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Development of Validated Analytical Method for In-vitro Dissolution Study of Sertraline Hydrochloride Capsules.

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Abstract
Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Sertraline hydrochloride belongs to BCS class-II i.e. drug having low solubility in water and high permeability. Sertraline hydrochloride is available in market for oral administration as scored tablets, hard gelatin capsules and oral concentrate. An isocratic High Performance Liquid Chromatographic (HPLC) procedure was developed for the estimation of Sertraline HCl in dissolution study of its capsule dosage forms. HPLC separation was carried out by reverse phase chromatography on Zorbax Eclipse XDB C-18 column (150mm x 4.6mm I.D.; 4µm particle size), held at 30^0C.The mobile phase consisted of Methanol and Acetate buffer, pH 4.5 (75:25, v/v), run at a flow rate of 1ml/min and UV detection at 270nm. Method validation investigated parameters such as linearity (r^2=0.9997), precision, accuracy, robustness and specificity. The dissolution test conditions and dissolution medium was chosen as Acetate buffer, pH 4.5 (1000ml, USP Type -1 Apparatus) at stirring rate of 100rpm for 60 minutes. The validated HPLC method was found to be specific, linear, precise and accurate and can be successfully employed for the dissolution study of Sertraline HCl capsules.

Key Words
Sertraline HCl, Dissolution, HPLC, Validation, Capsules.

Introduction
Dissolution is an official test used by pharmacopoeias for drug evaluation, release of solid and semisolid dosage forms, and it is routinely used in Quality Control (QC) and Research and Development (RandD). The purpose of in-vitro dissolution studies in QC is to check batch to batch consistency and detection of manufacturing deviation while in RandD the focus is to provide some predictive estimate of the drug release in respect to the in vivo performance of a drug product[1]. Sertraline hydrochloride (Molecular Weight: 342.7, Chemical Name: (1S-cis)-4-(3, 4-dichlorophenyl)-1, 2, 3, 4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration[2,3]. The efficacy of Sertraline for depression is similar to that of older tricyclic antidepressants, but its side effects are much less pronounced. Differences with newer antidepressants are subtler and also mostly confined to side effects. Evidence suggests that sertraline may work better than fluoxetine for some subtypes of depression[4]. Sertraline is highly effective for the treatment of panic disorder, but cognitive behavioral therapy is a better treatment for obsessive-compulsive disorder, whether by itself or in combination with Sertraline. Although approved for social phobia and posttraumatic stress disorder, sertraline leads to only modest improvement in these conditions[5,6].Sertraline also alleviates the symptoms of premenstrual dysphoric disorder and can be used in sub-therapeutic doses or intermittently for its treatment. Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Sertraline is primarily used to treat major depression in adult out patients as well as obsessive–compulsive, panic, and social anxiety disorders in both adults and children. Sertraline hydrochloride is available in market for oral administration as scored tablets, hard gelatin capsules and oral concentrate. Capsules are formulated to contain sertraline hydrochloride equivalent to 25, 50 and 100 mg of Sertraline.

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Dissolution study is particularly important for insoluble or low soluble drugs where absorption is dissolution rate limited (BCS Class-II drug). Sertraline hydrochloride belongs to BCS class-II i.e. drug having low solubility in water and high permeability[2]. Literature survey revealed that there is no official monograph and no dissolution test has been reported for capsule formulation. Few methods have been reported for estimation of Sertraline in bulk drug, tablets and capsule formulation[7, 8]. Hence, this project was taken up with an intention to develop a discriminatory dissolution method for Sertraline hydrochloride capsules to support product development and quality control efforts. The aim of the present work was to develop and validate an accurate, specific and repeatable method for dissolution study of Sertraline hydrochloride capsules.

Materials and Methods

Drugs and Chemicals

Sertraline hydrochloride API (Active pharmaceutical ingredient, Purity = 99.9% w/w) was obtained from Flamingo Pharmaceutical Ltd., Taloja. Empty hard gelatin capsules were purchased at the local market. All reagents and solvents used were analytical grade. All the buffer solutions were prepared according to the procedure given in the USP Pharmacopoeia. HPLC grade water and solvents were used for HPLC analysis.

Instrumentation

Dissolution test was performed in an Electrolab dissolution test system (n=6), in accordance to USP Pharmacopoeia general method. A double-beam UV-Vis spectrophotometer (Shimadzu, Japan) with 1.0 cm quartz cells was used for all absorbance measurements. An Agilent High Performance Liquid Chromatograph (HPLC) equipped with Quaternary pump and UV detector was used for analysis of dissolution samples. Detection was made at 270 nm. Chemstation Software was used.

