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DEVELOP A VALIDATED METHOD FOR STABILITY STUDIES OF DULOXETINE TABLETS USING LC-UV @ LC-MS

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ABSTRACT

A medical product contains a substance that is pharmacologically active and that substance is called the active ingredient (AI) or active pharmaceutical ingredient (API) any substance intended to be used in the manufacture of a medicinal product and that, when so used, becomes an active ingredient of the medicinal product. Formulation is the process in which different chemical substances, including the active ingredient and excipients are combined to produce a final medical product. Duloxetine was studied under various conditions of stress, and the acid degradants were identified by LC-MS based on the behaviour of duloxetine under stress conditions. Under basic, oxidative and photolytic conditions, the drug has been found to be stable.

Keywords: Mass Spectrometry, Liquid Chromatography, Determination, Duloxetine.

INTRODUCTION

Pharmaceutical Analysis: This chapter briefly reviews the life of medical products and the manufacture of medical products according to international regulations and guidelines. Based on this review the major areas and usage of pharmaceutical analysis. Applications and Definitions The European Pharmacopeia defines a medical product as: (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings and/or animals; or (b) any substance or combination of substances that may be used in or administered to human beings and/or animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [1].

Drug substances are administered very rare as the pure active substance. Typically, the active substance and excipients (auxiliary substances) are combined into dosage forms to produce the final medical product. An excipient is: Any constituent of a medicinal product that is not an active substance [2].

LC-MS

LC/MS systems facilitate the analysis of samples that traditionally have been difficult to analyze. Despite the power and usefulness of gas chromatography/mass spectrometry (GC/MS), many compounds are impossible to analyze with GC/MS.

LC/MS significantly expands the effective analytical use of mass spectrometry to a much larger number of organic compounds. Gas chromatography and GC/MS can be used to analyze a small percentage of the 9 million registered compounds, LC and LC/MS-based methods can be applied to most organic compounds. Sample types range from small pharmaceutical compounds to large proteins.

Because it is a much more widely applicable method than GC/MS, LC/MS is suitable for the analysis of large, polar, ionic, and thermally unstable and in volatile compounds. Some of these compounds can be made amenable to GC/MS by derivatization, but LC/MS eliminates the need for time-consuming chemical modifications. This permits MS analysis of non-volatile, thermally labile, or charged molecules [3].

Using MS in combination with other LC detectors gives richer information. For example, a DAD acquires data on selected ultraviolet (UV) and visible (Vis) wavelengths and spectra.

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This information is useful for identifying unknown peaks and for determining peak purity or for both. An MS acquires mass information by detecting ions; it offers molecular-weight and structural information [4]. The LC/MS can be used with analytes that do not have chromophores. The two orthogonal sets of data can be used to confidently identify, confirm, and quantitate compounds. In addition, an LC/MS can be used as a highly selective and sensitive tunable detector. An MS chromatogram for a single mass often produces an interference-free signal that offers high precision and low minimum detection limits [5].

Methodology

Drug substances and Reagents

Duloxetine reference standard was provided by aurobindo pharma Ltd. (Hyderabad) as a gift sample, 20 tablets of duloxetine (Brand name: Dulokem-30 label claim: 30mg per each tablet) were procured from local pharmacy in Andhra Pradesh. The reagents such as methanol, triethylamine and ammonium acetate (0.05M – pH-6.5) were procured from local supplier. All chemicals and reagents used were of analytical grade [6].

UV-Spectral Analysis of Duloxetine

Instrumentation

Instruments used were UV-visible double beam spectrophotometer model Shimadzu UV1800 with one cm matched quartz cells and AJ-Vibra electronic balance manufactured by Essae Teraoka Ltd., Made in Japan. The glass wares used in each procedure were soaked overnight in a mixture of chromic acid and sulphuric acid rinsed thoroughly with double distilled water and dried in hot air oven for prior use. The absorption spectra of standard were carried out in a one cm quartz cells over the range of 200-400 nm.

reparation of standard stock solution

Weigh accurately 10 mg of Clobazam into 10 ml volumetric flasks, add methanol to dissolve the drug and then volume was made up to 10 ml with mobile phase. The concentration of standard stock solution is 1 mg/ml.

