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Original Research Article

Development of a Novel Method for Determination of Sertraline in Pharmaceutical Products and its Quality Control Application

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Abstract

Background: Sertraline is an antidepressant drug from the family of selective serotonin reuptake inhibitors (SSRIs) and is used in the treatment of depression. ***Aim:*** The aim of this work was to develop a sensitive, precise, accurate, and specific analytical method for quantitative estimation of sertraline in pharmaceutical product for the purpose of using it as a quality control tool for testing sertraline products pre and post-market distribution, ensuring the presence of claimed drug amount in the pharmaceutical dosage form. ***Methods:*** Sertraline estimation in commercial drug products administered in hospitals and community drugstores and prescribed to patients through the development of an in-house High-Performance Liquid Chromatographic (HPLC) method to contribute with a validated, specific and sensitive method to literature methodologies. ***Results:*** The method is sensitive, specific, and selective, and showed linearity R^2>0.999 within concentration range of 2.5 to 100 µg/mL for dissolution medium USP (pH 4.5), pH1.2, and 6.8. Accuracy results within the range of 98% - 102%, precision CV% less than 2%. The assayed tablets mean recovery is 100.676%. Moreover, the dissolution results meet the required 80 percent dissolution limit within 30 minutes for the USP dissolution medium (pH 4.5). ***Conclusion:*** The analytical method developed is very sensitive and totally validated for use in the quantitative analysis of sertraline.

Keywords: Sertraline; Analytical method; Depression; anxiety, pharmacopeia, Dissolution, Validation.

1. INTRODUCTION

Depressive disorders are one of the common mental disorders that may be chronic or recurrent. Depression has a negative impact on the individual's social and economic state, and can lead to committing suicide. Sertraline is one of the selective serotonin reuptake inhibitors (SSRIs) that blocks serotonin reuptake at CNS. Sertraline is therapeutically efficient as traditional tricyclic antidepressants. Besides, it has beneficial effect in treatment of anxiety, panic and obsessive compulsive disorders. But, it may show more side effects other than traditional antidepressants [1].

It is strongly suggested as a desirable therapeutic option for COVID-19 patients, as it has strong anti-inflammatory effects by reducing and controlling inflammatory cytokines. Besides, Sertraline reported antiviral efficacy when it is used effectively to mitigate lung inflammatory responses induced from influenza virus and lower mortality when combined with oseltamivir in a treated mice trial. And finally, it has a broad therapeutic index and minimal anticholinergic activity that makes it a safe choice for geriatric persons and those with underlying cardiovascular diseases [2].

Sertraline is available in the form of oral tablets as 25, 50, 100 mg, and solution form 20mg/ml, and administered once daily. Absorption of the drug may be improved when taken with food [3]. Sertraline is deemed safe in individuals who have a previous myocardial infarction, heart failure, or other cardiac problems, as well as during pregnancy and lactation [1].

Various analytical methodologies for the estimation of sertraline in biological samples and pharmaceutical formulations, including HPLC-UV, [4, 5] GC-MS [6, 7], and spectrophotometric methods,

have been developed [8]. Also, sertraline has been estimated by LC-MS/MS [9].

In this work, the proposed validated in-house developed method is a sensitive, precise, accurate, and specific analytical method for sertraline determination in pharmaceutical formulations, and in dissolution testing. Validation items are performed as per ICH and FDA guidelines [10, 11]. Assay testing, in-vitro dissolution procedures, and criteria are performed in accordance with FDA Biowaiver / BCS Guidelines [12], and USP [13].

Performing invitro testing like assay, uniformity of dosage units and dissolution is an important step in determining the validity of dosage form for intended use. Moreover, predicting dosage form behavior before conducting bioequivalence studies if required. Some research institutes are working on correlation between In-vivo and In-vitro results to predict pharmacokinetic behavior and bioequivalence of generic drug products from in-vitro dissolution results. Drug assay should be within the limit of 90 to 110% of the labeled claim, and dissolution limit should be not less than 80% of the drug dissoluted within 30 minutes for dissolution medium USP (pH 4.5) in order to ensure valid and safe for administration of sertraline tablets, to obtain an effective therapeutic outcome. Being sertraline a BCS class II drug with poor solubility, it will not attain the required USP dissolution limit in media pH 1.2, and 6.8.

