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SYNTHESIS, CHARACTERIZATION AND PROCESS VALIDATION OF OLANZAPINE INTERMEDIATES

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ABSTRACT

N-Formyl compounds have been widely used in organic synthesis as Protecting of amines, precursor isocyanide preparation, an intermediate For mono methylated amines from primary amines, and catalyst for allylation or Reduction. Thus a number of formylating methods have been reported Acetic formic Anhydride continues to be the most widely used formylating reagent, but it is sensitive to atmospheric moisture and cannot be stored due to decomposition to acetic Acid and carbon monoxide. Many other useful formylation reagents have been Reported such as chloral, activated formaldehyde using DCC or EDCI, activated Formic ester and ammonium formate. Despite the usefulness of these reagents, such as high yields and mild conditions, they are less practical they are either toxic or Expensive and the preparation and use of these reagents require strictly anhydrous Conditions. We were reported a practical formylation procedure using aqueous 85% Formaldehyde. The documented evidence for the manufacturing process for the Olanzapine Intermediate was shown that the process has consistently produced the product within the Predetermined specifications.

KEYWORDS: N-Formyl Piperazine, piperazine, formaldehyde.

INTRODUCTION

A process is a series of inter related functions and activities using a variety of specified actions and equipment which is designed to produce a defined result. To validate the reproducibility and consistency of a process, the full defined process is carried out using validated equipment, under the established procedure usually at least 3 times. The process must successfully and consistently meet all acceptance criteria each time, to be considered a validated process.[1]

Process validation studies examine a process under normal operating conditions to prove that the process is in control. Once the process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications to the process are made, or problems occur, or equipment or systems involved in the process are changed, a re-validation of the process would be required.[1]

N-Formylation of amines

When the amount of formaldehyde was reduced and toluene was used as a solvent with Dean Stark trap, yields were dramatically increased. The effect of changing the solvent was studied with equivalents of formic acid. When the reaction was carried out in benzene, the formamide was obtained in only 40% yield The yield was improved to 98% when the reaction was run in either toluene or xylene. The best result was obtained with equiv. of formic acid in refluxing toluene using Dean-Stark trap.[2] Use of molecular sieve also gave satisfactory result with less convenience. Based on these preliminary results, the application of this procedure (with 1.0-1.2 equiv. of formic acid in toluene with Dean-Stark trap) to various amines was investigated. Aromatic amines such as aniline and N-methylaniline proceeded smoothly to give the corresponding N-formyl compound in quantitative yields, whereas, p-nitroaniline was inert under the condition. Primary amines were easily formylated to provide alkyl formamide in excellent yields. Also, secondary amines readily reacted to afford the corresponding formamide in 98 and 94% yields, respectively. O-formylation of alcohol or phenol derivatives under these reaction conditions was not successful. No reaction was observed with phenol.[2] with alkyl alcohol the reaction proceeded to only 25% conversion after 24 hours. It was found that this reaction is chemo selective, then only N-formylated product was formed with molecules containing both the hydroxyl and the amino group. N-Formyl amino acid esters could be obtained in good to excellent yields without racemization using the procedure outlined in this report. L-Proline benzyl ester was converted to the corresponding N-formyl compound without racemization in 99% yield.[2]

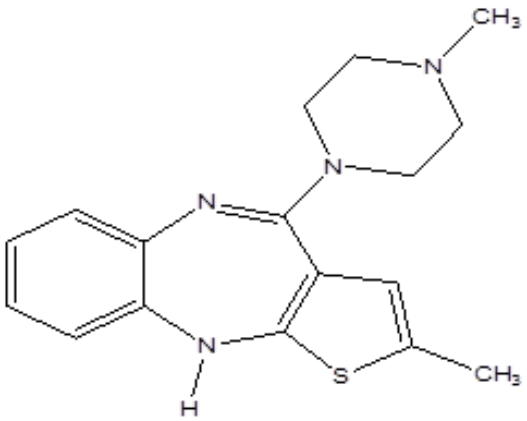


Figure 1: Olanzapine Structure.