Preparation of working standard solution

Transferred 5 ml from the above standard stock solutions in to 50 ml volumetric flasks and diluted up to the mark with mobile phase to get working standard solution of concentration 0.1 mg/ml. From this 2ml is diluted to 10 ml to get 20µg/ml [7].

Determination of λ max

Most of drugs absorb light, UV wavelength (200-400 nm) since that contains aromatic double bonds. The solution containing 20µg/ ml of Clobazam was prepared and scanned over the range of 200-400 nm against acetonitrile as blank using Shimadzu UV1800 double beam UV spectrophotometer.

Calibration Curve for Duloxetine

From the stock solution, a concentration of various dilutions gives 10, 20, 30, 40, 50µg/ml concentration of duloxetine respectively. The absorbance was measured using UV spectrophotometer [8].

Instrumentation

HPLC-UV

The LC system included a Jasco Inc. (Easton, MD) Model PU 2080 Intelligent LC Pump with sampler programmed at 20 mL injection and a UV detector (Jasco Model UV 2075) operated at a wavelength of 228 nm. Data were integrated using the Jasco Borwin Version 1.5, LC-Net II/ADC system. The column used was SymmetryShield column C18 (5 mm, 250 mm 4.6 mm i.d.) from Waters, Milford, USA.

LC-MS

LC–MS studies were carried out on a 4000 Q-TRAP Linear Ion Trap Quadrupole Mass Spectrometer (Applied Biosystems Sciex, USA). The mass spectra of duloxetine and the Degradation product were taken in ESI (Turbo Ion Spray) positive mode in mass range of 40–600 amu and analyzed in the triple quadrupole analyser [9].

Development process

The whole process was controlled using analyst 1.4.2 software. The mobile phase used was a mixture of 0.2% (v/v) triethylamine in ammonium acetate (0.05 M; pH 6.5) and methanol (40:60) and the column used was C18. The flow rate was 1 mL/min and the effluent from the column was introduced into the mass spectrometer through a flow splitter which splits volume of mobile phase and deliver minimum amount of mobile phase in MS. The split ratio was 20:80.

Preparation of stock solutions

Duloxetine stock solution (1000 µg/ml) was prepared by weighing 50 mg of duloxetine in a 50 mL amber volumetric flask and making up to volume with mobile phase. Working solutions for HPLC injections were prepared on a daily basis from the stock solution in a solvent mixture of 0.2% (v/v) triethylamine in ammonium acetate (0.05 M; pH 6.5) and methanol (40:60). Solutions were filtered through a 0.45 mm membrane filter prior to injection [10].

Forced Degradation Studies/Specificity

Forced degradation studies were performed to evaluate the stability indicating properties and specificity of the method. The study was intended to ensure the effective separation of duloxetine and its degradation

peaks of formulation ingredients at the retention time of clobazam.

A stock solution (1 mg/mL) containing 100 mg duloxetine in 100 mL methanol was prepared. This solution was used for forced degradation to provide an indication of the stability indicating property and specificity of proposed method. In all degradation studies, the average peak area of duloxetine (60µg/mL) after application of seven replicates was obtained.

Acid and base induced degradation

Acid decomposition studies were performed by refluxing the solution of drug in 1M HCl at 80^{o}C for 8 h. The studies under alkaline conditions were performed in 5 M NaOH and the solution was refluxed for 8 h at 80^{o}C. The resultant solutions were diluted to a concentration of 60 µg /mL and 20 µL was injected into the LC system.

