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Synthesis & Identification of Sertraline Hydrochloride Related Impurities

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Abstract

Sertraline hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, which is synthesized for commercial use as a drug substance in the highly pure form of this known impurity. Major Depressive Disorder- Sertraline hydrochloride is indicated for the treatment of a major depressive disorder**.**Sertraline HCl (SRT) oral disintegrating tablets (ODTs) were formulated using a direct compression technique through a 3 x 22 factorial design. Since disintegration time is an essential pharmacopoeial test for ODTs and tablet hardness testing is important for product development, this study aimed to develop an optimized formula with adequate disintegration time and hardness. The effect of different types of sugar-based diluents (xylitol and maltitol), disintegrating agent (Ac-di-sol, crospovidone (CP), and co-processed mixture of Ac-di-sol and crospovidone) and disintegrating agent concentration (5%, 10%) were studied.The impurity was identified as 4-(4-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-ol impurity, synthesized and identified, and the process of its formation was discussed in detail.

Keywords: Sertraline hydrochloride; Method development; Isolation; Introduction Sertraline is chemically known as (1S,4S)-4-(3,4-dichlorophenyl)- N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine.

1. INTRODUCTION

Sertraline, having a chemical structure as shown in **Figure 1,** has a molecular weight of 306.229 and its molecular formula is C17H17Cl2N. Sertraline (trade names Zoloft and others) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class **[1-5].** It was introduced to the market by Pfizer in 1991. Sertraline is primarily prescribed for major depressive disorder in adult outpatients as well as obsessive-compulsive disorder, panic disorder, and social anxiety disorder, in both adults and children. In 2013, it was the most prescribed antidepressant and second most prescribed psychiatric medication (after alprazolam) in the US retail market, with over 41 million prescriptions. Sertraline hydrochloride

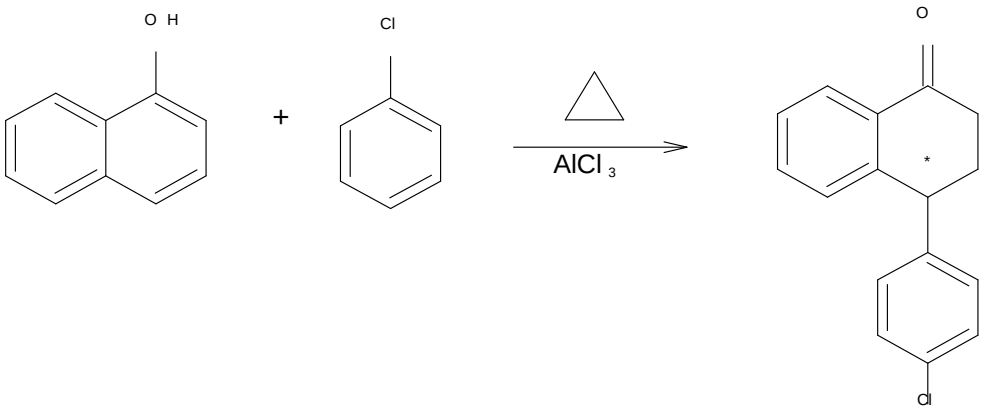
drug substance is official in United State Pharmacopeia (USP) as well as European Pharmacopoeia (EP)**[6-9**]. The listed organic impurities and method of analysis by gas chromatography**[10-12**] arethe same in both pharmacopeias.

2. Materials and Methods :

2.1 Manufacturing process of Sertraline

- **Stage-** I: Preparation of 4-(4-chlorophenyl)-3,4- dihydronaphthalen-1(2H)-one:

Reaction scheme:



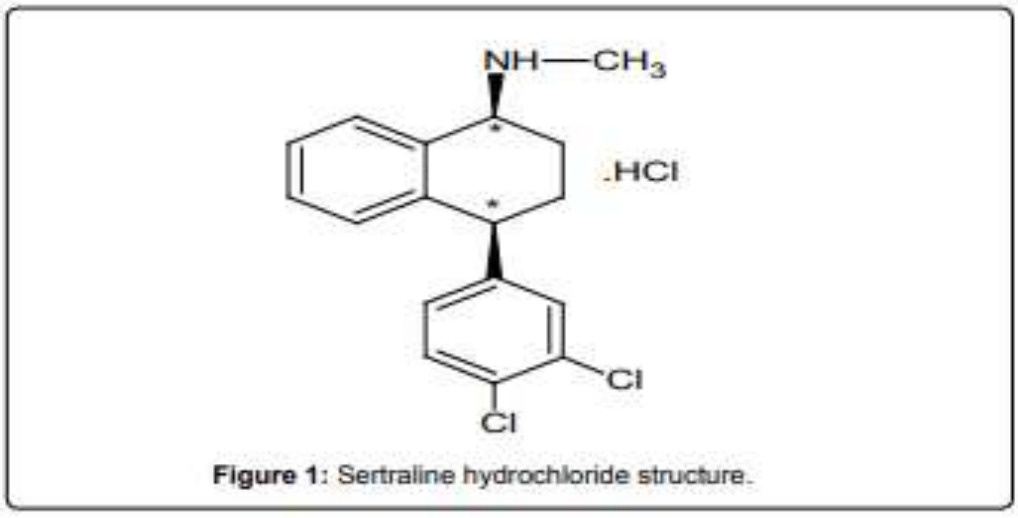


Figure 1: Sertraline hydrochloride structure.

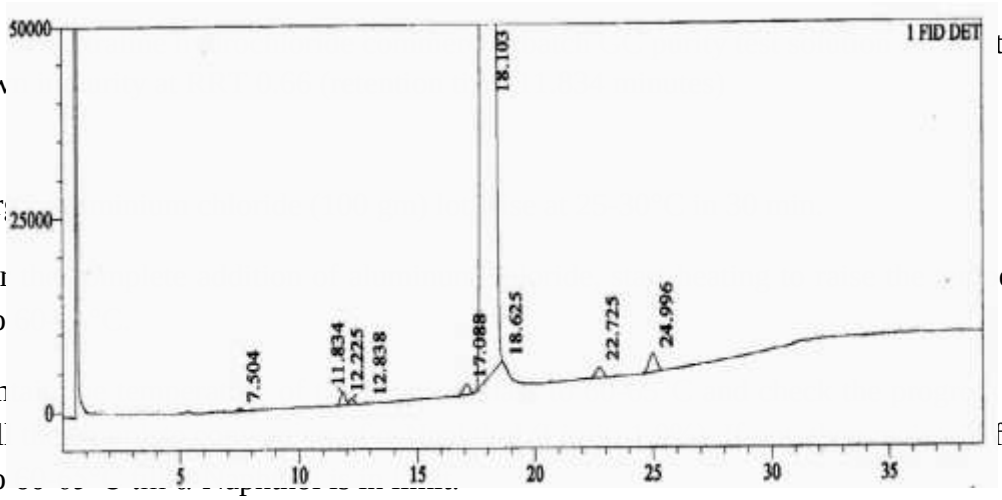
α-Naphthol Chlorobenzene 4- (4 - c h l o r o p h e n y l) - 3 , 4 - dihydronaphthalen-1(2H)-one

S. No.	Raw Material	Qty.	Unit	Mol. Wt.	Moles	Molar Ratio
1	α-Naphthol	50	gm	144.17	0.346	1
2	Chlorobenzene	275	ml	112.56	-	5.5 T
3	Aluminium chloride	100	gm	133.34	0.74	2.2
4	Water	500	ml	18	-	10 T

- **Process:**

1. In a 500 ml four-neck RBF in an oil bath with a reflux condenser, charge α-Naphthol (50 gm).

2. Add Chlorobenzene (175 ml) and start stirring.

Figure 

togram with unknow

3. Char

4. After erature of reaction mass to

5. Main of the reaction on TLC til further the reaction mass to

6. After completion of the reaction, cool the reaction mass to 30-35°C.

7. Add the reaction mass slowly into ice-cold water (500 ml) with maintaining thetemperature to 10-15°C.

8. Separate out the organic and aqueous layer; wash the aqueous layer with chlorobenzene (50 ml x 2 times) and send the aqueous layer to ETP as waste.

9. Collect all organic layers and distill out chlorobenzene under a vacuum at 70-75°C completely to get the oily product. This product is a mixture of 4-(4-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-one and 4-(2-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-one