Routine random drug samples should be selected from community and hospital pharmacies and subjected for quality control testing in order to guarantee that the dosage form is keeping its integrity and the labeled claim of active ingredient is in compliance with the required specification after they are exposed to market transportation conditions and shelf-storage in pharmacies. Also, the absence of any drug degradative or toxic product is important and should be checked.

Finally, accurate investigations of sertraline in pharmaceutical products could not be relied upon unless a valid analytical method is well- developed for drug determination. The aim of this routine check is to ensure that the patients are administering a valid and safe therapeutic product to obtain the desired therapeutic outcomes and avoid the incidence of drug toxicity or adverse events.

2. MATERIALS AND METHOD

Routine random drug samples are selected from community pharmacies and hospital pharmacies. Quality control testing like assay testing and dissolution testing is performed on those samples to ensure that the dosage form preserving its integrity and no degradative product formation, and the labeled claim of active ingredient is in compliance with the required specification after they are exposed to market transportation conditions and shelf-storage in pharmacies. The aim is to make sure that the patients are administering safe and valid drug products to attain the required therapeutic efficacy and avoid any potential drug toxicity or side effects.

2.1. Materials

Sertraline USP reference standard. All solvents were of the HPLC grade and were purchased from Merck (Germany). The rest of chemical agents used were of AR grade and were purchased from Scharlab (Spain).

2.2. Analytical Procedure

2.2.1. Instrumentation

The analysis was performed by using the analytical balance Sartorius, pH meter portable BOECO, the HPLC used is Thermo Spectra System 4000 HPLC system, equipped with Spectra system P4000 Gradient Pump, Spectra system Autosampler fitted with a 100 µl loop and Spectra system P1000 Ultra-Violet Detector was used. The output signal was monitored and processed using a Chromoquest 4.2 Software. The chromatographic column used was a 250 mm x 4.6 mm, C_8 with 5µm particles.

Before use, the mobile phase was vacuum-filtered through a 0.45 µm membrane filter and degassed with Sonication. The water was distilled and then purified by a ELGAPURE water purification system (England).

2.2.2. Chromatography conditions

The eluting solvent composed of 0.5% phosphoric acid: Acetonitrile (45: 55 V/V). Mobile phase flow rate was 0.85 ml/min. Peaks were monitored at 270nm. Analysis performed at ambient temperature, and a 15µL volume of sample solution was injected.

2.2.3. Preparation of stock and standard solutions

A master solution of sertraline (100 µg/ml) was prepared by accurately weighing an equivalent amount to 10 mg of sertraline into 100 ml volumetric flask and dissolved in 70 ml of methanol and volume completed with methanol. From this solution, aliquots were transferred into 10ml volumetric flask and the volume was completed with mobile phase to obtain concentrations of 2.5 to 100 µg/ml.

2.2.4. Method Validation

The in-house developed HPLC method validation was performed following ICH guidelines.

2.2.4.1. Specificity

It is the capability of the analytical method to determine target analyte in presence of all potential

impurities. Stress studies were performed at concentration of 50 µg/mL sertraline active pharmaceutical ingredient (API) and formulated tablet samples to indicate stability and specificity of the developed analytical method. Intentional drug degradation was performed under stress conditions of heat (Exposed at 85°C for 1 hr), acid (1N HCl for 1 hr at 85°C), and base (1N NaOH for 1 hr at 85°C).

2.2.4.2. Linearity

Linearity was studied by preparing standard solution at nine concentration levels from 80 to 120% of the target analyte concentrations i.e. Concentrations ranging from 2.5 - 100 µg/ml for dissolution conditions pH1.2, 4.5, and 6.8 These analyses were performed in triplicate [10, 11].