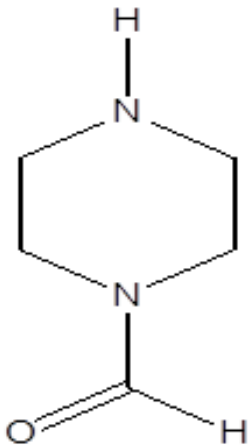


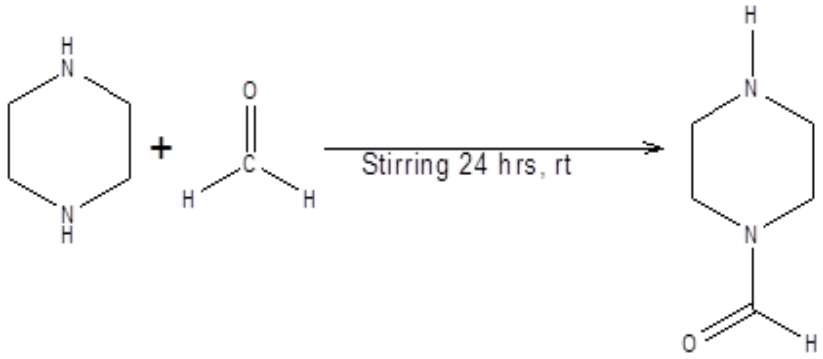
Figure 2: N-Formyl Piperazine.

MATERIALS AND METHODS

Piperazine anhydrous, Formaldehyde ethyl acetate, ethanol DCM was obtained from Globe Chemie pvt. Ltd. Nasik. Solvents and all other chemical reagents used were of analytical grade.

Synthesis of N-Formyl Piperazine

1 mmole of Piperazine anhydrous (0.08614 gm) was taken in conical flask And the in conical flask 1.2 m mole of formaldehyde solution (0.03 ml) was added. Conical flask was placed above plate with magnetic stirring at room temperature for 24 hours. Then Reaction mixture was filtered. Reaction mixture was extracted with ethyl acetate. The Reaction was monitored by TLC using mobile phase Ethanol: Ethyl acetate (5:5). Then reaction Mixture was transferred in container.



Piperazine Anhydrous | Formaldehyde | N-Formyl Piperazine

Scheme 1

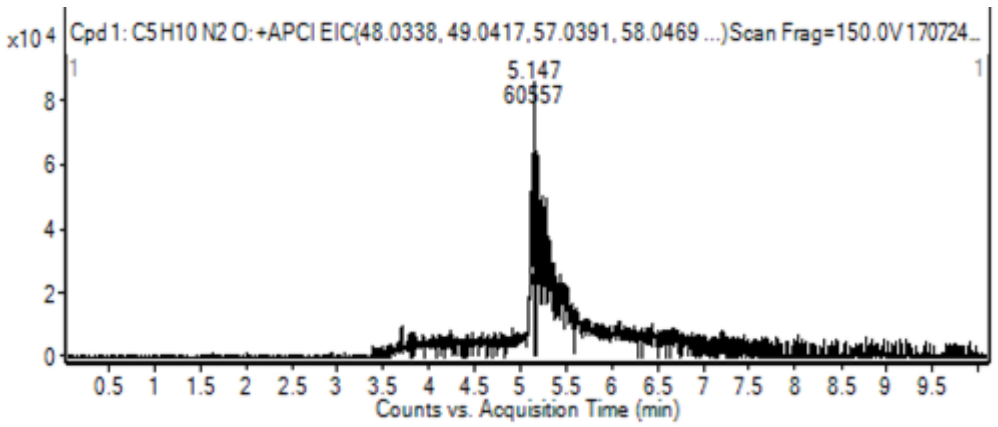
GC-MS of N-Formyl Piperazine

Table No.1: Observed Rt and Reference Mass.

Label	Tgt Score	Mass Error (ppm)	MFG Formula	Tgt. Formula	Obs. RT	Ref .Mass	Obs. Mass
cpd1: C5H10N2O	99.68	1.38	C5H10N2O	C5H10N2O	5.161	114.0793	114.0795

Table No.2: Observed Retention time and Tangential Mass.

