Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2013, 4(3):173-177

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Understading and controlling the formation of process related impurity during development of eszopiclone

Neelakandan K.*[2], Anil B. Chavan[2], N. Santosha[2], B. Prabhakaran*[2,3] and N. Santhi[1,3]

[1]*Department of Chemistry, GOVT Arts College, Chidambaram, Tamilnadu*
[2]*Emcure Pharmaceuticals Ltd, R & D Centre, M.I.D.C., Pimpri, Pune*
[3]*Department of Chemistry, Bharathiar University, Coimbatore, India*

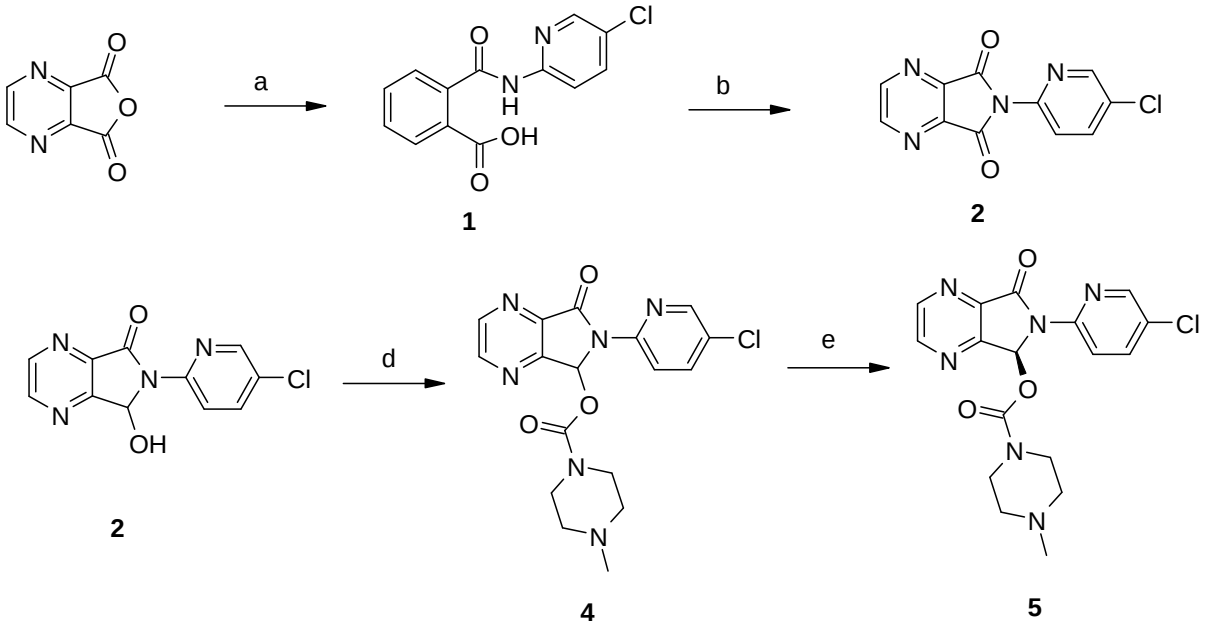
ABSTRACT

*Eszopiclone (**5**) belongs to a novel class of non-benzodiazepine hypnotics which is structurally unrelated to existing hypnotics. During commercialization, upto 3.85% of a unknown impurity was observed in penultimate step. This was identified as a N-methyl piperazine related impurity of Eszopiclone. Subsequent investigation and design of experiments led to the identification of factors responsible for the formation of this impurity. Implementation of knowledge gained from the reproducible experiments enabled the suppression of this impurity to the acceptable levels. In this manuscript different parameters for process developments such as optimization of critical parameters to control the new impurity, identification, synthesis origin and control of impurity of a scalable process for Eszopiclone are discussed.*

INTRODUCTION

For synthesis of API on large scale, selection of route plays important role not only to meet the cost effective process but also quality of API conforming to ICH guidelines. Process related impurities during synthesis of API are very specific to the scheme selected for its preparation. Removal of process related impurities from API sometimes requires number of crystallization or preparative HPLC or needs change in the synthetic route. Repeating prior art process in laboratory and achieving 98.0% product formation is very easy but for the chemist if the API is to be prepared as per ICH guidelines, then reducing known impurity below 0.15% and unknown impurity below 0.10% is very difficult or sometimes impossible if API functionality is same as process related impurity[1]. Process related impurities can be controlled if it is addressed in raw material or sometimes by addressing critical parameters responsible for formation of impurity and by successive purification of final API. Out of these above parameters for controlling impurity, successive purification of API to eliminate impurity is not plant feasible process. If critical process parameters responsible for generation of impurities are optimized and impurity is controlled below 0.10% would be the plant feasible process. Here we would like to discuss process research and development attempts for identification synthesis origin and control of impurities by controlling critical parameters during synthesis of Eszopiclone. The chemical synthesis of Eszopiclone as shown in Scheme -1 has been reported.[2-6]

