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Application of Quality by Design (QbD) Approach in Degradation Study of Nisoldipine

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ABSTRACT

The critical parameter affecting potency, purity, and safety of a drug is its stability. While developing any formulation of API it is necessary to identify stability requirements. In forced degradation study drug is subjected to severe chemical and environmental conditions. Degradation products formed are helpful for the determination of breakdown levels, preliminary degradation kinetics, and can be used to assess the inherent stability of the drug and to determine storage conditions as well as packaging requirements. The application of QbD is based on the identification of critical quality attributes. In the degradation study of Nisoldipine strength, quantity and time of exposure to degradation agent which will affect degradation in hydrolytic, oxidative, thermal, and photolytic conditions were identified and optimized like for acid hydrolysis 1ml 0.01N HCl, for alkaline hydrolysis 2ml 0f 0.01N NaOH and oxidative degradation 1ml of 0.01% H_2O_2 was found to be optimized strength and quantities to get degradation in the range of 5-20% as per ICH guidelines.A simple, precise, accurate, and stability-indicating UV-method has been developed and validated as per ICH guidelines for estimation of Nisoldipine and its degradation products simultaneously. The λmax was found to be 237 nm, Beer's range was found to 5-45µg/ml.

1. INTRODUCTION

In the process of product development, one of the major steps is to carry out force degradation study. It provides information about possible degradation pathways and the intrinsic stability of the drug. Forced degradation involves the application of stressful conditions that are much more severe than accelerated conditions which increase the rate of natural degradation. These degradation products are used to study the stability of a drug molecule.[10]For the study, the development of an analytical method is done whereby drug and its degradation product can be simultaneously determined. The degradation products are going to act as impurity and are bound to affect the safety and efficacy of the pure drug. Though the degradation product or impurities are going to present in a very small amount, some of them are considered to cause carcinogenicity, genotoxicity, or cytotoxicity. In the case of patients diagnosed with diabetes or hypertension, for the rest of his life, he/she is going to be on medication, the patient is going to get exposed to impurities for a prolonged period. Hence, regulatory authorities like ICH, USFDA are insisting for providing impurity profile as well as purity requirement of drug substance.[6]

QbD is "a systematic approach applied in the development of process or method, that begins with predefined objectives and emphasizes, understanding and controlling of factors needed for quality risk management".[3] Application of QbD will result in a process that consistently gives an intended performance which is predetermined with the well understood product. In present work related to forced degradation study critical quality attributes related to force degradation, as well as analytical method development, have been optimized to get more accurate reproducible results. During the development of the UV spectroscopic method or carrying out forced degradation study involving Acid, Alkali, oxidative, thermal, and photolytic degradation QbD approach has been applied in the form of identifying strength, quantity, and time required for getting degradation product in a predefined range as per ICH guidelines. While developing an analytical method, validation is done using ICH guidelines due to which results are obtained in greater accuracy and precision. The application of QbD has added further components of making the process of force degradation and developed method more accurate and precise.

2. MATERIAL AND METHODS

2.1 Instruments

A Shimadzu UV spectrophotometer (UV1800 Shimadzu) with spectra management software and 10 mm cuvettes made up of quartz was used for spectral measurements.

2.2 Material

A sample of Nisoldipine was obtained as a gift sample from Emcure Pharmaceuticals Pvt. Ltd Pune, India. Analytical graded methanol, Hydrogen peroxide, hydrochloric acid, and sodium hydroxide were purchased from fissure scientific, Mumbai, and Merck Laboratory, Mumbai.

2.3 Solvent

Analytical grade Methanol was used as a solvent.

2.4 Stock solution

A standard stock solution containing 100 µg/ml of Nisoldipine was prepared from which aliquots for preparation of required concentrations were withdrawn and appropriate dilution was carried out.

2.5 Determination of wavelength of maximum absorption

For the selection of analytical wavelengths, a solution of Nisoldipine having concentration30µg/ml was prepared and scanned in the range of 200- 400 nm against a blank solution of methanol. The λmax of the drug for spectral analysis was found to be 237nm. (Figure. no.1)

2.6 Preparation of calibration curve

By using standard stock solutions, different aliquots were withdrawn and dilutions were done. All the solutions were screened at a fixed wavelength of 237nm. It was observed that Nisoldipine follows Beer's law in a range of 5- 45µg/ml.