Hydrogen peroxide induced degradation

To study hydrogen peroxide induced degradation, initial studies were performed in 3% hydrogen peroxide at room temperature for 24 h. Then drug was exposed to 6% hydrogen peroxide at room temperature (2572^{o}C) for a period of 8 days and then heated in a boiling water bath for 10 min to completely remove the excess hydrogen peroxide. The resultant solutions were diluted to obtain a concentration of 60µg/mL and 20 µL was injected into the LC system.

Photochemical degradation

The photochemical stability of the drug was studied by exposing the stock solution (1000 µg/mL) to direct sunlight (60,000– 70,000 lx) for 15 days on a wooden plank kept on a terrace. The photochemical stability of the drug was also performed by keeping the stock solution (1000 µg/mL) in the stability chamber (light providing an overall illumination of 1.2 million lx h and an integrated near ultraviolet energy of not less than 200 W h/m^{2}) for 15 days.

The solution was diluted with methanol to obtain a concentration of 60µg/mL and then 20 µL of the solution was injected into the LC system [11].

Method Validation

Analytical Method Validation

Method validation is a process to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Analytical testing of a pharmaceutical product is necessary to ensure the purity, stability, safety and efficacy. Analytical method validation is an integral part of the quality control system. The method was validated for the following parameters: linearity, precision, accuracy, selectivity, robustness, limit of quantitation (LOQ), limit of detection (LOD) and system suitability.

Linearity

The linearity of an analytical procedure is its ability (with in a given range) to obtain the test results which are directly proportional to the concentration (amount) of analyte in the sample.

Linearity of an analytical procedure is established minimum of five concentrations. It is established initially by visual examination of plot of signals as a function of analyte concentration of content. If there appears to be a linear relationship, test results are established by appropriate statistical methods (i.e., by calculation of the regression line by the method of least squares).

Linearity of the method was studied by injecting seven concentrations of the drug prepared in the mobile phase in the range of 10–80 mg/mL in triplicate into the HPLC system keeping the injection volume constant. The peak areas were plotted against the corresponding concentrations to obtain the calibration graphs.

Precision

The precision of an analytical procedure express the closeness of the agreement between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions. The precision of an analytical procedure is usually expressed as the variance, standard deviation or co-efficient of variation of a series measurement.

System precision

A system precision is evaluated by measuring the peak response for the six replicable injection of the same standard solution prepared as per the proposed method. The %RSD is calculated and it should not be more than 2%.

Method precision

A method precision is evaluated by measuring the peak response for six replicate injection of six different weigh of sample solution prepared as per proposed method. The %RSD is calculated and it should not be more than 2%.

Determination

Precision of the method was verified by repeatability and intermediate precision studies. Repeatability studies were performed by analysis of three different concentrations (10, 40, and 80 mg/mL) of the drug in hexaplicate (n=6) on the same day. Intermediate precision of the method was checked by repeating studies on three different days.

Recovery Study (Accuracy)

Accuracy of the developed method was determined by applying the method to a drug sample (duloxetine tablets) to which a known amount of duloxetine standard powder corresponding to 80%, 100%,

and 120% of label claim was added (standard addition method). The percentage recoveries were calculated from the slope and Y-intercept of the calibration curve.

Limit Of Detection (Lod)

The limit of detection (LOD) is defined as the lowest concentration of an analyte in a sample that can be detected, though not necessarily quantitated. It is a limit test that specifies whether or not an analyte is above or below a certain value.

ICH has recommended some method for determining the limit of detection. The method may be either instrumental or non-instrumental. Limit of detection (LOD) based on standard deviation of the response and the slope of calibration curve.

$$LOD = \frac{3.3\ s}{S}$$

S = Slope of calibration curve

S = Standard deviation of the response

Limit Of Quantification (Loq)

The limit of Quantitation (LOQ) is defined as the lowest concentration of the analyte in a sample that can be determined with acceptable precision and accuracy under the stated operational conditions of the method.