2.2.4.3. Precision

It is an assessment of intra-day variability in results obtained at three concentrations, with nine determinations in one laboratory, on the same day. Calculated %RSD is used to express precision [10, 11].

2.2.4.4. Detection Limit (LOD) / Quantitation limit (LOQ)

It is defined as the concentration of analyte that would yield signal-to-noise ratios of 3 for LOD and 10 for LOQ respectively. Detection and quantitation limit was estimated by y-intercepts standard deviation and slope of calibration curve [10, 11].

2.2.5. Estimation of sertraline in pharmaceutical dosage form

To determine the assay of sertraline in tablet (labeled claim: 50 mg sertraline) not less than 10 tablets were weighed and transferred to 1000ml volumetric flask. 500 ml of 0.1% phosphoric acid were added. Sonication was performed for 15 minutes. 400 ml of methanol were added. Then sonication was continued for another 10 minutes. Then the flask was left to cool at room temperature. The volume was completed with methanol. A 1 ml aliquot from the previous preparation was transferred to 10 ml volumetric flask and volume was completed with diluent (Methanol: 0.1% phosphoric acid 1:1 V/V). And 0.45 µm nylon filter was used to filter solutions. Sample solution was injected into HPLC with injection volume 15µl, three times, under the predetermined validated chromatographic conditions. Drug chromatographic responses were determined at 270 nm and sample concentrations were calculated by evaluating the chromatographic response of the sample against that of standard.

2.2.6. Estimation of sertraline in In-Vitro Dissolution testing of pharmaceutical dosage form.

Dissolution testing procedures were applied on twelve dosage units (Tablets) under USP dissolution medium pH4.5, and media pH1.2, and pH6.8 using UPS Type II device at 75 rpm as follows:

1. The above-mentioned dissolution conditions were applied and performed by placing six tablets in six vessels (one tablet in each vessel). Five ml of each sample was withdrawn after 10, 15, 20, 30, 45, and 60 minutes of dissolution where, 5ml of blank (dissolution media) was added to replace this withdrawn volume and achieve a constant volume of dissolution medium (900ml).
2. The withdrawn 5ml at each sampling interval was added in a coded labeled test tube and then filtered through a syringe membrane filter (PTFE 0.45µm).
3. The previously mentioned procedures were repeated on another six tablets.
4. The filtered withdrawn samples were then injected into the HPLC-UV apparatus for drug detection and quantification at 270 nm.

3. RESULTS

Determination of sertraline was carried out by RP-HPLC using Mobile phase having a composition of 0.5% Phosphoric acid: Acetonitrile (45: 55 V/V). Then finally filtered using 0.45µ nylon membrane filter and degassed in sonicator for 10 minutes. The column used was C_8 250X4.6 mm p.s. 5um. Flow rate of mobile phase was 0.85 ml/min, system suitability parameters such as theoretical plates were above 5000, and tailing factor less than 1.4.

3.1. Method validation

After development of the analytical method, it was subjected to method validation according to ICH and FDA guidelines [10, 11]. The aim of validation is to demonstrate whether the method is acceptable for its required application or not. A standard procedure is followed to evaluate required validation items.

3.1.1. Specificity

Bank samples containing solvent were injected and showed no drug detected (figure 1). The drug was unstable under heat, acidic, and basic stress conditions. The drug was degraded to about 24% under heat, and acidic conditions (figure 3, and 4). Under basic conditions (figure 5) the drug was totally degraded. The stability of stock solution under conditions of (2 to 8 ^{o}C) was determined by quantitation of sertraline and comparison to freshly prepared standard (figure 2). No remarkable change occurred in the stock solution response, in comparison to freshly prepared standard.

All forced degradation samples were analyzed with the aforementioned HPLC conditions using a UV detector to monitor the homogeneity and purity of the sertraline peak. Individual related substances, placebo, and sertraline showed no interference, thus providing a specific analytical method.