3. VALIDATION OF DEVELOPED METHOD

3.1 linearity study:

For linearity, some aliquots of standard Nisoldipine were prepared in different concentrations in the range of 10-50 µg/ml. The aliquots were analyzed on UV and absorbance was recorded for all the peaks. Then by plotting concentration versus absorbance, the calibration curve for Nisoldipine was obtained. (Table No.1 Figure. No. 2)

3.2 Accuracy:

The accuracy of the method was determined by performing a recovery study with different concentrations of drugs at three levels, i.e. 80%, 100%, and 120%. After the UVanalysis percentage recovery of the pure drug was calculated from the difference between absorbance obtained. [2]The results and mentioned in Table No. 2.

3.3 Precision:

Precision was performed by using six replicates of the standard solution of Nisoldipine. For those different concentrations, on the same day were analyzed and the values of relative standard deviation (R.S.D.) were calculated to determine intra-day precision. On the same set determination of inter-day precision was also carried out. [2]The results are mentioned in Table No.3 & 4.

3.4 Robustness:

Robustness was carried out within the same laboratory the same instrument by changing analyst and wavelength. [2]The results are mentioned in Table No.5.

4. DEGRADATION STUDY

For the force degradation study, the stock solution of Nisoldipine having a concentration of 100µg/ml was prepared. The QbD approach was applied in the form of determination of critical quality attributes like strength, volume, and time of exposure to various reagents used in the degradation study. All of the critical quality attributes were identified and optimized.

4.1 Acid degradation study using hydrochloric acid:

The 3 ml of stock solution of Nisoldipine was exposed to different volumes, the concentration of acid, and the time interval. The volumes used were 0.5, 1, 1.5, and 2 ml while the strengths

used were 0.01 N, 0.1N, and 1N of HCl. The time interval used was 30 minutes, 1hr, 1.5hr, and 2hr at room temperature. The samples were exposed to 237nm. The strength, volume, and time for acid degradation study using HCl were found to be 0.01N, the volume of 2ml, and a time interval of 30 minutes. The degradation product was obtained in the range as per ICH guidelines. The results are mentioned in Table No. 6 & Fig. No 4.

4.2 Base degradation study using sodium hydroxide:

For base degradation also the same procedure as that used in acid degradation was carried out. The results of degradation are presented in Table No.7 Fig No 5.

4.3 Oxidative Degradationusing hydrogen peroxide:

By using the same procedure as acid degradation, an oxidative degradation study was carried out. The results are mentioned in Table No.8 Fig No 6.

4.4 Thermal degradation:

A solid drug sample was placed in an oven at 100˚c. The sample was collected after 1, 2, 3….6 hours. The solution containing 30 µg/ml concentrations were prepared. The absorbance was recorded at 237nm. Results are presented in Table No.9 Fig No 7.

4.5 Photolytic degradation:

The photochemical stability of the drug was studied by exposing solid drugs placed in the Petri plate to UV light in the UV cabinet for 2 and 4 days. The solution having 30 µg/ml concentration was prepared. The absorbance of the sample was recorded at 237nm. Results are presented in Table No.10 Fig No 8.

