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DEVELOPMENT OF VALIDATED RP - HPLC METHOD FOR THE DETERMINATION OF ZIPRASIDONE HYDROCHLORIDE IN CAPSULE DOSAGE FORM

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Abstract:

This study presents a simple and rapid RP – HPLC method for the determination of ziprasidone hydrochloride in capsule dosage form. To optimize the chromatographic condition, the mobile phase system employed was potassium dihydrogen orthophosphate: ACN: methanol in the ratio of 30:70% v/v. The pH was adjusted to 4.9.The flow rate was maintained at 1ml /min.The developed method was validated for linearity, accuracy, precision, LOD and LOQ and recovery as per the ICH guidelines.Good linearity was obtained over the concentration ranges of 1-10 µg/ml. The percentage recovery was more than 98%.The relative standard deviation by intraday and inter day studies were less than 2%.The LOD and LOQ values were found to be 0.1 µg/ml and 0. 5 µg/ml respectively. The proposed method is less time consuming and with minimum dilution the sample preparation is simple. So the method can be applied for the estimation of ziprasidone hydrochloride in capsules.

Keywords: *Ziprasidone hydrochloride, RP – HPLC, C_{18}column, method validation, ICH guidelines.*

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INTRODUCTION:

Ziprasidone hydrochloride is approved by FDA as an atypical antipsychotic agent which is a derivative of benz-isothiazoyl-piperazine.Currently the drug is been used to treat conditions like schizophrenia,mania and bipolar disorders.Ziprasidone is highly potent with specific antagonistic activity on the D2, D3, 5HT1 and 5HT2 receptors. Chemically the drug is named as 5-[2-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydroindol-2-onehydrochloride [Figure 1]. The empirical formula of the drug is $C_{21}H_{21}ClN_4OS$ and the molecular weight is 412.936. Ziprasidone HCl appears as white or pale pink powder.The drug is freely soluble in chloroform, methanol and ethanol, soluble in ether, sparingly soluble in acetonitrile and insoluble in water. In order to protect from light, the drug should be kept in a tightly closed container. It is marketed as capsules in different strengths [1].

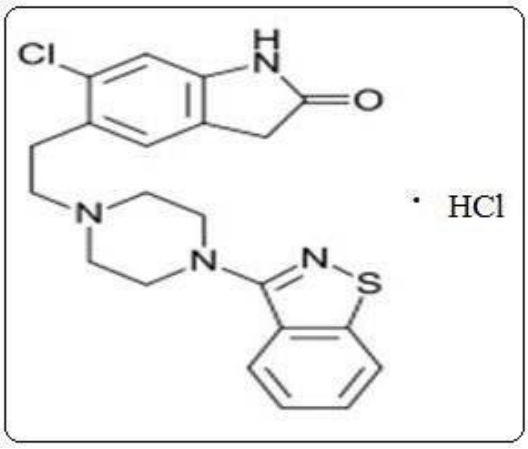

Fig1: Chemical Structure of ZHM

Literature survey reveals that, there are various methods reported to analyse ziprasidone hydrochloride. The methods include UV spectrophotometric method [2-3], HPTLC method [4], RP-HPLC method [5-8], LC-MS-MS in human plasma [10] and LC-MS-MS in rat plasma [11].The current study has focussed on developing a simple and cost effective method and the results of validation parameters were found to be satisfactory.

MATERIALS AND METHODS:

Chemicals and reagents:

The sample of ziprasidone hydrochloride was obtained from sigma Aldrich, India with certificate of analysis. Methanol, acetonitrile, potassium dihydrogen orthophosphate and orthophosphoric acid were supplied by S.D. Fine chemicals Ltd India and Qualigens fine chemicals Ltd., Mumbai, India. Ziprasidone capsule dosage forms were purchased from the retail pharmacy.

Instrumentation and analytical conditions:

A Shimadzu LCMS - 2010EV system equipped with a binary gradient pump, degasser (DGU-20A3), with a variable wavelength programmable PDA detector (SPD-M20A) and an auto sampler system (SIL-20AC) was used to perform chromatographic technique under ambient conditions.

The newly developed method utilized Hibar® C18 HPLC column as stationary phase, dihydrogen orthophosphate buffer, acetonitrile and methanol as the mobile phase. The flow rate was set at 1.0 ml/min and the injection volume was 20 µl. The detection λ max was fixed at 318 nm with run time of 10 mins.