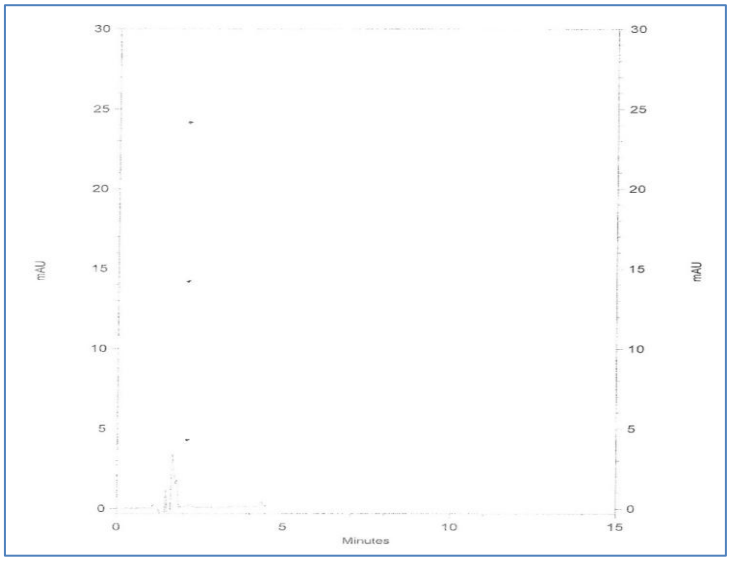

Fig-1: Chromatogram of Blank solvent

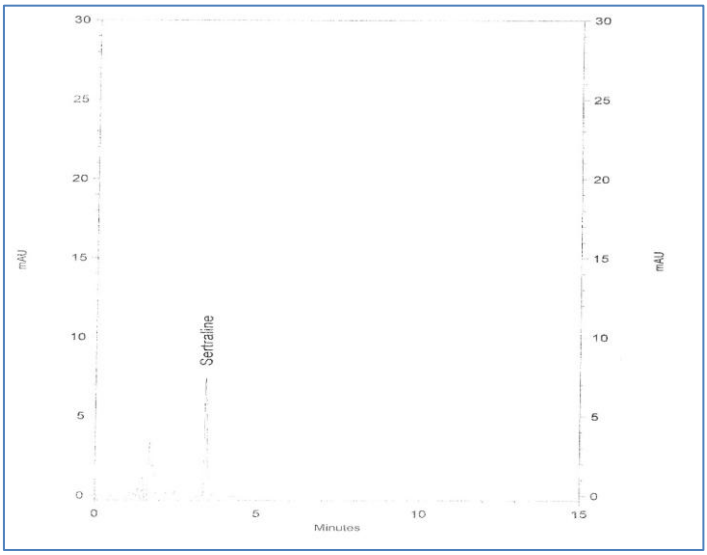

Fig-2: Chromatogram of Sertraline Stress Heat

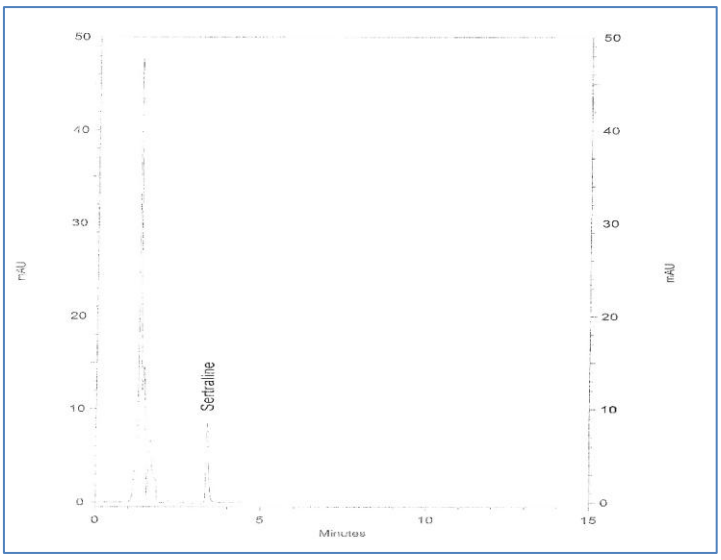

Fig-3: Chromatogram of Sertraline Stress HCL

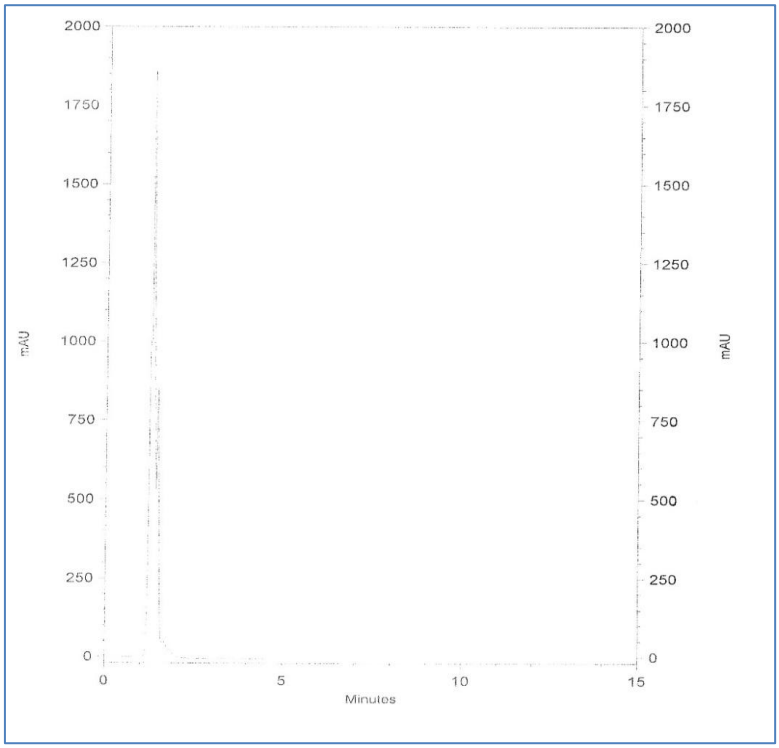

Fig-4: Chromatogram of Sertraline Stress NaOH

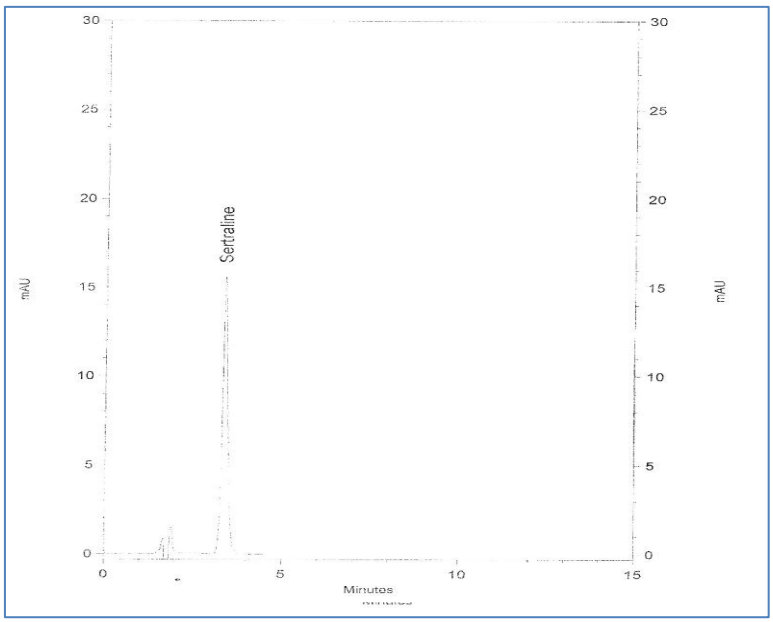

Fig-5: Chromatogram of Standard Sertraline

3.1.2. Linearity

Sertraline showed linearity from 2.5 to 100 µg/ml in dissolution medium pH 1.2, 4.5, and 6.8 with (r^2 = 0.999) for HPLC. Linearity was estimated by quantifying nine standard working solutions within a concentration range of 2.5 to 100 µg/ml in triplicate using media pH 1.2, 4.5, and 6.8 as a solvent. Drug responses were plotted against sertraline concentration (µg/ml) and analysis for linear regression was performed (table 1). High-value Correlation Coefficient (r^2) and low value intercept CV% (below 5%) indicate validation of analytical method linearity adherence of the system to Beer's law. The resulted chromatogram showed a sharp, symmetrical, and well-separated peak at retention time of 3.3 min (figure 5).