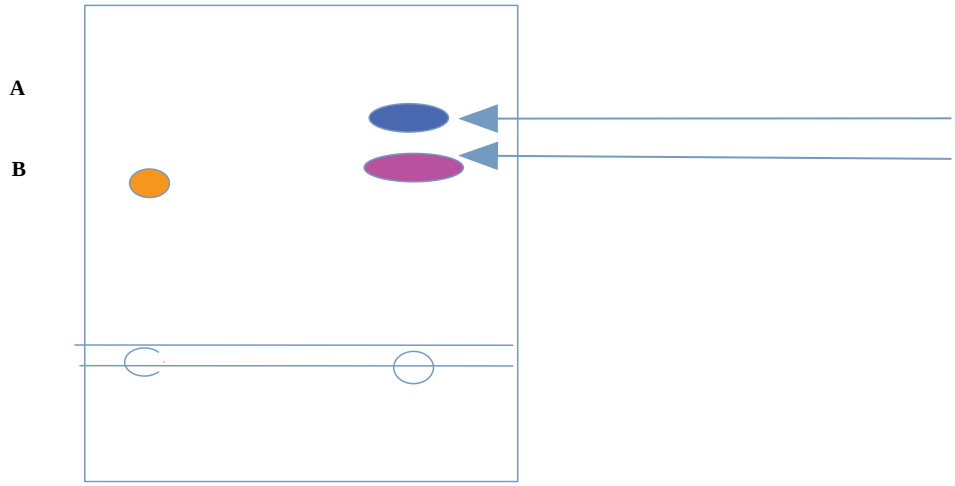
Observed Yield=58 gm

Theoretical Yield=88.75 gm

Percentage Yield=65.35%

10. These two products are separated by column chromatography [Silica bed (60-120 mesh) and mobile phase used is Ethyl acetate:

Hexane=2: 8]



A=4-(4-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-one and

B=4-(2-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-one

11. Separate out 4-(4-chlorophenyl)-3,4-dihydronaphthalen1(2H)-one with the requisite amount and proceed further for the next reduction step.

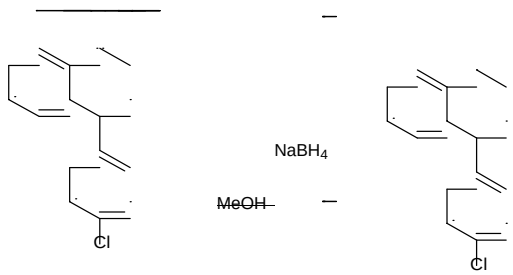
The experimental data is as follows:

S.	Batch number	Input	Output	Reaction	Result

No				condition	
1	SET/40/I/270/45-B	17 gm	2.5 gm	Column purification	Desired Unknown = 99.39%
2	SET/40/I/270/48	15 gm	3 gm	Column purification	Desired Unknown = 98.19%

Stage-II: Preparation of 4-(4-chlorophenyl)-3,4- dihydronaphthalen-1(2H)-ol

Reaction scheme:



4-(4-chlorophenyl)-3,4-dihydro- 4 - (4 - chlorophenyl)- 3 , 4 - dihydronaphthalen-1(2H)-ol naphthalen-1(2H)-one naphthalen-1(2H)-one

Raw materials

S. No.	Raw Material	Qty.	Unit	Mol. Wt.	Moles	Molar Ratio
1	4-(4-chlorophenyl)3,4-dihydronaphthalen-1(2H)-one	3	gm	256.72	0.0116	1
2	Methanol	50	ml	--	--	--
3	NaBH4	0.5	gm	37.83	0.0132	1.14
4	MDC	150	ml	--	--	--

2.2 Methodology:

1. Arrange 250 ml four neck RBF in the water bath and take methanol (50 ml) into it.

2. Add 4-(4-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (3.0 gm) and start stirring.

3. Cool the reaction mass to 10-15°C.

4. Add NaBH4 (0.5 gm) to the reaction mass under stirring with maintaining the temperature of the reaction mass at 10-15°C.

5. Maintain the reaction mass for 2 hr at 10-15°C and check for the complete conversion of 4-(4-chlorophenyl)-3,4-dihydronaphthalen- 1(2H)-one on TLC (Limit: NMT1.0%). If not, then add NaBH4 (0.1 gm) and check for completion.

6. After completion of the reaction, distill out methanol from the reaction mass completely.

7. Add water (50 ml) and stir the reaction mass at 30-35°C.

8. Extract the compound with MDC (50 ml x 3 Times) and separate the organic MDC layer.

9. Collect all organic MDC layers and wash with water (25 ml). Separate out the organic layer and distill out MDC completely at 40- 45°C.

