AN INVESTIGATION INTO THE FORMATION OF IMPURITY DURING THE PROCESS DEVELOPMENT OF SUMATRIPTAN SUCCINATE

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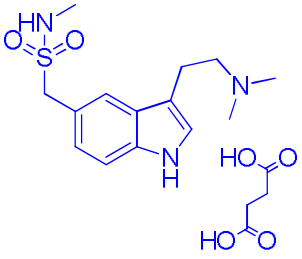
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Abstract: During the process development of sumatriptan succinate, we have observed the formation of unknown impurity at enhanced level which was identified as a cyclized impurity 7. Present article discussed about the development of robust process for the commercial production of sumatriptan succinate substantially free from impurities. Identification, isolation and characterizations of impurity were also discussed.

Keywords: Sumatriptan Impurity, Cyclized Impurity, Indole.

I. INTRODUCTION

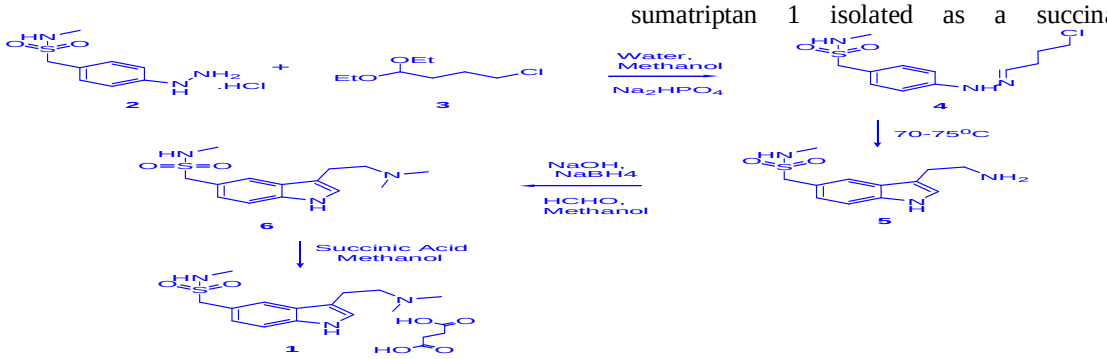
Sumatriptan succinate **1** (Sumatriptan, Imitrex, Treximet, Imigrane) a synthetic drug belonging to the triptan class, which is widely used for the treatment of migraine headaches.[1,2] Structurally, it is an analog of the naturally occurring serotonin (5-hydroxytriptamine, 5-HT) receptor family. Sumatriptan, the first selective 5-HTID agonist has shown to be a selective vasoconstrictor of cranial blood vessels and has proven efficacy in the acute treatment of migraine. Tryptamine derivatives have the common feature of possessing an amide function or a small-ring heterocyclic attached to the C-5 atom of the indole nucleus through a methylene spacer.Sumatriptan succinateis chemically known as 1-[3-(2- dimethylaminoethyl)-1H-indol-5yl]-*N*-methylmethanesulfonamide succinate which represented by chemical formula **1**.



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Indoles are heterocyclic compounds that are widely distributed in nature, and their synthesis has attracted massive attention due to their vast biological importance. Starting from the Fisher indolization in 1896, till today there are several methods available for the functionalization of indoles.[3,4] On the whole the Fisher indole synthesis is the greenest synthetic method, which used frequently in the indole chemistry.[5,6] Fisher indole synthetic method was used extensively during the discovery of migraine drugs such as Sumatriptan, Rizatriptan, Almotriptan etc.,. One of the major disadvantages of this method is may be lower yield. The reason is highly acidic nature and the harsh reaction conditions leads to the decomposition of the product and substrates.[7]

During the process development for large-scale production of sumatriptan succinate **1** project we selected the Grandberg variation[8-14] of Fisher Indole route of synthesis. As per the regulatory point of view this particular process was adapted because this was not infringing and can be used for the scale up activity. The overall process for the preparation of sumatriptan (**Scheme 1**) consist the reaction of substituted phenyl hydrazine **2** and halo acetal **3** in the presence mild acidic environment leads to the formation of **4**, which undergoing the further reaction and forms the substituted indole ring at 70-75°C. Further preceded the N-methylation reaction using the HCHO/$NaBH_4$ combination and finally sumatriptan 1 isolated as a succinate salt.