Obs.m/z	Obs.RT	Obs. Mass	DB Formula	Tgt. Formula	Tgt. Mass	Tgt.Mass Error	Find cpds Algorit
115.0867	5.161	114.0795	C5H10N2O	C5H10N2O	114.0793	1.38	Find by Formula



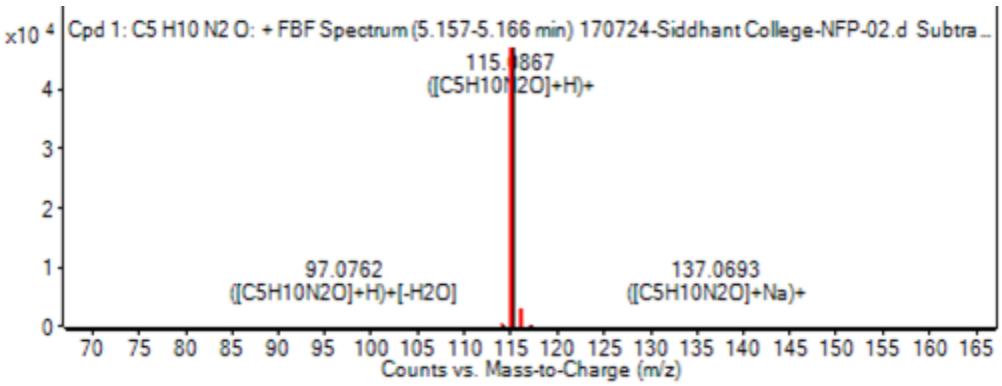
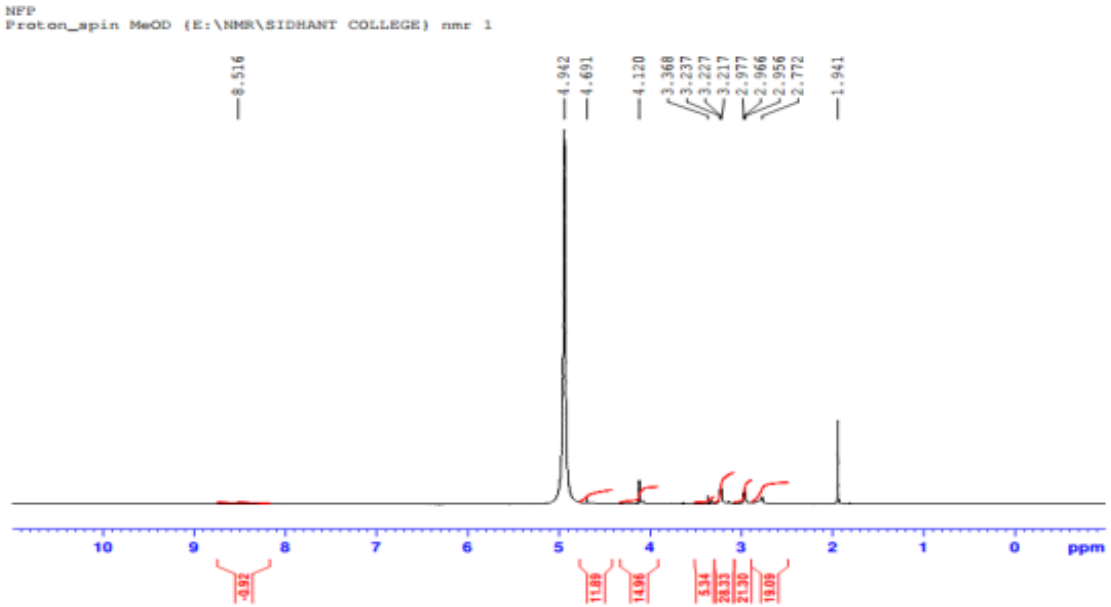


Table No.3 MS Spectrum Peak List.