Limit of Quantitation (LOQ) is also based on standard deviation of the response and the slope of calibration curve.

$$\mathbf{LOQ} = \frac{\mathbf{10\ s}}{\mathbf{S}}$$

S = Slope of calibration curve

S = Standard deviation of the response

Determination of the detection and quantification limits was performed based on the standard deviations of y-intercept and the slope of the least square line parameters as defined in the International Conference on Harmonization (ICH) Q2 guidelines

Determination

The signal to noise ratio was determined. LOD was considered as 3:1 and LOQ as 10:1. The LOD and LOQ were experimentally verified by diluting known concentrations of standard solution of duloxetine until the average responses were approximately 3 or 10 times the standard deviation of the responses for six replicate determinations.

Robustness

To evaluate robustness of the HPLC method, few parameters were deliberately varied. The parameters included variation of flow rate, percentage of methanol in the mobile phase, pH of mobile phase. Robustness of the method was done at three different concentration levels 10, 40, and 80 mg/mL for duloxetine

Specificity

The specificity of the method towards the drug was established through study of resolution factor of the drug peak from the nearest resolving peak. Overall selectivity was established through determination of purity for each degradation product peak using PDA detector [12].

Analysis Of Marketed Formulation

To determine the content of duloxetine in conventional tablets (Dulokem-30 label claim: 30mg per each tablet) were procured from local pharmacy in Andhra Pradesh. The contents of 20 tablets were weighed, their mean weight determined and finely powdered. An equivalent weight of the powder/triturate was transferred to a 50 mL volumetric flask containing 10 mL methanol, sonicated for 30 min and diluted to 50 mL with methanol. The resulting solution was centrifuged at 3000 rpm for 5 minutes. Supernatant was taken and after suitable dilution the sample solution was then filtered using a 0.45 mm filter (Millipore, Milford, MA). The above stock solution was further diluted to get sample solution at three different concentrations of 10, 40, and 80µg/mL. A 20 µL volume of each sample solution was injected into the LC system, six times, under the conditions described above. The peak areas were measured at 288 nm and concentrations in the samples were determined using multilevel calibration developed on the same LC system under the same conditions using linear regression equation [13].

RESULTS

UV-Spectral Analysis of Duloxetine

With the help of a UV spectrophotometer and with dilutions of medication (20µg/ml) in solvent the absorbance of duloxetine in the UV range of 200-400 was determined. At 290 nm, the maximum absorbance was determined and thus the absorption maximum of the drug was determined.

Preparation of calibration curve

Concentration of various dilutions 10, 20, 30, 40, 50 µg/ml concentration of duloxetine has done. The regression values were also calculated to be $r^2 = 0.999$, and the calibration values have been shown in table 1.

LC-UV chromatogram of Duloxetine

Duloxetine stock solution (1000 µg/ml) was prepared by weighing 50 mg of duloxetine in a 50 mL amber volumetric flask and making up to volume with mobile phase. Working solutions for HPLC injections were prepared on a daily basis from the stock solution in a solvent mixture of 0.2% (v/v) tri ethylamine in ammonium acetate (0.05 M; pH 6.5) and methanol (40:60). Solutions were filtered through a 0.45 mm membrane filter prior to injection.

20 µL of these solutions were injected into the system and the peak area was recorded from the respective chromatogram.

Identification of major degradation product formed under acidic stress condition

LC–MS analysis was carried out for the acid stress sample of duloxetine using a 4000 Q-TRAP Linear Ion Trap Quadrupole Mass Spectrometer with suitable volatile buffer ammonium acetate (0.05 M, pH 6.5) as mobile phase. Satisfactory separation of degradation product was achieved using a C18 column. The degradation product formed shows the m/z of 246.5 which has 18 lesser m/z value than duloxetine m/z 264.4

Forced Degradation Studies/Specificity

Acid induced degradation product

Drug degradation by acid was found to be more rapid than degradation by alkali. Initially, 0.1 M hydrochloric acid was used at 80°C for 8 h with negligible degradation, so the strength of the acid was increased. When drug solution was heated with 1 M hydrochloric acid at 80°C for 8 h, 10–20% degradation was observed, accompanied by a rise in a major degradation product at 4.87 minute in HPLC.