5. RESULT

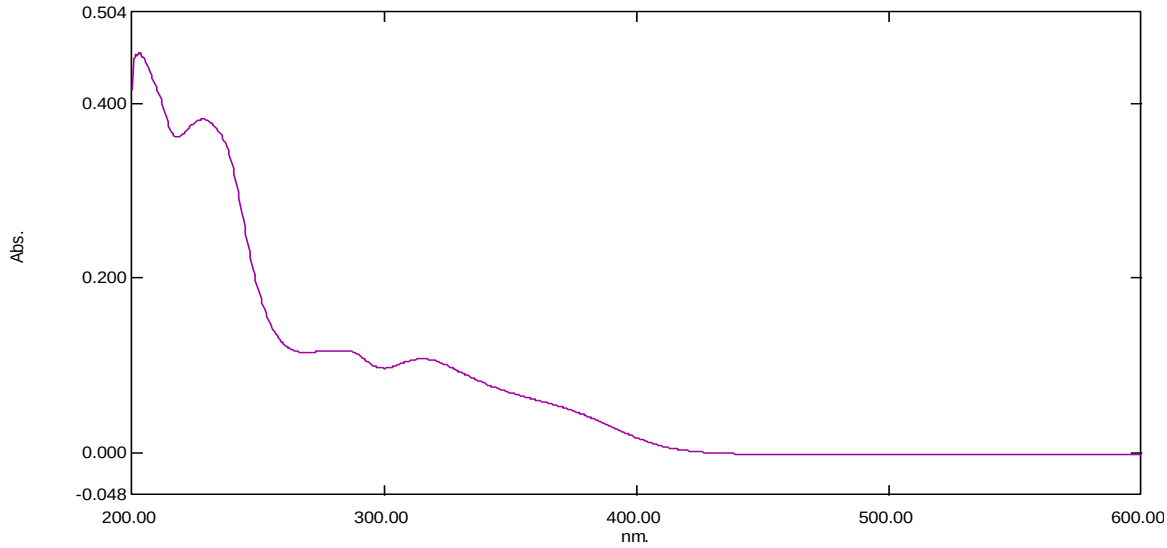

Figure No. 1: UV spectra of Nisoldipine at 237 nm

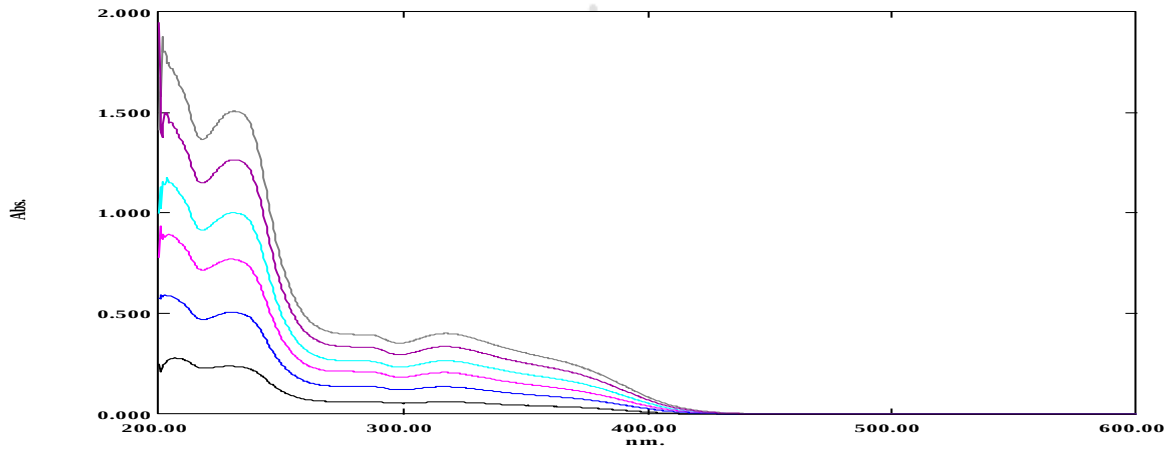

Figure No. 2

Table No. 1: Linearity of Nisoldipine

CONCENTRATION (µg/ml)	ABSORBANCE(nm)
5	0.094
10	0.284
15	0.535
20	0.847
25	1.122
30	1.456

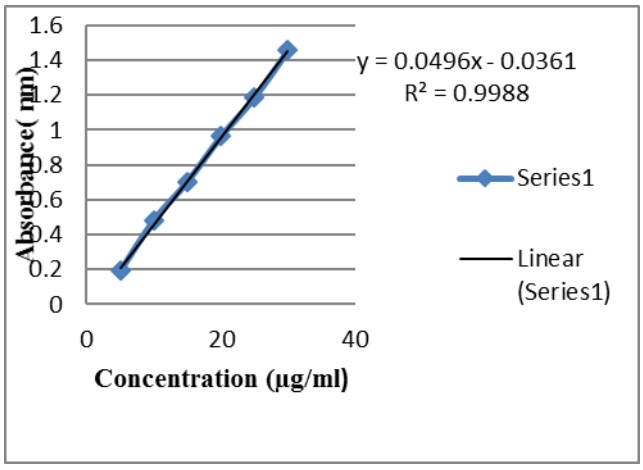

Figure No. 3: Linearity graph of Nisoldipine

Table No. 2: Accuracy of Nisoldipine

Sr. No.	% Drug Solution	% Drug Concentration			% RSD
1	80	75.40	76.5	76.84	0.009872
2	100	92.08	93.51	92.12	0.008797
3	120	102.76	104.40	103.83	0.008032