Scheme-1 Synthetic route to Eszopiclone



(a) 2-amino-5-chloro pyridine, CH_3CN, reflux (b) Ac_2O, reflux (c) KBH_4, 1,4 dioxane, H_2O (d) 4-methylpiperazine-1-carbonyl chloride HCl, Et_3N, pyridine reflux (e) Tartaric acid or Maleic acid

2-amino-5-chloro pyridine was condensed with pyrazine-2,3-dicarboxylic anhydride afforded acid compound **1** which on treatment with acetic anhydride at reflux temperature furnished cyclized compound **2**. Reduction of cyclised compound was achieved utilizing sodium borohydride to give imino alcohol **3**. Most important and critical step in this process was coupling of imino alcohol **3** with 4-methylpiperazine -1-carbonyl chloride for formation of racemic Zopiclone **4** which resolved using tartaric acid to afford Eszopiclone **5**. After getting success in laboratory, our next target was to commercialize the product on large scale, we sucessfully prepared imino alcohol on plant scale, while preparing Zopiclone **4** we encountered difficulties that after complying reaction monitoring with imino alcohol content not detected and isolating Zopiclone in solid form, we observed that upto 3.85% area of new impurity was detected by HPLC at RRT 0.82 which was not observed during reaction monitoring. We thought that during resolution impurity will be eliminated from the API hence it was decided to resolve using tartaric acid followed by neutralization and crystallization in ACN to afford chirally pure Eszopiclone **5**. After its analysis we observed that this new impurity turned out to be difficult to remove from the API. Thus we decided to initiate study to identify this impurity under where and how it was being formed and could be controlled in the process.

MATERIALS AND METHODS

Experimental section:

All chemical were purchased from commercial suppliers. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian 400 MHz, and mass spectra were determined on an API 2000LC/MS/MS mass spectrometer, Applied Biosciences. HPLC were recorded on Shimadzu or waters instrument.

HPLC Method:

Column: Inertsil C-18 (4.6mm x 250), 5µ or equivalent; flow rate 1.5 mL/min; wavelength: 303 nm; Injection volume20 µL; Run Time: 70 mins. Mobile Phase: 8.1 gm of Sodium lauryl sulfate and 2.1gm Sodium dihydrogen phosphate dihydrate in water (1000mL), Prepare a homogenous mixture of 60 volumes of above prepared buffer and 40 volumes of Acetonitrile. Adjust the pH of the mobile phase to 3.5 ± 0.05 with 10 % orthophosphoric acid. Relative retention time: Compound- 4: 1.0, Impurity-6: About 0.82

Preparation of Zopiclone [Improved process.] (4)

To the suspension of imino alcohol (10 kg, 38.07 mol) in DCM (100 L) and N-Methylpiperazine carbonyl chloride HCl (11.4 kg, 57.10 mol) was added triethyl amine (30.22L) and DMAP (0.25 kg , 2.04 mol) at 25 to 30 °C. The solution was stirred for 6.0 hrs at 35 to 40° C, cooled and organic layer was washed with 3 X 5 L DM water and concentrated under vacuum below 40°C followed by methanol stripping (1.0 L) to remove traces amount of DCM was carried out below 40°C and methanol (4.0 L) was added and the mixture cooled to 0 to 5°C, filtered and dried under vacuum below 45°C to give 11.30 Kg (76.3%) Zopiclone with purity 99.80% and any individual impurity less than 0.10% and identified impurity **4** was 0.08%. ^{1}H NMR (400 MHz, $CDCl_3$) : 2.04-2.42 (m, 3 H), 3.25-3.65 (m, 4H), 7.78-7.81 (dd, 1H), 8.02 (s, 1H), 8.40 (d, 1H), 8.52 (d, 1H), 8.85 (d, 1H), 8.89 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) : 43.90, 45.94, 54.33, 78.93, 115.92, 128.12, 137.97, 143.69, 146.57, 147.60, 147.67, 148.29, 153.28, 155.38, 162.76 Anal. Calcd for $C_{17}H_{17}ClN_6O_3$: C, 52.52; H, 4.41; N, 21.61. Found : C, 52.49; H, 4.48; N, 21.67. Purity by HPLC: 99.80 %; *m/z*: 388.9, 410.9.

Preparation of Eszopiclone (5) .