Base induced degradation product

In the initial study, sodium hydroxide solutions of 1 M and 2 M were used for 8 hours at 80°C without degradation, hence the alkali strength was increased. Following this, 5 M sodium hydroxide was refluxed at 80°C for 8 hours. Alkali conditions were found to be highly stable for the drug.

Hydrogen peroxide induced degradation product

After eight days of exposure to 6% hydrogen peroxide at room temperature, the drug showed negligible degradation.

Photochemical degradation product

After eight days of exposure to 6% hydrogen peroxide at room temperature, the drug was found to be stable against photochemical. In photo-stability chambers as well as direct sunlight exposure, the drug solution exhibited negligible degradation after 15 days.

Method Validation

This study uses a mixture of 0.2% (v/v) triethylamine, ammonium acetate (0.05 M; pH adjusted to 6.5 with glacial acetic acid), and methanol (40:60) as a mobile phase for the validation of a stability-indicating method developed for duloxetine.

Linearity and Range

The linearity of response obtained between 10 to 50 µg/ml concentrations and calibration curve were obtained by plotting absorbance versus concentration data and treated by linear regression analysis. The calibration curve equation for clobazam is Y= 0.0203x + 0.0038 and calibration curve was found to be linear in the above mentioned concentration and correlation coefficient (R^2) was 0.999. The linearity and range resulted from regression analysis of bivalirudin was found to be 10-50µg/ml.

Table 1: Calibration data of duloxetine

S. No	Concentration (µg/ml)	Absorbance (nm)
1	10	0.2081
2	20	0.4131
3	30	0.60874
4	40	0.8198
5	50	1.012

Table 2: Precision studies of Duloxetine.

Conc (µg/ ml)	Intra-day n=6			Inter-day n=6		
	Measured concentration (µg/ml)	RSD%	Recovery (%)	Measured concentration (µg/ml)	RSD%	Recovery (%)
10	**9.87**	**1.13**	**98.70**	**9.89**	**0.23**	**98.90**
40	**39.92**	**1.01**	**99.80**	**40.01**	**0.03**	**100.02**
80	**78.99**	**1.22**	**98.73**	**79.88**	**0.38**	**99.85**

Table 3: Robustness studies for duloxetine n=6

Factors	Levels	t_R	*k*	*T*
Flow Rate (ml/min)				
0.9	-1	3.71	1.62	1.20
1.0	0	3.60	1.75	1.01
1.1	+1	3.47	2.04	1.11

Mean ± SD		3.59±0.12	1.80±0.21	1.80±0.09
Change in mobile phase percentage				
59	-1	3.70	2.40	0.98
60	0	3.60	2.89	1.24
61	+1	3.61	1.23	1.13
Mean ± SD		3.63±0.05	2.17±0.85	1.116±0.13
pH of Mobile phase				
6.4	-1	3.32	2.45	1.23
6.5	0	3.60	2.87	1.02
6.6	+1	3.67	2.99	1.01
Mean ± SD		3.53±0.18	2.77±0.28	1.08±0.12

Table 4: Analysis of commercial formulation- Dulokem-30

Commercial formulation Dulokem-30	Drug found (Mean± SD, mg)	Recovery (Mean± SD, %)
1st lot	**30.09±0.14**	**100.18±0.21**
2nd lot	**29.91±0.45**	**99.81±0.41**

Table 5: Accuracy study of Duloxetine

Label claim (mg per tablet)	Amount added (%)	Total amount (mg)	Amount recovered (mg) ±RSD (%)	Recovery (%)
30	80	90	89.21±0.12	99.12
	100	100	98.90±0.11	98.90
	120	110	110.20±0.11	100.18

