. The percent RSD for sample application and sample measurement repeatability was determined to be 1.03 and 0.44, respectively, indicating that the method was repeatable. The method was found to be precise, with percent RSDs ranging from 0.42 to 1.67 for inter-day precision and 0.37 to 1.60 for intra-day precision, respectively. The accuracy findings reveal a good recovery, with recoveries ranging from 99.5 to 100.61 percent. Table 9 shows a summary of the validation parameters.

Table 8: Results of force degradation study.

Sr. no.	Stress type	Stress conditions	% Degradation
1	Acid hydrolysis	0.1 M HCl at 80°C for 1 hr	58.40 %
2	Alkaline hydrolysis	0.05 M NaOH at 80°C for 1 hr	74.12 %
3	Oxidative degradation	3% H_2O_2 at 80°C for 1 hr	37.89 %
4	Photolytic degradation	Direct sunlight for 8 hr	0.21 %
5	Dry heat Degradation	Dry heat at 110°C for 4 hr	0.5 %

Table 9: Summary of analytical method validation.

Sr. no.	Parameters	Results
1 2	Linearity Range Regression equation	20-100 ng/band y = 27.66x + 346.4
3	Regression co-efficient (R^2)	0.9984
4	Precision (%RSD) Repeatability of sample measurement Repeatability of sample application Intermediate precision (%RSD) Intra-day precision (n=3) Inter-day precision (n=3)	 0.44 1.03 % 0.37-1.60 % 0.42-1.67 %
5	% Recovery	99.5-100.61
6	Limit of Detection (LOD)	1.021
7	Limit of Quantification (LOQ)	3.095

Assay of marketed formulation

The assay value varied between 99.86 –100.03% of label claim. The chromatogram shows an edoxaban tosylate monohydrate peak at R_f of 0.51 with no extra peak, indicating that excipients did not interfere with edoxaban tosylate monohydrate quantification. The method was successfully applied to the development of an HPTLC method for estimating edoxaban tosylate monohydrate in commercial formulations.

CONCLUSION

A QbD based stability indicating HPTLC method is developed for assay of edoxaban tosylate monohydrate in its tablet dosage form applying quality risk assessment and design of experiment. Literature survey shows various analytical methods developed for estimation of edoxaban tosylate monohydrate but method development using HPTLC was lacking in estimation. Implementation of AQbD is current need for robust analytical method development. Hence AQbD approach is used in HPTLC method development for estimation of edoxaban tosylate monohydrate. By preliminary analysis and expert review >30 risk factors have been identified and categorized using a fishbone diagram which may affect the analytical method development and alter the results. FMEA concept has been applied to identify potential method variables that can affect method development and RPN number has been allotted to each risk factor. Seven factors having RPN>60 were selected for further analysis and applied for screening to identify method variables that affect the potential quality attributes critically. Potential quality attributes were also screened to identify the critical quality attributes whose response is critically affecting the analytical target profile. Screening found three critical method parameters, which were then put through response surface modelling to see how they related to critical method features. Quadratic model for response surface modeling was found significant. Method operable design region (MODR) was selected, working in which always gives resolution above 1.5. Based on MODR, optimized chromatographic condition was decided for stability indicating HPTLC method development. The developed approach was then validated using the ICH Q2 R1 guidelines and found to be specific, accurate, precise, and repeatable. The method was applied on tablet dosage form.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AQbD: Analytical Quality by Design; **ATP:** Analytical Target Profile; **CMP:** Critical Method Parameters; **CQA:** Critical Quality Attributes; **DoE:** Design of Experiment; **FMEA:** Failure Mode Effect Analysis; **HPTLC:** High Performance Thin Layer Chromatography; **ICH:** International Council for Harmonization; **Taguchi OA:** Taguchi Orthogonal Array.

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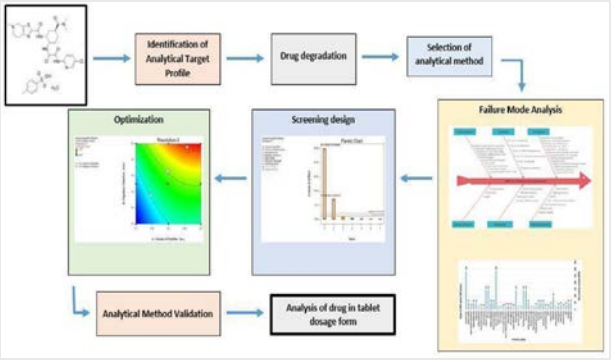
SUMMARY

The current study looks at how to use design of experiment (DoE)-based failure mode effect analysis (FMEA) as part of quality by design (QbD) in the development of a high performance thin layer chromatographic (HPTLC) method for quantifying edoxaban tosylate monohydrate in its pharmaceutical dosage form. The drug was found to be degraded in acidic, alkaline, neutral, oxidative, and photolytic circumstances, with acidic, alkaline, and oxidative situations being the most common. Multiple risk factors (failure modes) were found, categorised, and depicted in a fishbone diagram after brainstorming sessions and pilot trials. Number of risks to be prioritised RPN was tasked with categorising failure modes based on their severity, occurrence, and detectability. As a result of high RPN, seven risk factors were identified as having potential for estimation. Seven potential method factors were identified and then evaluated to find key method variables. Through a 3^2-factorial response surface design, the correlations between critical method variables and critical analytical attributes were found. For the estimation of edoxaban tosylate monohydrate, a design space was produced from the response surface model by model optimization and a control strategy was devised. The method was validated using the Q2R1 guideline from the International Council for Harmonization (ICH) and was effectively used for estimation of edoxaban tosylate monohydrate in tablet dosage form.

PICTORIAL ABSTRACT



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