Formulation development of Sertraline hydrochloride capsules

Two capsule formulations of Sertraline hydrochloride were compounded in the Lab scale using different excipients and were evaluated for various physical parameters such as weight variation, disintegration time etc. The composition of the compounded formulation is mentioned below,

Product A

Labeled to contain 100 mg of the drug and the following excipients: Lactose and Magnesium stearate.

Product B

Labeled to contain 100 mg of the drug and the following excipients: Starch and Magnesium stearate.

The assay of the above two products was performed using previously validated spectrophotometric method, and the contents results were used to calculate the percentage release on each time of dissolution profile.

Dissolution test conditions

Solubility of Sertraline hydrochloride was determined in 1000 ml of pH 1.2,2.1,4.5,6.8 and 7.0 using an amount of the drug equivalent a three times of the dose in the pharmaceutical formulation. The samples of solubility study were analysed by UV-Spectrophotometer using 270nm wavelength. For dissolution tests, 1000 ml of each medium (Acetate buffer, pH4.5) were deaerated in ultrasonic bath for 15 minutes. Drug release tests were carried out according to conventional dissolution procedures recommended for single-entity products using basket (USP Apparatus 1) at 100 and 150 rpm. The test time was set on 60 min. Sampling aliquots of 5.0 ml were withdrawn at 0, 15, 30, 45 and 60 minutes, and replaced with an equal volume of the fresh medium to maintain a constant total volume. After the end of each test time, samples aliquots were filtered, diluted in dissolution medium, when necessary, and analysed by injecting the solution into HPLC using above mentioned optimized HPLC parameters. The invitro dissolution data of Product A and B was compared by two- tailed student's t-test. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors, f1 and f2[9] .

$$f_1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100$$

$$f_2 = 50 \times \log \{[1 + (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where Rt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. The factor f1 is proportional to the average difference between the two profiles, where as factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The factor f2 measures the closeness between the two

profiles. Because of the nature of measurement, f1 was described as difference factor, and f2 as similarity factor[10].FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles.

Optimization of Chromatographic Parameters

The HPLC parameters were optimized on trial and error basis. The optimized chromatographic conditions are as mentioned below,

Mobile Phase: Methanol: Acetate buffer, pH 4.5 (75:25). Column: Zorbax Eclipse XDB-C-18, 150mmX4.6mm, 5micron

Temperature : 30ºC
Flow rate : 1.0 ml/min
Detector : UV-Visible
Wavelength : 270nm
Injection volume : 20µl
Retention time : About 3.5minutes
Run time : About 5 minutes

HPLC Method Validation

Preparation of standard solution

The standard solution was prepared by dissolving 100mg of Sertraline hydrochloride in 100ml dissolution medium. Aliquot of 1ml of this standard solution was transferred to 10 ml volumetric flask and diluted with the same diluent obtaining the final concentration of 100 µg ml-1. The solution was filtered in a 0.45 µm membrane filter before the injection in the column.

Method validation

The dissolution test was validated to Sertraline hydrochloride capsules through the determination of specificity, linearity, intermediate precision, and solutions stability.

System Suitability Testing

System suitability testing is used to verify that the precision / reproducibility of the system is adequate for the analysis to be performed. Parameters such as therotical plates, tailing factor and reproducibility (%RSD for area of five replicates) were determined and compared against the specifications. Five replicate injections of the standard solution were made into HPLC system. The mean, SD and % RSD were calculated.

Specificity

The dissolution tests specificity was evaluated by preparing samples of each placebo of the commercial formulation of capsule and tablets. These samples were transferred to separate vessels with 900 ml of the dissolution medium and stirred for 1 hr at 150 rpm using the Basket apparatus. The interference of the excipients of each formulation was evaluated.

Linearity

Linearity of response was performed using the standard solution and sample solution in the range of 20mcg/ml to 120 mcg/ml (about 20% - 120% of the standard concentration 100 mcg/ml).

Method precision

Dissolution was performed on six capsules of single batch and samples were analyzed as per the test method.

Robustness

The robustness was tested by changing the flow rate by ± 0.2 ml/min and wavelength by ± 2nm. System suitability was evaluated in each condition and sample was analyzed in triplicate

Solutions stability

The solutions stability was analyzed over a specified period of time, verifying the response of the standard and sample solution stored at room temperature.

Results and Discussion

The solubility study of in different buffer solution indicated pH 4.5 is the better dissolution medium for the Sertraline hydrochloride. The results of pH dependent solubility are summarized in Table-1.