Figure 1: Absorption spectra of clobazam

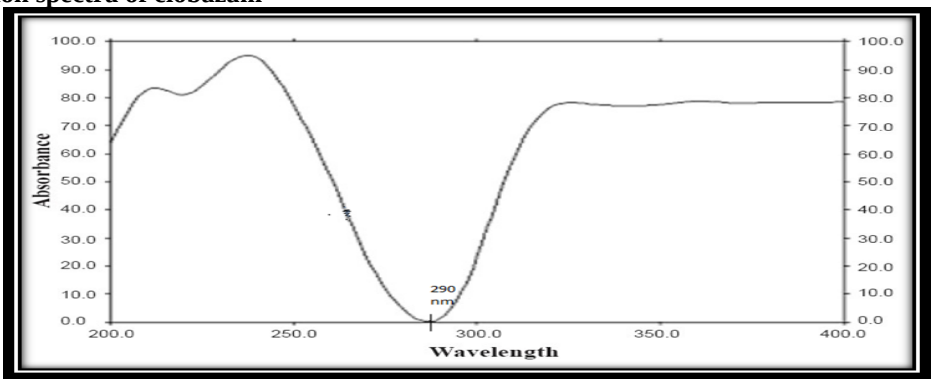


Figure 2: Linearity curve of Duloxetine

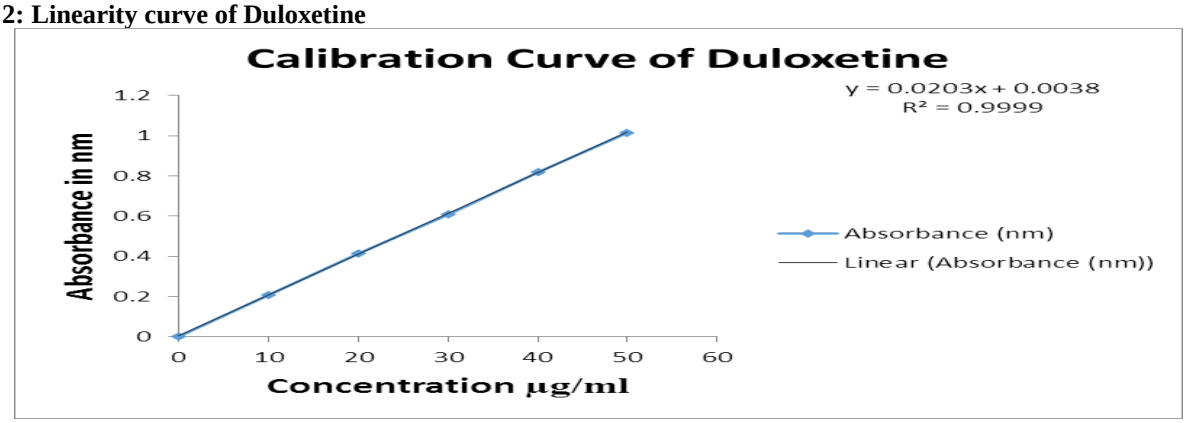


Figure 3: Chromatogram of standard duloxetine, peak tR: 3.60 min. mixture of 0.2% (v/v) tri ethylamine in ammonium acetate (0.05 M; pH 6.5) and methanol (40:60)