Scheme 1. General scheme for the preparation of Sumatriptan succinate

During the development of this process in lab scale operation we have observed the usual Grandberg method impurities[15] such carbazole formation, indole N-methylation and indole dimer in negligible amount. So our focus turned to addressing the above impurities in terms of formation conditions, removal methods and finally developing the robust process for impurity free formation of sumatriptan succinate in a commercial scale.

II. EXPERIMENTAL SECTION

Commercially available solvents and regents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHZ spectrophotometer with a multinuclear BBO probe with TMS as internal standard in $CDCl_3$. Chemical shifts are reported in δ scale (ppm). Single crystal XRD was recorded on Bruker Axs Kappa Apex2 CCD Diffractometer. Mass spectra were measured on a PE-SCIEX API-3000 LC/MS/MS with a Turbo ion spray mass spectrophotometer.

III. GENERAL PROCEDURE

1-[4-(5, 6-Dihydropyridazin-1(4H)-yl) phenyl]-N-methyl methanesulfonamide (7). A solution of 4-Hydrazino-N-methylbenzene methanesulfonamide hydrochloride 2 (10 g, 0.04 mol) in water (40 ml) and methanol (80 ml) was stirred at 25°C. To the homogeneous reaction mass 4-Chlorobutyraldehyde diethyl acetal 3 (7.6 g, 0.042 mol) and di sodium hydrogen phosphate (5.6 g, 0.04 mol) was added one by one at 25°*C*. The resulting reaction mass was heated to 75°C and maintained for 5 hours. The reaction mass was allowed to cool to 25°C. The reaction mass was filtered to remove the un-dissolved particles and the filtrate was distilled till 50 ml under reduced pressure at 40-45°C. Reaction mass pH was adjusted into 2.0 to 2.2 with diluted hydrochloric acid and extracted with 3x90 ml of dichloromethane. Combined MDC layer was dried over sodium sulphate and distilled completely, obtained crude product purified using silica gel column chromatography (Eluent - Hexane and Ethyl acetate) to give the title compound 7 (yield 28%, yellow solid). ^{1}H NMR (400 MHZ, $CDCl_3$) δ 2.04 (m, 2H), 2.23 (m, 2H), 2.68 (d, 3H), 3.58 (t, 2H), 3.97 (d, 1H), 4.19 (s, 2H), 6.80 (t, 1H), 7.15 (d, 2H), 7.27 (t, 2H). ^{13}C NMR (100 MHZ, $CDCl_3$) δ 18.2, 22.9, 29.9, 43.3, 57.2, 77.2, 113.7, 119.9, 131.3, 137.4, 148.2 ppm. MS, *m/z* 268.2 ($M+H^+$).

IV. RESULT AND DISCUSSIONS

The overall process for the formation of sumatriptan we have almost adopted the literature method for further optimization. The optimization starts with the step one shift base **4** formation in mild acidic environment, among checked various buffer acidic buffer reagents sodium hypophosphate selected and carried out the reaction with water along with methanol. For the short reaction time it is necessary to add the alcoholic solvent as a co-solvent also it is highly effective in the cyclization step.

After formation of shift base elevated temperature were given to the system to increase the rate of 3,3-sigmatropic rearrangement, which leads to the formation of tryptamine as an anticipated product. Lower temperature slows down the rearrangement and thus ultimately results the more impurity formation. Under vigorous reflux condition the usual impurity formation was less which does eliminated during the workup procedure. Here, unexpected way we faced the problem with one new unknown impurity formation with 10-15% level in almost all the batches.