Selection of mobile phase: To select the appropriate mobile phase, various trials were performed based on the literatures. Freshly prepared mobile phase solutions with various buffers, solvents, flow rate and run time was tried. Disodium hydrogen phosphate buffers were used to obtain optimal separation. After all these trials, mobile phase composition of potassium dihydrogen orthophosphate (10mM): methanol: acetonitrile (50:50) at a ratio of 30:70 was finalised to carry out the study, where symmetric peak, ideal retention time, tailing factor < 2 and plate count above 4000 was obtained.

Preparation of buffer: To prepare 0.01M buffer, 0.6804 gms of potassium dihydrogen orthophosphate was weighed and dissolved in 500 ml of millipore water and the pH was adjusted to 4.9 using orthophosphoric acid (OPA).

Preparation of stock solution of ziprasidone hydrochloride: The stock solution of ziprasidone was prepared by transferring accurately weighed 10 mg of drug in a 10ml volumetric flask. Methanol was used as a solvent; the volume was made up resulting in a concentration of 1000 µg/ml. Further serial dilutions were made to get the concentrations required for the study.

RESULTS AND DISCUSSION:

Analytical method validation:

The method was validated by assessing the linearity, accuracy, precision, LOD, LOQ, stability, system suitability, robustness and specificity as per the ICH guidelines [12].

Linearity: Analyzing peak areas of various concentration of ziprasidone reveals linearity in the concentration range of 1-10 µg/ml. Linearity data of ziprasidone is given in table 1. The concentrations against the peak area were plotted and the obtained

calibration graph is represented in fig 2. The recorded chromatogram is depicted in fig 3. Analysis of calibration graph reveals correlation coefficient (r2) of 0.9990 with a slope of 12062.3 and intercept of -2069.93.

Table 1: Linearity data of ziprasidone hydrochloride

S. No	Concentration (µg/ml)	Peak area
1	1	9739
2	2	19670
3	3	35643
4	4	47889
5	5	57586
6	6	72184
7	7	82161
8	8	92111
9	9	107912
10	10	117831

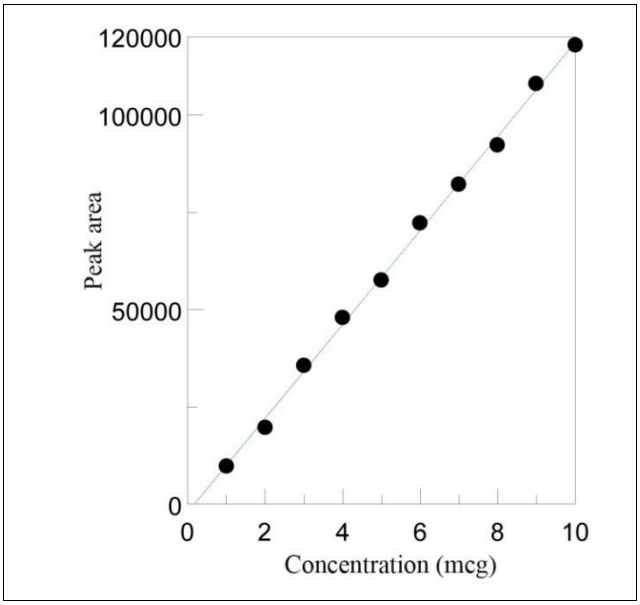

Fig 2: Calibration graph of ziprasidone hydrochloride

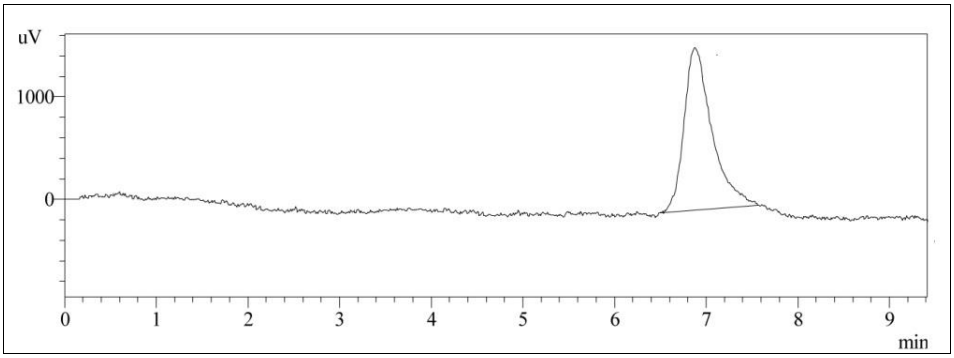

Fig 3: Chromatogram of ziprasidone hydrochloride

Accuracy: The accuracy of the method was determined by calculating recovery of ziprasidone by standard addition method. Known amount of ziprasidone (50%, 100%, and 150%) was added to a pre quantified sample solution. The amount of percentage recovery and % RSD were calculated.The results(table 2) reveal the accuracy of the developed method by obtaining > 98 % recovery of ziprasidone hydrochloride.

