ISSN 0975 – 2633
Research Article
Arch Pharm Sci & Res Vol 1 No 2 123 - 126 October 2009

Long Term Stability Studies and Shelf-Life Prediction of Sertraline Hydrochloride in 100mg Tablets

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In the present study, long term stability studies (30° C ± 2° C, 65 ± 5 % RH, 12 month) in-house tablets of Sertraline hydrochloride was carried out according ICH Q1A(R), for estimation of shelf life and degradation product at long term stability storage. Accelerated stability studies were also carried at the 40° C ± 2° C and 75 ± 5 %RH for 6 month as per ICH guidelines. The parameters evaluated were physical appearance, percentage drug content, percentage dissolution and percentage related impurities studies of the tablets. The degradation rate constant was found to be 0.197/month and the predicted shelf life was 4.34 years. There was not any significant change from the initial value in accelerated and long term stability conditions and the formulation was found to be stable during the study. The results were demonstrated that accelerated stability testing can reveal the degraded impurities of formulation to an extent.

Key words: Sertraline hydrochloride, ICH guideline, Accelerated stability studies, shelf life.

INTRODUCTION

Stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical products. Many protocols have been used for stability testing, but most in the industry are now standardizing on the recommendations of the International Conference on Harmonization (ICH). These guidelines were developed as a cooperative effort between regulatory agencies and industry officials from Europe, Japan, and United States [1]. Proper design, implementation, monitoring and evaluation of the studies are crucial for obtaining useful and accurate stability data. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product from early phase development through the lifecycle of the drug product [2].

Sertraline is a new antidepressant of the selective serotonin reuptake inhibitor class. The chemical structure of the Sertraline hydrochloride is shown in the fig.1 [3].

Determination of Sertraline in biological samples and pharmaceutical preparations has been reported in the literature using techniques namely GC, GC-MS, LC/MS, LC/UV, MECK and CE [4-9]. But there is not any studies related to long term stability and shelf life determination of Sertraline hydrochloride in tablets.

Thus aim of our work was to carry out stability studies as per ICH guidelines. Hence the present study was carried out at temperature of 40° C ± 2° C and 75 ± 5 % RH for six months as accelerated stability condition and the long term stability studies at was 30° C ± 2° C and 65 ± 5 %RH for 12 month, as India falls under climatic zone III. The parameters evaluated are physical appearance, %age drug content, % dissolution and % related impurities studies of the tablets. An in-house developed and validated stability-indicating analytical procedure by HPLC was applied for determination of Sertraline hydrochloride.

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EXPERIMENTAL

2.1. Chemicals and reagents

All chemicals and reagents were of the highest purity. Sertraline hydrochloride its isomer's standards were purchased from Torrent Pharmaceutical Limited, Ahmadabad. HPLC-grade methanol and triethylamine were obtained from RFCL (Delhi, India). Water was purified using a Milli-Q system (Millipore, Tokyo, Japan). Other reagents and solvents were HPLC grade or the highest grade commercially available, and used without further purification.

2.2. Equipment

An HPLC system (LC-10A, Shimadzu, and Kyoto, Japan) was composed of an auto sampler (SIL 10ADvp), a pump (LC-10AD or LC-10ADvp), a column oven (CTO-10Acvp or CTO-10ASvp), a UV detector (SPD-10AV or SPD-10AVvp), SPD M-10AVP photo diode array detector and a data processor (CLASS-LC10 or CLASS-VP). Detection was performed at 215

nm, and the injection volume was 10µl throughout the work. The long term storage for stability studies was done in Environmental Stability Chamber (TH80 S), Thermo lab Instrument, Mumbai.

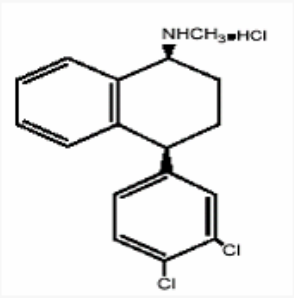

Fig. 1: Chemical structures of Sertraline hydrochloride

2.3. Chromatographic conditions

Separations were carried out on a Zorbax RX C_8 column (250 mm x 4.6 mm, 5 µ, Agilant, USA) with the mobile phase consisting of 50mM KH_2PO_4 containing 0.1% Octane Sulfonic acid sodium salt (pH: 2.5 with Dil. H_3PO_4, 0.2% Triethylamine) and methanol (43:57, v/v). Flow rate was kept at 1.0ml/min with an analysis time of 40 minute and column oven temperature 35ºC. The sample temperature was kept at 15 ± 2° C in autosampler.