Table No. 3: Intra-day precision of Nisoldipine

Sr. No.	Time	% Drug Concentration			% RSD
1	Morning	88.63	89.78	89.55	0.006813
2	Afternoon	90.49	91.43	90.72	0.005392
3	Evening	93.63	93.29	94.13	0.019714

Table No. 4: Inter -day precision of Nisoldipine

Sr. No.	Time	% Drug Concentration			% RSD
1	Morning	85.72	85.61	86.15	0.003325
2	Afternoon	87.54	86.92	87.23	0.003554
3	Evening	90	89.39	89.77	0.003434

Table No. 5: Robustness of Nisoldipine

Sr. No.	Analyst	% Drug Concentration			% RSD
1	1	92.25	93.74	93.97	0.010006
2	2	95.19	94.14	95.00	0.005903

Table No. 6: Acid Degradation of Nisoldipine

Sr. No.	Concentration (µg/Ml)	Normality of HCl	Vol. of HCl	% Of Degradation
1	30	0.01 N	1ml	16.89
			2ml	19.29
2		0.1 N	1ml	24.03
			2ml	25.86
3		1 N	1ml	34.06
			2ml	44.78

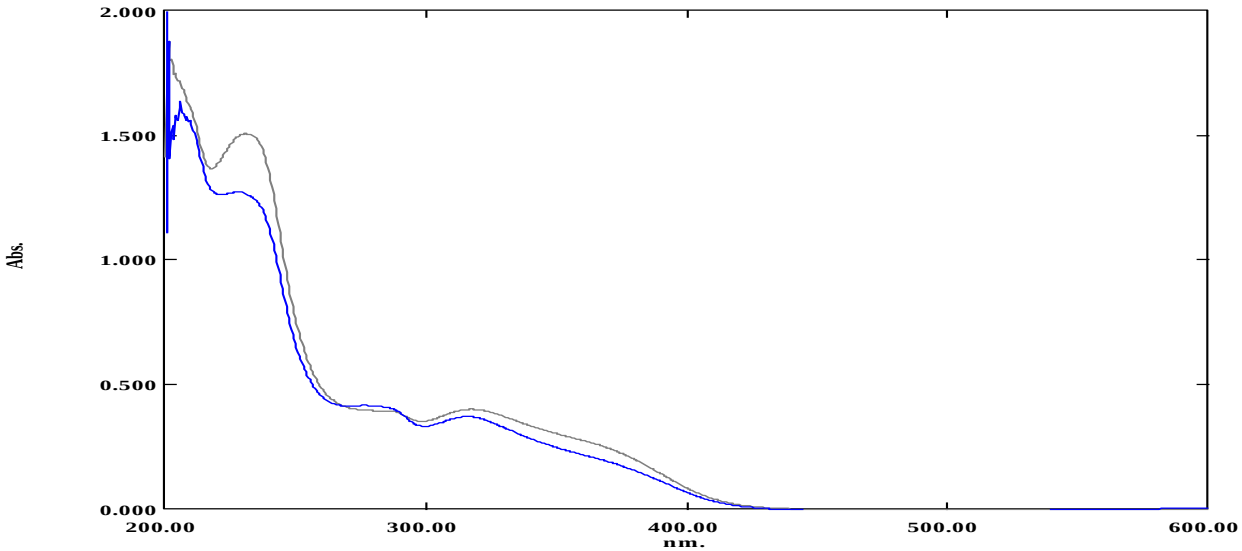

Figure No. 4: Acid Degradation of Nisoldipine

Table No. 7: Base degradation of Nisoldipine

Sr. No.	Concentration (µg/ml)	Normality Of NaOH	Vol. of NaOH	% of Degradation
1	30	0.01 N	1ml	6.730
			2ml	13.80
2		0.1 N	1ml	23.42
			2ml	34.75
3		1 N	1ml	37.98
			2ml	40.45