Table-1: Linearity Results

Analyte	Sertraline
Range	2.5 to 100 µg/mL
Linearity correlation equation	
At Dissolution medium (pH1.2)	Y = 7252.235719x + 884.249163
At Dissolution medium (pH4.5)	Y = 1963.814689x - 1215.630885
At Dissolution medium (pH6.8)	Y = 1267.438606x - 396.345417
Linearity correlation coefficient R^2	
At Dissolution medium (pH1.2)	0.999991
At Dissolution medium (pH4.5)	0.999945
At Dissolution medium (pH6.8)	0.999918
Mean Slope ±SD	
At Dissolution medium (pH1.2)	7252.236 ± 6.917
At Dissolution medium (pH4.5)	1963.815 ± 5.182
At Dissolution medium (pH6.8)	1267.439 ± 1.448
Mean Intercept ± SD	
At Dissolution medium (pH1.2)	884.249 ± 157.848
At Dissolution medium (pH4.5)	-1215.631 ± 85.322
At Dissolution medium (pH6.8)	-396.345 ± 130.012
Standard error of slope	
At Dissolution medium (pH1.2)	3.993
At Dissolution medium (pH4.5)	2.992
At Dissolution medium (pH6.8)	0.836
Standard error of intercept	
At Dissolution medium (pH1.2)	91.134
At Dissolution medium (pH4.5)	49.260
At Dissolution medium (pH6.8)	75.063

Where, n=3, average of three determinations, SD (±): standard deviation.

3.1.3. Precision

The intra-day variations can be demonstrated in terms of % RSD values. The %RSD values in dissolution medium USP (pH 4.5), 1.2, and 6.8 showed to be less than or equal to 2 %, indicating good precision. It is acceptable according to acceptance limit of these parameters. The mean RSD% in medium USP (pH 4.5), 1.2, and 6.8 were 1.195, 0.449, and 0.519 % respectively.

3.1.4. Detection limit (LOD) and Quantification limit (LOQ)

The LOD and LOQ of the method were determined by injecting progressively low concentrations of the standard solutions using the developed RP-HPLC method. The detection Limit for sertraline was 0.143, 0.072, and 0.339µg/mL for dissolution media pH 4.5, 1.2, and 6.8 respectively. The quantitation limit was 0.434, 0.218, and 1.026µg/ml for dissolution media pH 4.5, 1.2, and 6.8 respectively.

3.2. Assay (Potency) of Sertraline

The developed method was applied for sertraline assay in tablet dosage form. Results were found out as mean % recovery 100.676% for sertraline reference tablet. The results indicating that the method is selective for the drug assay with no interference from the inactive ingredients.

3.3. Dissolution of Sertraline

The developed and validated method was applied for dissolution testing of sertraline tablet. Results were found out as a dissolution profile for mean percentage drug dissoluted of sertraline in Reference tablets. The results showed that reference product is in compliance with FDA Biowaiver / Biopharmaceutics classification system Guidelines [12], and United States Pharmacopeia (USP) [13].

The results of dissolution percent of sertraline 50mg tablet upon dissolution in pH4.5 (USP medium) after 10, 15, 20, 30, 45, and 60 minutes was 83.096, 86.538, 89.372, 92.616, 95.983%, 98.500% respectively.

The results of dissolution percent of sertraline 50mg tablet upon dissolution in medium pH1.2 after 10, 15, 20, 30, 45, and 60 minutes was 54.645, 59.717, 65.273, 70.283, 75.816, 82.379% respectively.