2.4. Tablet formulation

Tablets used correspond to the "Sertraline hydrochloride film coated tablet 100 mg" was formulated in our pharmaceutics laboratory. The main excipients of tablet formulation were Hydroxy Propyl Cellulose, Hypromellose, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Sodium Starch Glycolate, and Titanium dioxide. The placebo was also prepared with these excipients.

2.5. Assay of Sertraline hydrochloride 100mg tablet

Standard solution (100µg/ml) of Sertraline hydrochloride was prepared in mobile phase. The five replicates injection (10µl) of standard solution was performed.

Sample solution was prepared by weighing five tablets into a 500 ml volumetric flask. About 400 ml of mobile phase was added and sonicated for 45 minutes to disperse. The solution was cooled and made up the volume with mobile phase and mixed properly. The preparation was centrifuged at 3500 rpm for 15 minute. Five ml of that preparation was diluted to 50 ml with mobile phase and mixed. A portion (10µl) of the solution was injected into the HPLC column. The preparation was repeated in duplicate.

2.6. Dissolution conditions

The dissolution efficiency for Sertraline hydrochloride film coated tablet was highest in acetate buffer 4.5. The dissolution conditions involved USP XXIII paddle (Apparatus 2) apparatus with 900ml of dissolution media at the rotational speed of 75 rpm and temperature 37 ± 0.5° C. 10 ml of the sample was withdrawn at the end of 60th minute. The collected sample was filtered and 10µl was injected in HPLC system.

2.7. Calculations

The stability samples were analyzed at 15 days for first month, every month for first three months and every three month for sixth month, because to derive the degradation constant, to verify the container and closure system and to predict the shelf life to extent. The woolfe equation has been used to estimate the shelf life of a product from data obtained at the same temperature/conditions as those expected for the final product [10]. The time at which drug content diverges from its specifications is estimated by extrapolating the time course of degradation at a specific temperature/condition. When the time course of the drug content (C) is represent by

$$t = t_{avg} = C - C_{avg}/k$$

where, t_{avg} is the average of t, C_{avg} is the average of C, and k is rate constant.

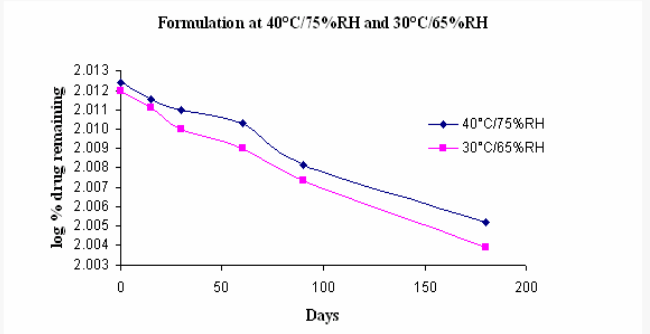

Fig. 2: Comparison of formulation at 30°C/65%RH and 40°C/75%RH (Up to six month)

Table 1: Evaluation of formulation at accelerated and long term stability study

Condition	Sampling Period	Parameters Evaluated					
		Physical appearance	Drug content (%Age)	% Dissolution (60 Min)	Related Impurities		
					% MKI*	% SUMI**	% Total Impurity
30°C± 2°C, 65 ± 5 % RH	Initial	White	102.9	96.9	0.06	≤ LOQ	0.07
	15 days	White	102.7	97.8	0.06	0.02	0.10
	1 Month	White	102.5	96.3	0.06	0.04	0.11
	2 Month	White	102.5	96.0	0.07	0.04	0.13
	3 Month	White	101.9	95.8	0.05	0.08	0.17
	6 Month	Pale white	101.2	95.2	0.05	0.11	0.19
	9 Month	Pale white	100.9	94.8	0.05	0.14	0.21
	12 Month	Pale white	100.5	94.5	0.04	0.13	0.20
40°C± 2°C, 75 ± 5 % RH	Initial	White	102.8	97.1	0.07	≤ LOQ	0.07
	15 days	White	102.6	96.9	0.07	0.02	0.10
	1 Month	White	102.4	97.2	0.06	0.04	0.11
	2 Month	White	101.4	96.2	0.08	0.04	0.15
	3 Month	Pale white	101.7	95.8	0.05	0.10	0.18
	6 Month	Pale white	100.9	94.2	0.05	0.12	0.20

* Maximum Known Impurity
†† Single Unknown Maximum Impurity

RESULT AND DISCUSSION

The design of the formal stability studies for the Sertraline hydrochloride 100mg tablet was based on knowledge of the behaviour and properties of the Sertraline hydrochloride, and from stability studies on the active substance and on experience gained from pre-formulation studies and investigational pharmaceutical products. The parameters that were evaluated play a vital role in the stability studies. The physical appearance was prone to vary in the tablet dosage form. The physical appearance has changed from the initial white to pale white in formulations after subjecting in the accelerated stability conditions (40 ± 2° C, 75 ± 5 % RH) might be the formation of newer degradation products. The known impurity, 2, 3-di chloro isomer of Sertraline hydrochloride was detected at much lower to specification limit. The amount of that isomer was decreased with accelerated conditions. The amount of unknown impurities was increased because of formation of newer degradation