To a suspension of Zopiclone (10 kg, 25.71 mol)), acetonitrile (20 L) and DCM (40 L) was added DBDTA (6.78 kg, 17.99 mol)and heated the reaction mass to 45°C and maintained for 2 hrs. The suspension was cooled to 25 to 30°C, filtered, washed with acetonitrile and dried at 50°C to give chirally pure Eszopiclone DBDTA salt which was added in a mixture of DCM (50L) and DM water (50L) and pH of reaction mass was adjusted to 11.0 to 11.5 and DCM layer was separated and concentrated under vacuum below 40°C. The concentrated mass was dissolved at 80 to 82 °C in 90 L acetonitrile, charcoalised and filtrate was concentrated atmosperically upto 35 L, the suspension was cooled, filtered and dried under vacuum to afford 3.75 kg (37.5 % yield) Eszopiclone in which identified impurity level was 0.05 %.

Purity by HPLC: 99.92 %; *m/z* : 388.9, 410.9; ^{1}H NMR (400 MHz, $CDCl_3$) : 2.25 (s, 3 H), 2.26-3.48 (brm, 8H), 8.41 (d, 1H), 7.76 (dd, 1H), 7.76 (dd, 1H), 8.52 (d, 1H), 8.89 (d, 1H), 8.85 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) : 45.00, 43.89, 54.33, 78.93, , 115.92, 128.12, 137.97, 143.69, 147.60, 146.57, 147.67, 148.29, 153.28, 155.38, 162.76; Anal. Calcd for $C_{17}H_{17}ClN_6O_3$: C, 52.52; H, 4.41; N, 21.61. Found : C, 52.49; H, 4.48; N, 21.67.

Preparation of N-Methylpiperazine related impurity (6)

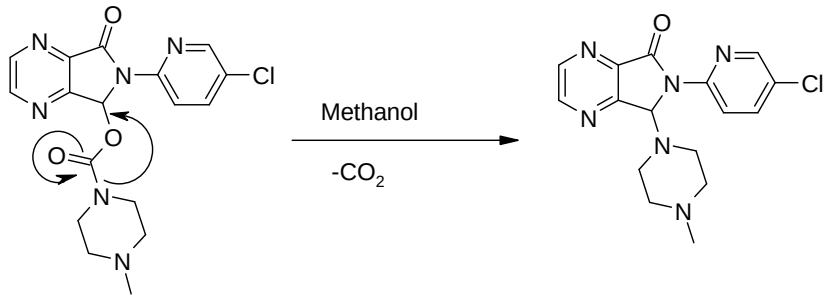
A suspension of racemic Zopiclone (25 gm, 0.064 mol) and methanol (125 ml) was heated at reflux for 6 hrs . The suspension was cooled to 25 to 30°C, filtered and dried to give 15 gm N-Methyl piperazine related impurity. ^{1}H NMR (400 MHz, $CDCl_3$) 2.20 (s,3H), 2.29-2.85 (m, 8H), 6.68 (s, 1H), 7.76-7.79 (dd, 1H), 8.12 (d, 1H, *J*=8.68 Hz), 8.42 (d, 1H, *J*=2.56 Hz), 8.81-8.84 (m, 2H), *m/z* : 345.1.

RESULTS AND DISCUSSION

After repeated attempts to isolate this new impurity by preparative HPLC, we were unable to do so and only molecular weight was established by HPLC-MS as 344. The molecular weight of this new impurity suggested it is nothing but process related impurity of API. A number of hypothesis were made for molecular weight 344 and concluded it could be due to decarboxylation of Zopiclone followed by reaction with N-methyl piperazine and forms the new observed impurity.

In order to understand the dynamics of the formation of impurity, we decided to investigate the impurity formation. The following features were chosen to be investigated for the formation of impurity. Temperature during reaction, amount of N-methyl piperazine carbonyl chloride, amount of triethylamine, temperature during DCM recovery and methanol distillation. A number of experiments were performed. In each case, samples from the reaction were analysed by HPLC and concluded that amount of N-methyl piperazine carbonyl chloride, amount of triethylamine, temperature during DCM recovery had no impact on the formation of new impurity. But surprisingly after DCM distillation, methanol stripping to remove traces amount of DCM from the reaction was carried at different temperature and observed that if methanol stripping is done inbetween 45-50 °C then the formation of new impurity was observed upto 1.80%. To know the temperature effect during methanol stripping, intentionally the reaction was kept in methanol at reflux temperature for 3 hrs and its HPLC confirmed that 60% formation of impurity was observed. It was purified by column and characterized to be N-Methyl piperazine related impurity. From mechanistic point of view, we postulated that at higher temperature in methanol decarboxylation of Zopiclone and formation of process related N-methyl piperazine impurity formation takes place.