The results of dissolution profiles of Sertraline hydrochloride capsules (Product-A) in pH 4.5 Acetate buffer using basket at stirring rate of 100 rpm and 150 rpm are mentioned in Table-2. F_2 value = 97.42 indicated that there was no statistically significant difference between the drug release percent ($P<0.05$) and suggested that any of the stirring speed could be used, for products A and B. However, it was observed that stirring speed of 100 rpm presents high drug release percent until 30 minutes. Fig.1 represents comparative dissolution profile of Product-A and B in pH 4.5 Acetate Buffer at 100RPM. The results of dissolution profiles of Sertraline hydrochloride capsules (Product-B) in pH 4.5 Acetate buffer using basket at stirring rate of 100 rpm are summarized in Table-3.

System Precision

System suitability was evaluated by injecting Standard solution during various days of validation. Theoretical plates were found to be more than 10000.Tailing factor for Sertraline from the standard chromatogram and % relative standard deviation for the peak areas of Sertraline from five replicate injections of standard are verified at every stage. The

% relative standard deviation (% RSD) and tailing factor as per USP of Sertraline peak was found less than 2. The areas of five replicate injection and calculated % RSD are shown in Table-4.

Specificity

There was no interference from blank (dissolution media) and placebo at the retention time of Sertraline. Refer Fig. 2 and 3 for the representative chromatograms placebo and standard respectively.

Method Precision

The results of method precision are represented in Table-5.The % RSD value of less than 2 indicated good precision of the method.

Linearity

The results of the linearity of Sertraline HCl are tabulated in Table-6.The calibration curve of % concentration of Sertraline hydrochloride versus peak area was plotted (Fig.4).The representative linear equation was y = 3.1529x, where x is concentration and y is the peak absolute area. The correlation coefficient was 0.9997, indicating good linearity. The method was found robust for change in flow rate and wavelength. The standard and sample solutions were stable up to 24 hrs at room temperature.

Conclusion

The dissolution test developed and validated for Sertraline hydrochloride capsules was considered satisfactory. The conditions that allowed the dissolution determination were 1000 ml of Acetate buffer pH 4.5 at 37.0 ± 0.5 ºC, basket apparatus and 100 rpm stirring speed. Sertraline hydrochloride was found to be stable for 24hrs indicated good stability of the drug in dissolution medium. The % drug delivery was higher than 90% in 30 minutes for both evaluated products. The validated HPLC method was found to be specific, linear, precise and accurate. The stated analytical method can be successfully used for in vitro dissolution and routine analysis of samples for Sertraline HCL capsules in quality control laboratory.

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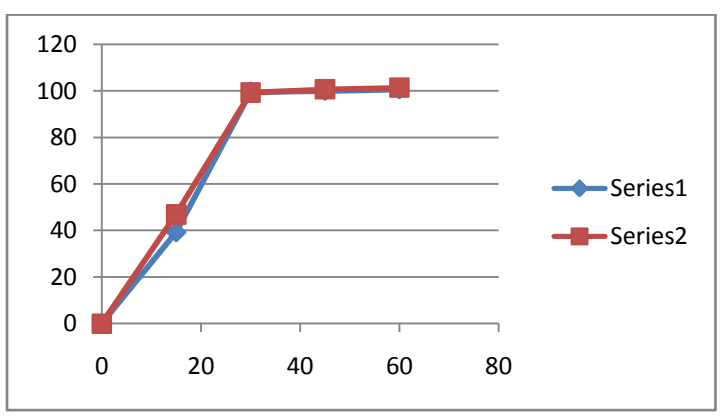

Fig.1: Dissolution Profile of Product-A and B in pH 4.5 Acetate Buffer at 100RPM.

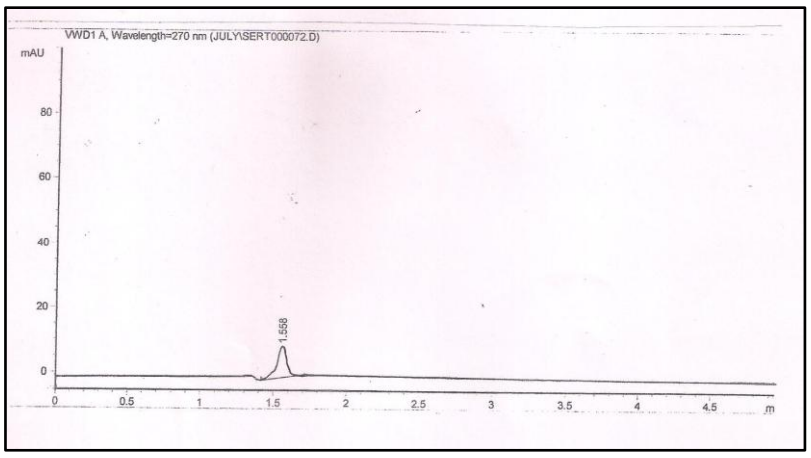

Fig.2: Representative chromatogram of placebo.