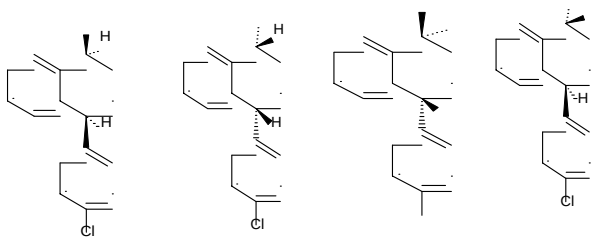
10. Apply vacuum to remove MDC completely to get oil as 4-(4-chlorophenyl)-3,4-dihydronaphthalen-1(2H)-ol.

Observed Yield=2.6 gm

Theoretical Yield=3.02 gm

Percentage Yield=86.09%

11. This product is a mixture of the following isomers



S. No	BatchNumber	Input	Output	Reactionconditio n	Result

1	SET/40/II/270/46	1.2 Gm	0.8gm	Reduction in NaBH4	RT-11.98=51.15%,RT-12.33=47.58%
2	SET/40/II/270/49	3gm	3gm	Reduction in NaBH4	RT-11.99=50.59%,RT-12.33=49.23%

3. Reverse-phase HPLC method of analysis for quantification of isomer I and isomer II of 4-(4-Chlorophenyl)-3,4-Dihydronaphthalen-1(2h)-ol

3.1 Instrumentation and liquid chromatographic conditions:

HPLC method was performed using a Shimadzu-2010$_{CHT}$ HPLC system with a UV detector and Lab Solution software. Separation was achieved with the mixture of Mobile Phase-A: Water: Acetonitrile: Methanol(500:450:50 v/v/v) and mobile phase-B: acetonitrile in gradient elution with timed program T_{min}/A:B:T_0/100:00;T_{20}/100:00;T_{40}/10:90;T_{60}/10:90; T_{61}/100:00 and T_{70}/100:00 with flow rate 1.0 mL/min. The column temperature was maintained at 30°C.Ultraviolet detection was performed at 210 nm.The injection volume is 10µL and the run time is minutes. HPLC column is Cosmosil C18, 250 mm length, 4.6 mm internal diameter, and 5 µm particle size.

3.2 Preparation of standard and sample solutions:

- **Diluent:** Acetonitrile: Water (50:50 v/v)
- **Blank preparation:** Same as diluent.
- **Standard stock solution:** Weigh and transfer accurately about 3.0mg each of Isomer-I and Isomer-2 Reference Standard into 20 ml volumetric flask, add diluent, sonicate to dissolve, and makeup to the mark with diluent.
- **Standard solution:** Transfer 1.0 mL Standard stock solution to 100mL volumetric flask and diluted up to mark with diluent.
- **Test solution:** Weigh and transfer accurately about 5.0 mg of sample intoa 5 mL volumetric flask, add diluent, sonicate to dissolve, and makeup to the mark with diluent
- **Procedure**

Inject blank (diluent), Standard solution, and Test solution in the chromatograph. The retention time of Isomer-I is about 24.5 minutes and Isomer-II is about 28.9 (Figures 4-6).

- **System suitability criteria:** The system is suitable for analysis, **if and only if**,

a) Resolution between Isomer-I and Isomer-II peak should be Not less than 3.0

b) % RSD for areas of Isomer-I and Isomer-II in six replicate injections of standard solution should be no more than 5.0.

- **Calculation**

Integrate the peaks of Isomer I and Isomer II in standard and test solution and calculate both isomers by the following formula.

Area of isomer I or isomer II peaks in the Test solution

Conc of specified isomer in std.solution mg / mL x P x 100 - % specified impurity

Avg. area of isomer I or isomer II peak in std. solution □

Conc of test solution □mg / mL□ x 100

Where P=Potency of specified isomer I or isomer II reference standard.

Chiral HPLC method of separation of enantiomers of isomer I and isomer II of 4-(4-Chlorophenyl)-3,4-Dihydronaphthalen- 1(2h)-ol

- **Instrumentation and liquid chromatographic conditions:** HPLC method was performed using a Shimadzu-2010 CHT HPLC system with a UV detector and Lab Solution software. Separation was achieved with the mixture of Mobile Phase- n-Hexane: Isopropyl alcohol: 1-Propanol: Diethylamine (490:0.5:2.5:0.5 v/v/v/v) in isocratic elution. The column temperature was maintained at 25°C. Ultraviolet detection was performed at 275 nm. The injection volume is 20 µL and run time is60.0 minutes. HPLC column is Chiralpak AD-H, 250 mm in length, 4.6mm internal diameter, and 5 µm particle size.