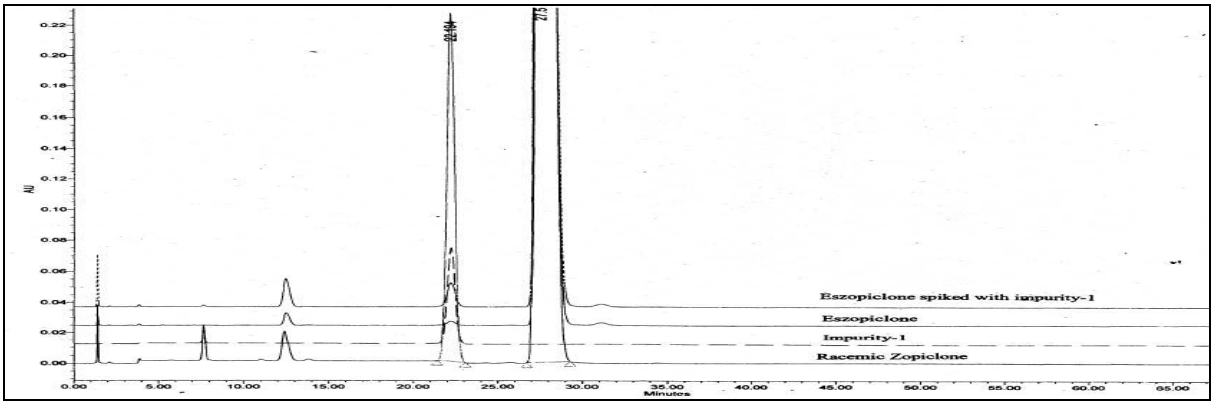
Proposed mechanism for formation of impurity6



4 **6**

After isolating the impurity in our hand, the unknown impurity in a contaminated batch of Zopiclone was compared with synthesized impurity via spiking experiment (Figure-1). To our delight, the synthetically prepared impurity matched unambiguously with unknown impurity seen in previously manufactured batches of Zopiclone**.**

Figure -1 Spiking studyof impurity 6 and contaminated batches



A higher temperature during methanol distillation for the formation of impurity couldnot be excluded and decided to evaluate this parameter. Accordingly reaction for the formation of Zopiclone was performed on higher scale. After completion and work up the DCM was concentrated followed by methanol stripping was given below 40°C and Zopiclone was isolated and analysed by HPLC. As per our expectations the impurity observed was only 0.08%. After having established good understanding of critical parameter for the formation of impurity three subsequent runs of this reaction confirmed the effectiveness of parameter and material of high quality with impurity-**6** levels of 0.08% is obtained. Experimental results for plant batches are shown table no 1.

Table -1 Efficiency of optimized process to control identified impurity (6)

Sr no	Compound Name	Reaction mass	Residue after MDC distillation	Residue after Methanol distillation	Zopiclone purity after filtration
910ZOP03S1 [10kg input]	Zopiclone(**4**) Identified imp (**6**) Imino alcohol content (**3**)	97.89 ND ND	97.89 ND ND	97.83 0.05 ND	99.92 0.05 ND
910ZOP03S2 [10kg input]	Zopiclone(**4**) Identified imp (**6**) Imino alcohol content (**3**)	97.75 ND ND	97.75 ND ND	97.65 0.08 ND	99.80 0.08 ND
910ZOP03S3 [10kg input]	Zopiclone(**4**) Identified imp (**6**) Imino alcohol content (**3**)	97.20 ND ND	97.20 ND ND	97.20 ND ND	99.93 ND ND

CONCLUSION

In conclusion we have successfully identified an impurity which was detected during commercialization of Eszopiclone. Subsequent experiments have enabled us to identify the critical parameter due to which impurity is controlled to acceptable level in small as well as commercial scale. Temperature during methanol distillation should be below 40°C to control the formation of newly identified impurity.

Acknowledgment
We wish to thank Mr. Samit Mehta, our management, IPD and ARD group of Emcure Pharmaceuticals Ltd. for their generous support and constant encouragement. Finally it is pleasure to acknowledge the reviewers and editor for valuable suggestions.

REFERENCES

[1] ICH Guideline Q3A (R), Impurities in new drug substances, February 7, **2002**
[2] H. Tamura, et al. *Phrmacometrics*, **1983**, 26(6), 969-1003
[3] C. Claude, J. Claude, M. Messer, US patent No. 3862,149
[4] C. Claude, J. Claude, M. Messer, US patent No 4220, 646
[5] J.Young, S. Brandt, WO93/10788
[6] T. Jerussi, Q. Fang, US2004/0147521A1