Obs m/z	Charge	Abund	Formula	Ion/Isotope
97.0762	1	56.91	C5H10N2O	(M+H)+[-H2O]
114.0762	1	122.34	C5H10N2O	M+
115.0867	1	47032.89	C5H10N2O	(M+H)+
116.0894	1	3230.42	C5H10N2 O	(M+H)+
117.0919	1	291.74	C5H10N2O	(M+H)
119.0611	1	77.75	C5H10N2O	(M+Na)+[-H2O]
137.0693	1	52.34	C5H10N2O	(M+Na)+

H_1 NMR Interpretation



H_1 NMR Interpretation of NFP: Batch A[1]

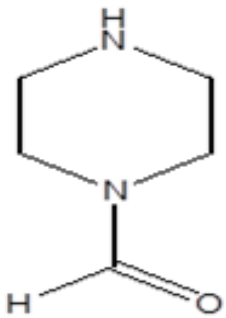


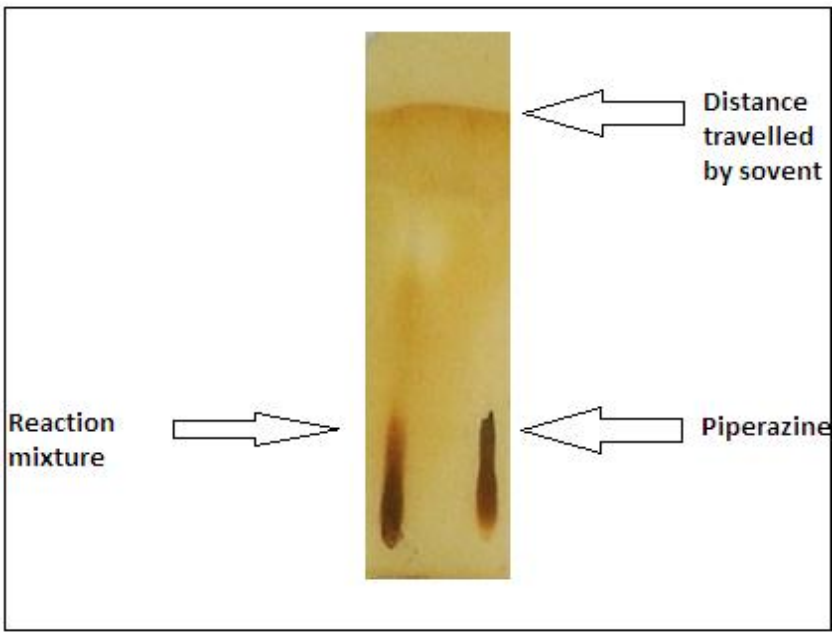
Table No. 4.

Sr.No	Chemical shift in ppm	Splitting	Assignment
a,b	2.956-2.977	4H t	CH_2 Alkyl
C,d	3.217-3.368	4H d,t	CH_2 Alkyl
e	2.772	1H	NH 2^0 Amine
f	8.516	1H s	CH Aldehyde
	Total Proton	**10 H**	**Complies**

Table No.5 Validation Protocol of N-Formyl Piperazine.

Parameters	Batch Code			
	A[1]	**B[1]**	**C[1]**	**D[1]**
Rf Value	O.241	0.423	0.262	0.273
Boiling Point	261^0 C	263^0 C	264^0 C	266^0 C
NMR	2.956-2.977	3.217-3.368	2.772	8.516
IR	1887, C=O	1700, C=O	1735, C=O	1765, C=O
GC-MS	Rt-5.161, Mol.Wt-114.0762	Rt-5.034, Mol.Wt-114.0867	Rt-5.135, Mol.Wt-114.0649	Rt-5.158 Mol.Wt-114.0527

TLC of N-Formyl Piperazine



CONCLUSION

The documented evidence for the manufacturing process for the Olanzapine Intermediate, was shown that the process has consistently produced the product within the predetermined specifications.

From the review of data recorded during manufacturing process, finished product analysis of all the four validation batches, it is concluded that the manufacturing process is consistent and meets the pre-determined specifications and quality attributes. Hence the manufacturing process of Olanzapine Intermediate, stands validated.

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