The results of dissolution percent of sertraline 50mg tablet upon dissolution in medium pH6.8 after 10, 15, 20, 30, 45, and 60 minutes was 40.761, 50.742, 60.098, 69.320, 74.988, 82.326% respectively.

The previous results of method validation, Assay testing, and dissolution testing indicate that the

validation and pharmaceutical drug product results are in compliance with the required specifications, and thereby will provide the required therapeutic effect in treatment of depression, anxiety, panic, and obsessive compulsive disorders.

4. DISCUSSION

It is worthy to mention that, the estimation and assaying of sertraline in pharmaceutical products including tablets, and evaluation of its in vitro behavior including dissolution with a validated analytical method are essential to ensure drug clinical efficacy.

As shown previously, the clinical importance of sertraline as an antidepressant drug in treatment of anxiety, and depression, panic, and obsessive compulsive disorders offering the same clinical efficacy like traditional tricyclic antidepressants [1].

Many analytical methods developed for sertraline determination in pharmaceutical dosage forms. An HPLC-UV method was developed and validated according to FDA guidance on validation of chromatographic methods and recommendations of ICH. The drug was chromatographed on column 4.6 × 150 mm of Hypersil Gold C18. Mobile phase of methanol: buffer pH 7.4 (80:20 V/V) was used. The method showed linearity between 10 and 300µg/mL and (R^2 > 0.9996). The method showed high precision and accuracy [14].

Another validated assay method for sertraline and alprazolam determination has been developed. Chromatographic separation on column C18 symmetry 4.6 × 250 mm. Acetonitrile mobile phase: phosphate buffer (60:40 V/V) has been used. The wavelength of detection was adjusted at 225nm. The method was linear between 100 and 500µg/mL and (R2 >0.999) for sertraline. The method has shown high accuracy and precision [15].

Analytical method for sertraline determination and its degradation products were developed using a reversed phase (RP-18e) column. The eluting solvent used was methanol:water (75:25 v/v). And UV detection was performed at 273 nm. The method was fully validated and response was found to be linear in range of 10 to 200 µg/ml. r^2 0.998, and LOQ 0.0855ug/ml [16].

The developed HPLC – UV method applied in this study was simple, and of excellent sensitivity, specificity, precision, and accuracy. Materials and reagents used analysis are common, convenient, and available, like C_8 column 550mm X 4.6mm, phosphoric acid, and Acetonitrile. Mobile phase pumped in an isocratic mood, and total run time was 4.5 minutes which permits analysis of up to 250 samples per 24 hours. The method showed an advantage over the reported methods regarding covered linear dynamic range from 2.5 to 100ug/ml [14 - 16].

The calibration curve using media pH 4.5, 1.2, and 6.8 as a solvent was linear over the range of 2.5 to 100 µg/ml, and LOQ was 0.434, 0.218, and 1.026µg/ml respectively. r^2 was equal to 0.999, accuracy of the results was in the limit of 98 - 102%, and RSD% were less than 2% which is in accordance with ICH and FDA guidelines [10, 11]. The standard deviation for intercept value was less than 5%, system suitability parameters as theoretical plates were above 5000, tailing factor less than 1.4, and so it could be used for determination of sertraline in bulk and pharmaceutical products.

The method is appropriate for use in preliminary and routine quality control check on distributed sertraline products in the market to ensure compliance of marketed distributed products under different storage conditions in pharmacies and hospitals with specifications, absence of probable degradative product formation, and reduction of active ingredient quantity in the dosage form, and safe administration of sertraline products with no side effects, and avoiding lack of clinical efficacy.

5. CONCLUSION

The HPLC analytical method developed for determination of sertraline in bulk and marketing products and dissolution samples as revealed by the validation data enables specific, accurate, and precise analysis of the drug. The developed analytical method showed enough sensitivity for sertraline quantification in pharmaceutical dosage forms and thus can be used for routine analysis, quality control, and stability studies of pharmaceutical preparations and consequently assuring to some extend the efficacy and safety of sertraline in treatment of depression, anxiety, panic, and obsessive compulsive disorders.

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