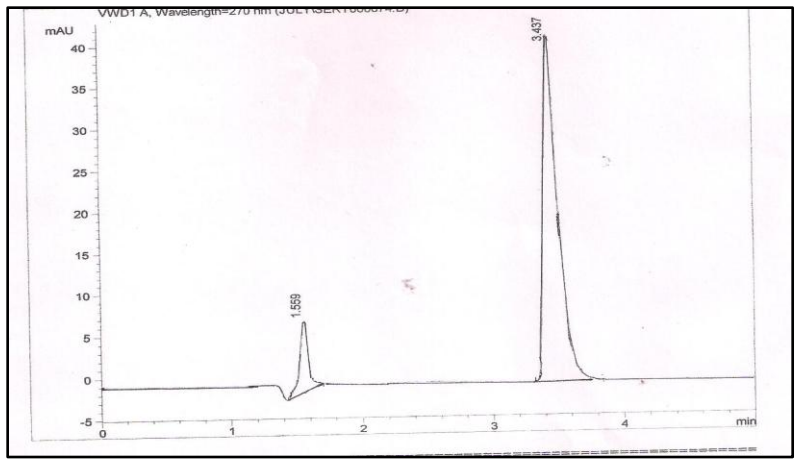

Fig.3: Representative chromatogram of standard.

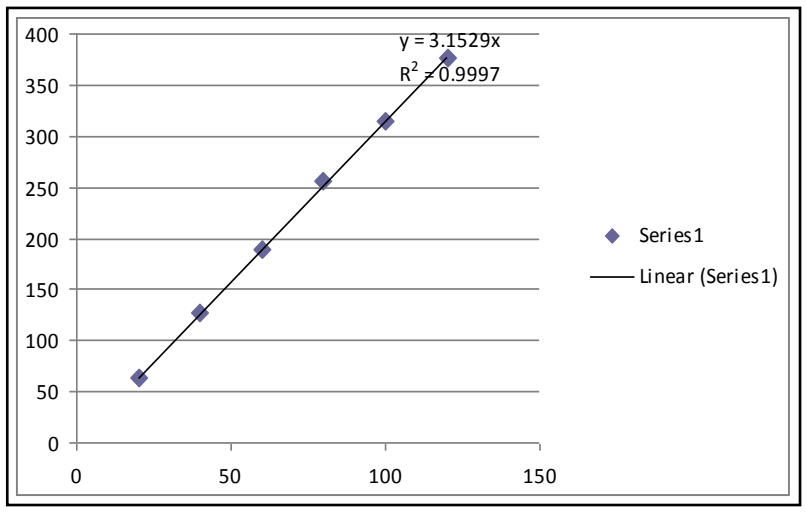

Fig.4: Calibration curve of % Concentration of Sertraline hydrochloride versus Peak Area.

Table 1: pH dependent solubility of Sertraline HCl in different buffer solutions.

pH	Solubility (mg/ml)
1.2	0.008
2.1	0.014
4.5	**0.041**
6.8	0.017
7.4	0.005

Table 2: Dissolution profiles of Sertraline hydrochloride capsules (Product-A).

Time(min)	% Dissolution	
	At 100 RPM	At 150RPM
15	39.2	38.6
30	99.5	97.7
45	99.9	98.8
60	100.6	99.9

Table 3: Dissolution profiles of Sertraline hydrochloride capsules (Product-B).

Time(min)	% Dissolution
15	46.9
30	99.2
45	100.6
60	101.3

Table 4: System Precision Data.

Std. inj. No.	Area
1	333.69485
2	329.50513
3	332.21454
4	330.53891
5	331.40378
Mean	331.47144
SD	1.60
%RSD	0.5

Table 5: Method Precision Data.

Capsule No.	% Dissolution
1	98.2
2	97.5
3	99.3
4	99.7
5	101.0
6	100.2
Mean	99.3
SD	1.3
%RSD	1.3

Table 6: Data for linearity of Sertraline HCl.

Level (%)	Inj.1	Inj.2	Mean
20	65.22201	62.55421	63.88811
40	127.8832	126.544	127.2136
60	188.2128	189.7424	188.9776
80	256.0286	255.7104	255.8695
100	314.523	314.9572	314.7401
120	370.6296	381.3113	375.9704

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