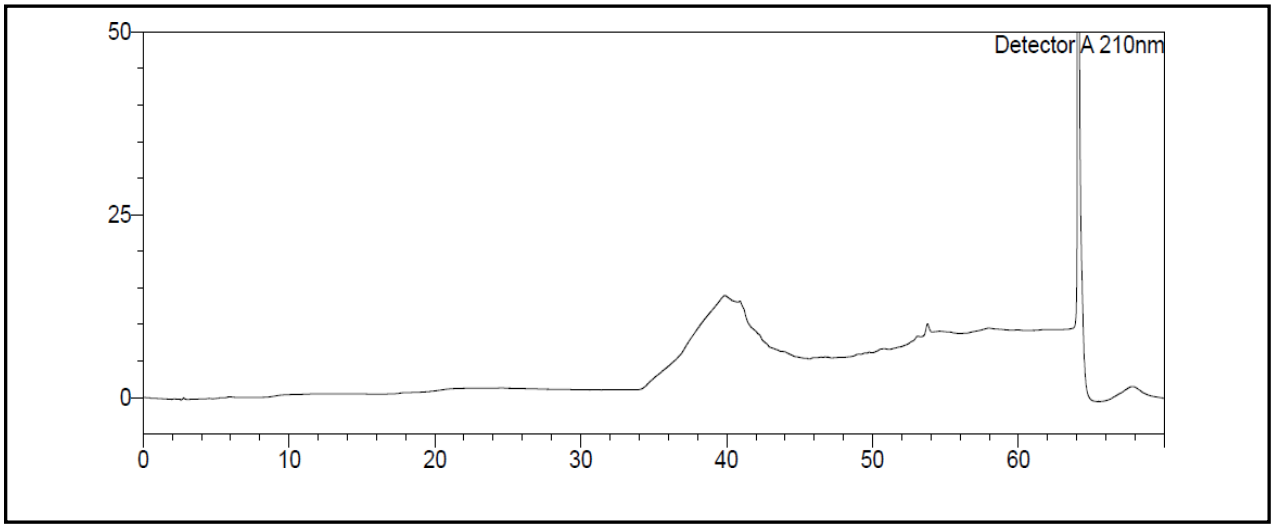
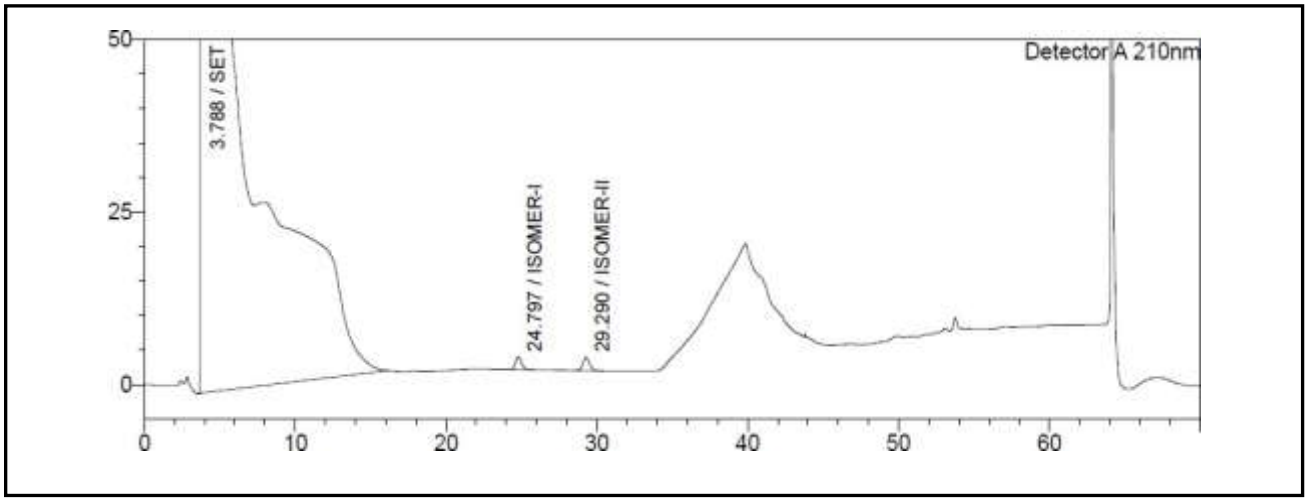