One of regulatory requirement says the unknown impurity will be less than 0.1%. We thought of isolating the unknown impurity and characterize the same, so that the impurity limit can be revised from 0.1% to 0.15%. Particular impurity isolated and analyzed with the use of various analytical techniques. Based on the analytical data the structure proposed as cyclized six membered ring impurity

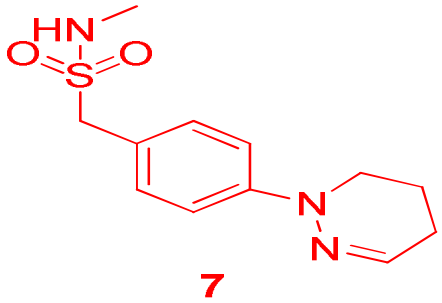
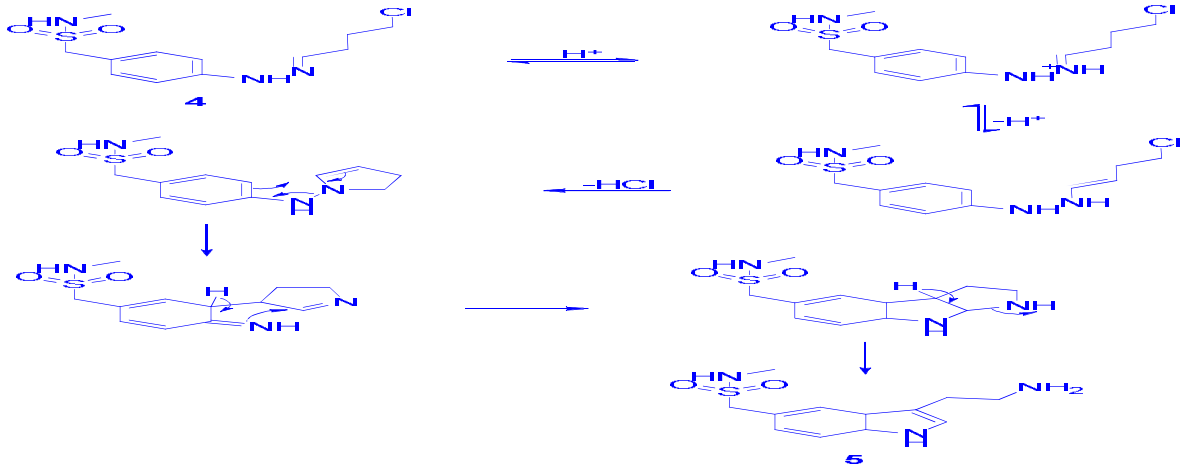
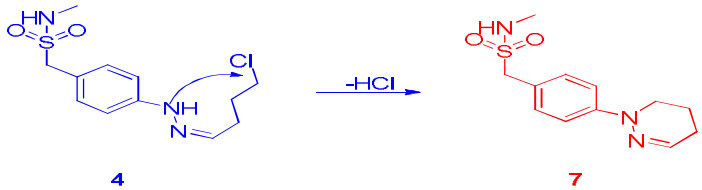


Figure 1. Structure of cyclized impurity 7

The reason for the formation of impurity may be the more labile nucleophilic displacement reaction of nitrogen leads to the formation of stable six member ring which is cyclized impurity **7.** Systematic literature survey reveals that this particular impurity not reported so far.[16] The mechanism for the formation of tryptamine **4** (Scheme **2** Path - A) involves a consecutive reaction of proton transfer, cyclization, 3,3-sigamatropic rearrangement and finally elimination of proton. Owing to the easy availability of loan pair on nitrogen atom and lower energy may result in the uncomplicated formation of six member ring instead of five member ring. According to the conformational point of view, both five and six member rings are free from angle strain therefore intermediate **4** has an equal possibility to form five and six member ring by the reaction of either nitrogen. Due to the equal reactivity of the both nitrogen atoms leading to the formation of impurity to the enhanced level, which is not participating in the further rearrangement and reside as a cyclized impurity **7**.