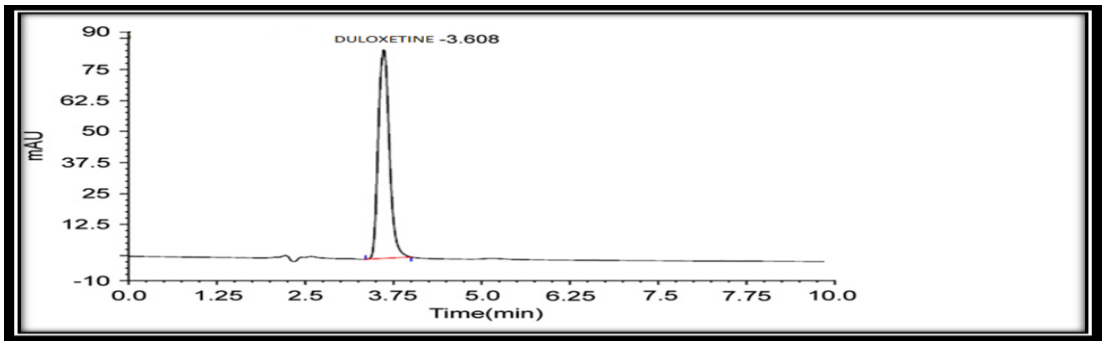
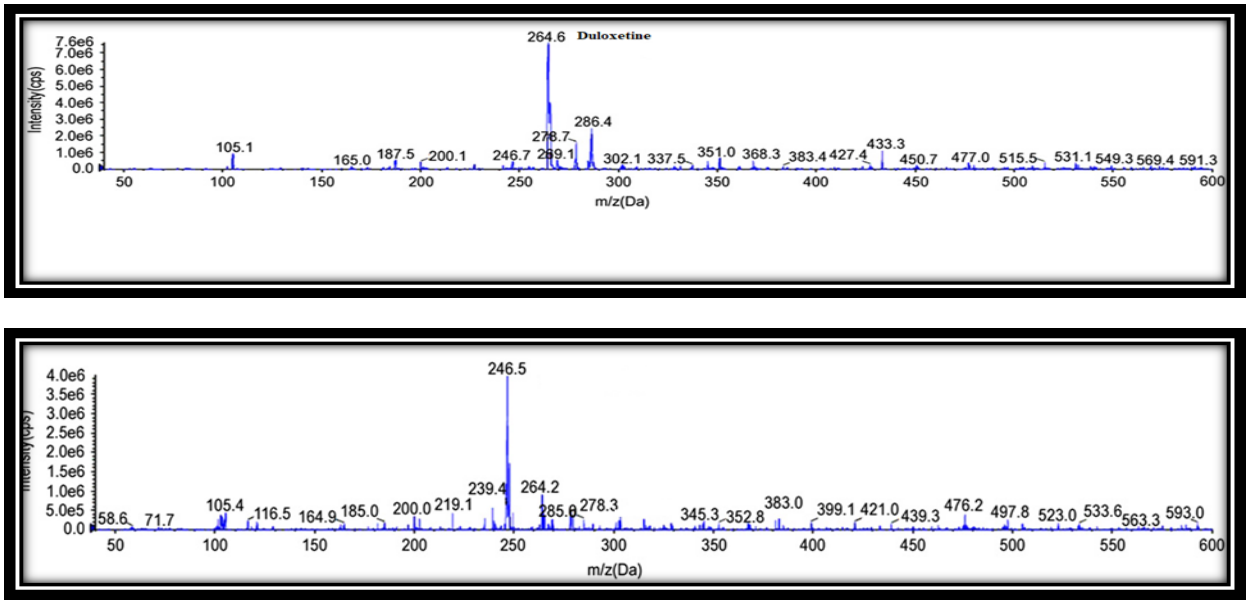


Figure 4: (a, b) Representative positive ESI-Quadrupole (+Q1) Mass spectra of duloxetine and acid degradation product.



Precision

The results of the repeatability and intermediate precision experiments are shown in Table The developed method was found to be precise as the RSD values for repeatability and intermediate precision studies were < 2%, respectively, as recommended by ICH guideline. Separation of the drug and degradation product in stressed sample was found to be similar when analysis was performed on different chromatographic systems on different days.

LOD AND LOQ

LOD and LOQ were determined based on signal: noise ratios of 3:1 and 10:1. There was a 5 µg/mL LOD and a 10 µg/mL LOQ.