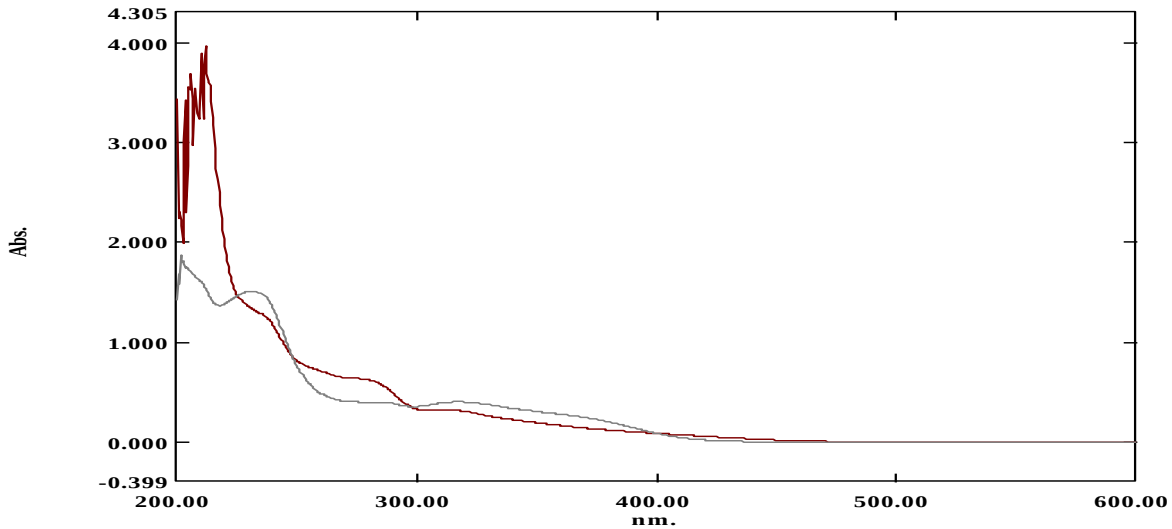

Figure No. 5: Base degradation of Nisoldipine

Table No. 8: Oxidative degradation of Nisoldipine

Sr. No.	Concentration (µg/ml)	Normality of H_2O_2	Vol. of H_2O_2	% of degradation
1	30	0.01 %	1ML	14.42
			2ML	23.69
2		1 %	1ML	26.44
			2ML	30.42
3		3 %	1ML	35.23
			2ML	48.07

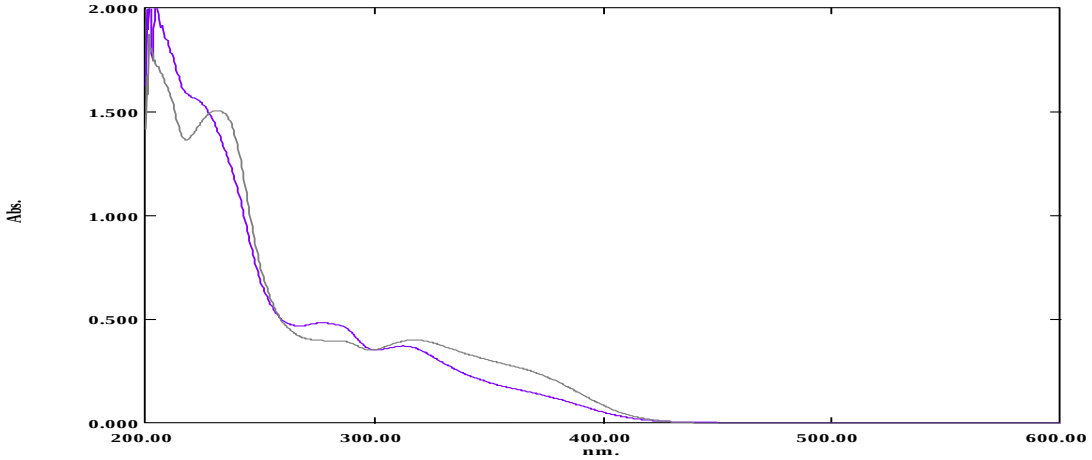

Figure No. 6: Oxidative degradation of Nisoldipine

Table No. 9: Thermal degradation of Nisoldipine

Sr. No.	Concentration(µg/ml)	Time (MIN)	% of Degradation
1	30	60	3.72
2		120	5.98
3		180	9.46
4		240	13.53
5		300	16.07
6		360	20.74