Product in accelerated stability conditions. The drug content was determined by stability indicating HPLC assay method that was validated as per ICH guidelines. There was no significant change from the initial value in accelerated and long term stability conditions as shown in table 1. The degradation rate constant was calculated to be 0.006575/day and the predicted shelf life was 4.34 years as per woolfe equation. The comparison of log % drug remaining with days (time) at 30ºC/65%RH and 40ºC/75%RH was shown in the fig. 2.

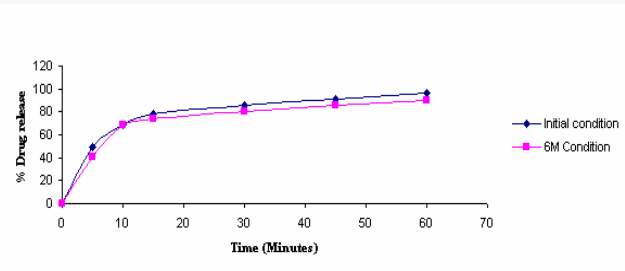

Fig. 3: Comparative dissolution release initial and after 6 month stability at 30°C

The release pattern was altered in the formulations when the formulations were subjected in accelerated stability conditions. The dissolution studies on the initial and stability subjected samples at long term stability conditions did not showed much difference. It indicated that the release pattern was unaffected

by long term stability conditions. The dissolution release of formulation of initial and after 6 month stability condition at 40°±2°C and 75±5%RH was compared as described in table 2.

Table 2: Comparative dissolution release initial and after 6 month stability at 40°C

Time (min)	Initial	After 6 month stability
5	49.2±3.5	40.5±4.2
10	68.6±2.4	62.2±3.0
15	78.3±1.9	73.6±2.3
30	86.2±1.5	80.8±2.4
45	90.8±1.3	86.2±1.8
60	96.3±0.9	92.4±1.1

The release of Sertraline Hydrochloride from the tablets at 40° C and 30° C followed the similar release profile. Even though there was a change in the appearance, the release pattern was unaltered as shown in the fig. 3 for long term stability conditions. Since there was not significant change in the drug content and total impurity, the formulation was found to be stable. The results were demonstrated that stress testing can reveal the degraded impurities of stability testing to an extent. The thermal degradation of stress testing was comparable with accelerated study for 180 days at 40 ± 2° C/75 ± 5 % RH and ambient relative humidity, that the degradation was lesser when compared to other stress conditions.

CONCLUSION

Stability testing is interwoven through the entire fabric of the drug product lifecycle. A detailed knowledge of the stability requirements and the impact on other areas (e.g., container closure, process changes) is needed to properly design and evaluate stability studies in order to ensure minimal delays and minimize costs in developing a new drug product. The developed Sertraline hydrochloride 100mg tablet was stable during its stability studies with a shelf life of about 4.34 years.

ACKNOWLEDGEMENT

The author would like to thank Torrent Research Centre (TRC, Ahmadabad) for providing gift sample and Dr. Praveen Jain for providing research facility.

REFERENCES

[1] ICH, “Stability testing of new drug substances and products Q1A (R2)”, International Conference on Harmonisation, IFPMA, Geneva, 1996.

[2] WHO, “Draft regional guidelines on stability testing of active substances and pharmaceutical products” World health organization, August 2006.

[3] Sertraline hydrochloride, Merck Index 12th, Edition, Merck & Co., New Jersey, 1996; page no. 8541.

[4] J.Snopek, I. Felinek, E.S.Keulemansova, J. Chromatogr A. 452 (1988) 571 – 590.

[5] E.Lacassie, J.M.Gaulier, P.Marquet, J. Chromatogr. B, 742 (2000) 229 – 238.

[6] Dallet P., Labat L., Richard M., J. Liq Chromatogr. & Rel Tech, 25 (2002) 101 – 111.

[7] Adam A.I., Bergold B.M., J. Pharma. Biomed. Anal., 26 (2001) 505-508.

[8] Yuzhu H., Shumin J., Yuying C., J Pharma. Biomed. Anal., 34 (2004) 239–245.

[9] Marilyn X., Foley J.P., J. Chromatogr. A, 1052 (2004) 13–23.

[10] Woolfe A.J., Worthington H.E.C., Drug dev. Commun. 1. (1975) 185-210.