Figure 3



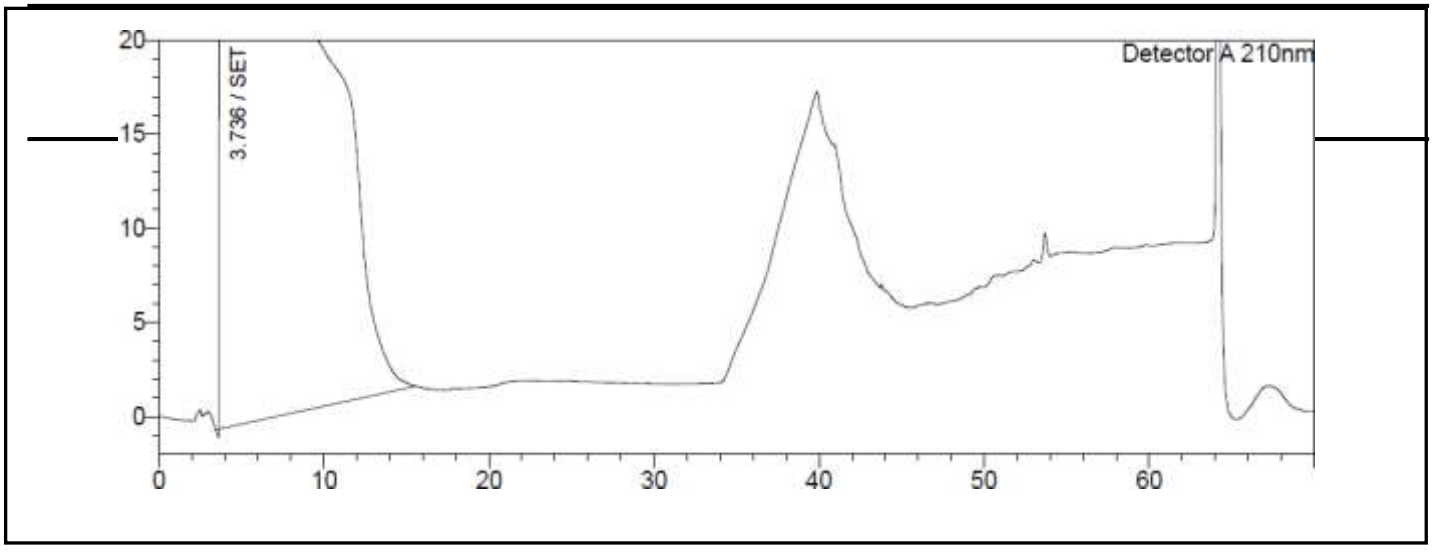


Figure 4 & 5

- **Preparation of standard and sample solutions**

- **Diluent:** Same as mobile phase
- **Blank preparation:** Same as diluent.
- **System suitability solution:** Weigh and transfer accurately about

2.0 mg each of Isomer-I and Isomer-2 Reference Standard into 20 mL volumetric flask, add diluent, sonicate to dissolve, and makeup to the mark with diluent.

- **Test solution:** Weigh and transfer accurately about 5.0 mg of sample into 5 mL volumetric flask, add diluent, sonicate to dissolve, and makeup to the mark with diluent

- **Procedure**

Inject blank (diluent), system suitability solution, and Test solution in the chromatograph. The retention time of Isomer-I peak-I is about

26.83 minutes, Isomer-II peak-I is about 31.24 min, Isomer-II peak-II is about 34.75 min and Isomer-I peak-2 is about 41.94 min (**Figures 3-5**).

- **System suitability criteria**

The system is suitable for analysis, if and only if,

Resolution between closely eluting Isomer-II peak-1 and Isomer- II peak-2 should be not less than 1.5 in the system suitability solution.

4. Results and Discussion

Organic impurities of Sertraline hydrochloride are determined by the gas chromatography method as per USP and EP monograph**[13-17**]. In most of the commercial batches, one major unknown impurity was observed at RRT 0.66 consistently at about 0.15%. This impurity is synthesized with help of chemical synthesis, thin-layer chromatography, and preparative HPLC**[18-21**].

During chemical synthesis, it had been observed that two impurities are formed which are eluting very closely in the GC purity method at RRT 0.66 and 0.67. This chemically synthesized crude material with a mixture of two impurities was applied on preparative HPLC and two separate pure impurities are isolated. The purity of isomer I am 98.29% and isomer II is 99.18%.

5. Conclusion

In conclusion, a process-related impurity of Sertraline hydrochloride is produced according to the synthetic route explained above. Two impurities were identified and synthesized. The reported route of synthesis can be used for isolation of impurity and the analytical methods can be used for routine determination of both impurities in Sertraline hydrochloride in quality control laboratories in the pharmaceutical industry.

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