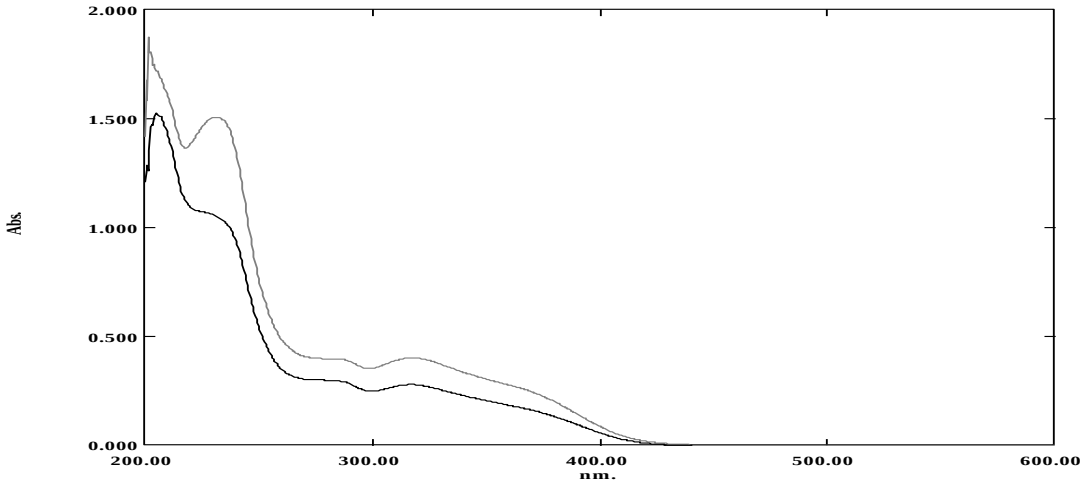

Figure No. 7: Thermal degradation of Nisoldipine

Table No. 10: Photolytic degradation of Nisoldipine

Sr. No.	Concentration (µg/Ml)	UV Light Exposure	Abs Before Exposure	Abs After Exposure	% of Degradation
1	30	2 DAYS	1.456	1.222	16.07
2		4 DAYS	1.456	1.005	30.97

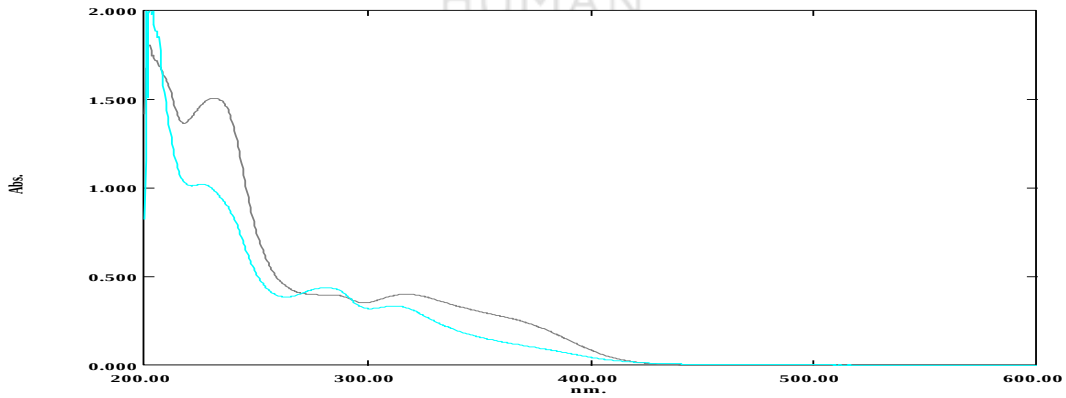

Figure No. 8: Photolytic degradation of Nisoldipine

6. DISCUSSION:

In the degradation study, critical quality attributes are strength and volume for which the studied API is exposed. This is the way by which the QbD approach was applied for force degradation study. In the case of acid degradation strength of 0.01N HCl, a volume of 1 ml was found to give degradation as per ICH guidelines.

In the case of alkali, 0.01N NaOH and 2 ml of the volume was found to be ideal.

While for oxidative degradation the strength and volume of hydrogen peroxide were found to be 0.01% and 1ml.

It is found that the drug is susceptible to all types of degradation**.**

7. CONCLUSION

The aim and objective of the application of the QbD approach were to increase the accuracy and precision of the developed and validated analytical method using ICH guidelines. From results and statistics applied it can be concluded that a more accurate, precise, and robustness method has been developed.

8. ACKNOWLEDGEMENT

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