Robustness

The selected factors were changed at three levels (-1, 0 and 1), except for columns from different manufacturers and solvents from different lots. To estimate the effect, each factor was changed one at a time. Under small changes in three chromatographic parameters (factors), replicate injections of mixed standard solution were performed at three concentration levels (n=6). There were insignificant differences in peak areas and less variability in retention times. The results were observed in below table 3

SPECIFICITY

Figure illustrates the specificity of the LC method. A complete separation of duloxetine was observed in the presence of its degradation product. The peaks obtained were sharp and clearly separated by their baselines. It was possible to measure all components in a mixture with a photodiode array detector in a wavelength range between 200 and 720 nm. The resolution factor for the drug from its nearest peak was >3. As a result of the method's specificity, there were no degradation peaks

hiding under or unresolved from the analyte peak (pure drug).

Analysis of marketed formulation

In this study, the proposed procedures were applied to two different lots of commercially available duloxetine tablets, and the results are summarized in table

ACCURACY (Recovery studies)

Various addition concentrations resulted in good drug recovery ranging from 98.9% to 100.18%, as shown in Table 5.

CONCLUSION

Duloxetine in the presence of degradation products was determined by a sensitive, specific, accurate, validated and well-defined LC method described in this study. UV spectrophotometric absorption is used as a solvent in the proposed method; maximum absorbance is 290 nm in UV region. Duloxetine was studied under various conditions of stress, and the acid degradants were identified by LC-MS based on the behaviour of duloxetine under stress conditions.

Under basic, oxidative and photolytic conditions, the drug has been found to be stable. There was a good separation of the degradation product from the drug substance, which indicates that the method was capable of demonstrating stability. The method has been validated for parameters such as linearity, precision, accuracy, specificity, etc. in addition to being applied to real marketed samples in order to confirm its efficacy. It is thought that the information presented here in could be very useful for quality monitoring of bulk samples and, in addition, could be used to check the quality of the drug during stability studies as well.

REFERENCE

1. Dahan A, Miller JM, Amidon GL, *et al*. Prediction of solubility and permeability class membership. Provisional BCS classification of world top oral drugs. *AAPS*. 11(4), 2009, 740-746
2. Navin A, Bedi KL. Bioenhancers: Revolutionary concept to market. *J Ayurveda Integr Med*. 1(2), 2010, 96-99
3. Volpe DA. Drug Permeability Studies in Regulatory Biowaiver Applications. *Drug Absorption Studies: Pharmaceutical Aspects*, 7, 2008, 665-680.
4. Maryadele J O, editor. The Merck Index. 14th Ed., Whitehouse Station, NJ: Merck and Co. Inc; 2006, 3465.
5. Mishra L. Drugs today. Delhi: Lorina Publications; 1, 2006, 489.
6. Cipriani A, Koesters M, Furukawa TA, Nosè M, Purgato M, Omori IM, Trespidi C, Barbui C, *et al*. Duloxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev*. 2012, 10, CD006533.
7. American Society of Health-System Pharmacists 2015; Drug Information 2015. Bethesda, MD. 2015, 2293.
8. Bymaster FP, Lee TC, Knadler MP, Detke MJ, Iyengar S, *et al*. "The dual transporter inhibitor duloxetine: a review of its preclinical pharmacology, pharmacokinetic profile, and clinical results in depression". *Current Pharmaceutical Design*. 11 (12), 2005, 1475–93.
9. Knadler, Mary Pat; Lobo, Evelyn; Chappell, Jill; Bergstrom, Richard "Duloxetine: clinical pharmacokinetics and drug interactions". *Clinical Pharmacokinetics*. 50 (5), 2011, 281–294.
10. Stahl S. Stahl's essential pharmacology, 4th ed. Cambridge University Press, *New York*. 2013, 305, 308, 309.
11. White C, Kwong WJ, Armstrong H, Behling M, Niemira J, Lang K. Analysis of Real-World Dosing Patterns for the 3 FDA-Approved Medications in the Treatment of Fibromyalgia. *Am Health Drug Benefits*. Sep, 11(6), 2018, 293-301.
12. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J. Winter*; 13(4), 2013, l533-40.
13. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL, *et al*. (June). "Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline". *Journal of Clinical Oncology*. 32 (18), 2014, 1941–67.