Scheme 2. Path – A: Reaction mechanism for the formation of sumatriptan tryptamine



Scheme 2. Path – B: Hypothetical reaction pathway for the formation of impurity

Structure of isolated cyclized 6 membered impurity further confirmed with the use of crystal structure (Fig 2)

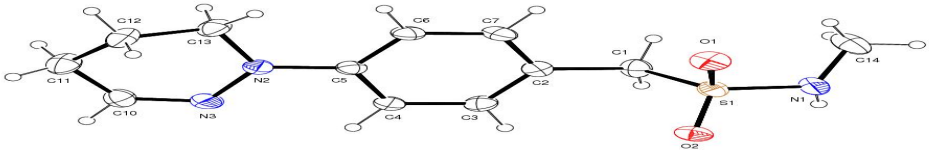


Figure 2. ORTEP diagram of Impurity 7

After confirmation of the impurity structure we studied detailed way to remove the same during the work up. By using various solvents and tried to remove the impurity from the product layer. Among tried solvents dichloromethane, ethylacetate and toluene, dichloromethane washing shows impurity elimination at pH 2.0-2.5 and no remarkable change observed below pH 2.0.

Table – I Solvent Screening experimental data:

Entry	Solvent	Reaction mass pH	% of Impurity 7 by HPLC (area normalization)
1	Reaction mass	6.5-7.00	10 - 15
2	Ethyl acetate	6.0-6.3	12.5
3	Ethyl acetate	3.5-3.8	10.8
4	Ethyl acetate	2.0-2.3	7.8
5	Toluene	6.0-6.3	13.5
6	Toluene	3.5-3.8	11.0
7	Toluene	2.0-2.3	9.5
8	Dichloromethane	6.0-6.3	12.7
9	Dichloromethane	3.5-3.8	8.5
10	Dichloromethane*	2.0 – 2.3	1.53
11	Dichloromethane*	1.5 – 1.8	1.48

* Three times dichloromethane washings required

Improved scalable process for the preparation of sumatriptan succinate:

1-[3-(2- dimethylaminoethyl)-1H-indol-5yl]-*N*-methylmethanesulfonamide succinate **(1).** 4-Hydrazino-N-methylbenzene methane sulfonamide hydrochloride **2** (10 g, 0.04 mol) was added to a mixture of water (40 ml) and methanol (80 ml) at 25°C. To the clear solution 4-Chlorobutyraldehyde diethyl acetal **3** (7.6 g, 0.042 mol) and di sodium hydrogen phosphate (5.6 g, 0.04 mol) was added at 25°C. The resulting reaction mass was heated to 75°C and maintained for further 5 hours, and allowed to cool to 25°C. The reaction mass was concentrated to till 1.0 to 1.5 residual volume under reduced pressure at 50-55°C. Reaction mass pH was adjusted into 6 to 6.5 using 10 % NaOH solution and filtered. To the filtrate charged to a 0.5% NaOH solution of sodium borohydrate and formaldehyde in methanol solution. After completion of reaction, the methanol was distilled under vacuum at 50-55°C then the pH adjusted to 2 to 2.3 using 1:1 HCl solution. Aqueous layer washed three times with 5V of Dichloromethane and aqueous layer further basified using 10 % NaOH solution and extracted using Ethyl acetate. Organic layer was distilled completely under reduced pressure at 40-45°C till residue formation. 10V of methanol was added to a residue; to the resulting clear solution succinic acid in methanol was added slowly. Obtained solid mass further cooled for complete precipitation and filtered to give yellow color title compound **1.**

CONCLUSION

We have demonstrated, through a detailed investigation, the chemistry of formation of cyclized impurity, thereby controlling the impurity formation and avoiding costly purification at final stage. This allowed us to develop an optimal process to prepare impurity free Sumatriptan succinate which can be scaled up in a commercial plant.

ACKNOWLEDGEMENTS

We thank the management and analytical research department of Kawman Pharma for their generous support. We also acknowledge the Management of National College, Tiruchirappalli for providing the facilities to carry out our research work.

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