Table 2: Recovery data of ziprasidone hydrochloride

Conc. of drug taken (µg/ml)	Conc. of standard added (µg/ml)	Mean peak area ± SD*	Mean Recovery (%)	% RSD*
4	2 (50%)	5.9719±0.0231	98.58	0.3868
4	4 (100%)	8.0245±0.0168	100.27	0.2093
4	6 (150%)	9.9174±0.0115	99.75	0.1159

Precision: The level of precision for the validated HPLC system was acceptable as the overall % RSD achieved was less than 2 %. The results (table 3) reveal the proposed method is precise.

Table 3: Intra-day & inter-day precision data of ziprasidone hydrochloride

Conc. (µg/ml)	Intra-day precision		Inter-day precision	
	Mean peak area ± SD*	% RSD*	Mean peak area ± SD*	% RSD*
1	9738±26.758	0.2747	9692±25.672	0.2648
2	19505±258.66	1.3261	20032±259.72	1.2965
3	35567.66±343.94	0.9670	34712.21±336.82	0.9703

LOD and LOQ: The LOD and LOQ values of ziprasidone were calculated using slope of calibration curve. The LOD and LOQ was found to be 0.1 µg/ml and 0. 5 µg/ml respectively.

Stability of Solution: The stock **s**olutions stored at normal laboratory condition and refrigerated conditions were evaluated for their stability. The results (table 4 & 5) reveal ziprasidone stock solutions stored under room temperature were stable for 48 hrs and refrigerated stocks were stable for 5 days.

Table 4: Stability data of ziprasidone hydrochloride (bench top)

Time (hrs)	Conc. of drug (µg/ml)	Peak Area	% amount remaining	%RSD (n=6)
0	4	47889	100	0.3904
4		46953	98.04	0.8551
8		46527	97.15	0.7900
12		46329	96.74	1.8723
24		45908	95.86	0.3321
48		43561	90.96	0.5435

Table 5: Stability data of ziprasidone hydrochloride (refrigerated)

Time (Days)	Conc. of drug (µg/ml)	Peak Area	% amount remaining	%RSD (n=6)
0	4	47889	100	0.3251
1		46998	98.13	0.7665
2		46732	97.58	0.8042
3		46213	96.50	1.0145
4		45460	94.92	0.2728
5		43389	90.60	0.4412

System Suitability Parameters: System suitability parameters of the developed method are shown in table 6. The listed parameters were found to be within the acceptable limits. Hence the method is suitable for the routine estimation of ziprasidone.

Table 6: System suitability parameters of ziprasidone hydrochloride

Retention time	Tailing factor	Plate count
6.8 min	1.295	4730

Robustness: In order to describe robustness, some chromatographic conditions were slightly altered. The changes includes flow rate by ± 0.1ml/min, volume of organic solvent in mobile phase by ± 0.5% and variation in pH of buffer ± 0.5. The peak shape and retention time were not altered due to the above changes. The results demonstrate the method is robust.

Specificity: Specificity of the method was determined by analyzing chromatograms of blank solution, placebo and assay samples. The chromatograms of blank and placebo did not result in any peak. The chromatogram of assay sample of ziprasidone was not containing any additional peaks other than the drug peak. The above observations confirm the specificity of the method.

Assay of marketed formulation: The average weight of 20 capsules was taken and the contents were powdered. Powder equivalent to 10 mg of drug was weighed and transferred in 10 ml volumetric flask. The powder was dissolved in required quantity of methanol and sonicated for 20 minutes. The volume was made up to the mark with methanol. Further dilutions were made with methanol to achieve concentration in the linearity range.The samples were injected and chromatograms were recorded in the optimized conditions. The percentage assay of the formulation was determined (table 7).

Table 7: Assay of ziprasidone hydrochloride capsules

Brand name	Labelled amount of Drug (mg)	Mean Assay ±SD	% Label Claim	%RSD (n = 6)
Zipsydon®	20	20.623 ±0.1243	99.98 %	0.6027

CONCLUSION:

The current HPLC method developed for the quantification of ziprasidone hydrochloride in capsule dosage is simple, cost - effective, rapid, precise and accurate. The results of the validation parameters were satisfactory. When compared to the previously published methods,simple experimental procedure, sensitivity and less run time are added advantages of the developed method.The method is suitable for the routine quantification of ziprasidone hydrochloride in capsule dosage form.

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