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Identification, Isolation and Origin of Potential Dimer Impurities of Dichlorphenamide: A Carbonic Anhydrase Inhibitor Drug (Antiglaucoma)

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Present work describes the identification, isolation and characterization of two new process related dimeric impurities of dichlorphenamide (**1**). During the synthesis of dichlorphenamide, the formation of two new dimeric impurities namely 2,3-dichloro-5-(3,4-dichloro-5-sulfamoyl-phenyl)sulfonyl-benzenesulfonamide (**2**) (1,1′-dichlorphenamide dimer) and 2,3-dichloro-5-(2,3-dichloro-5-sulfamoyl-phenyl)sulfonyl-benzenesulfonamide (**3**) (1,3′-dichlorphenamide dimer) was observed. In addition, origin and the strategies adapted to control these potential dimer impurities were also described. These impurities have a substantial impact on the quality of the drug substance as well as drug product.

Keywords: Dichlorphenamide, 1,1′-Dichlorphenamide dimer, 1,3′-Dichlorphenamide dimer.

INTRODUCTION

Dichlorphenamide (or diclofenamide) chemically known as 4,5-dichlorobenzene-1,3-disulfonamide. Oral dichlorphenamide (Keveyis™) is a carbonic anhydrase inhibitor which is approved in the US for the treatment of primary hyperkalaemic and hypokalaemic periodic paralysis and related variants [1]. As the first agent to be approved in the US for this indication, dichlorphenamide is a valuable treatment option for patients with primary hyperkalaemic and hypokalaemic periodic paralysis. The recommended starting dosage of dichlorphenamide is 50 mg twice daily; this dosage may be increased or decreased at weekly intervals. The maximum recommended dosage is 200 mg/day. Oral carbonic anhydrase inhibitor with twice daily administration reduces the frequency of paralytic attacks and incidence of acute intolerable worsening in patients with hypokalaemic periodic paralysis, generally reduces the frequency of paralytic attacks in patients with hyperkalaemic periodic paralysis, has long term efficacy in patients with hypokalaemic and hyperkalaemic periodic paralysis. Primary periodic paralysis are rare, autosomal-dominant disorders that affect sodium, calcium and potassium ion channels of skeletal muscle and are characterized by acute episodes of flaccid muscle weakness and variations in serum potassium levels [2,3].

US pharmacopeia [4] disclosed only one impurity *i.e.* 3,4-dichlorobenzenesulfonamide and the synthesis of this impurity was described by Bach *et al.* [5]. Few synthetic approaches are available in the literature for dichlorphenamide [6-16]. During the development of consistent, reproducible and suitable process in the aspects of safety and quality of the drug substance for the commercial scale synthesis of dichlorphenamide, several laboratory batches were conducted. Two new impurities were identified together at the level of ~1% consistently in the reaction. These impurities were identified by HPLC and LC-MS techniques. Hence, it is challenging to an organic chemist to get rid of these impurities from the active pharmaceutical ingredient (API) to meet the regulatory requirements. As per the monograph of US pharmacopeia (USP-42), the threshold limit of specified impurity of dichlorphenamide should be NMT 0.15%, while unspecified impurity should be NMT 0.10%.

Therefore, it is essential to identify, characterize and control these impurities in the API as per International Conference on Harmonization (ICH) recommendations [17]. Moreover, these impurities in a pure form have an extensive importance

in determining the analytical parameters such as accuracy, specificity, linearity, limit of detection (LOD), limit of quantification (LOQ) and relative retention factor [18]. Based on the above veracities and their importance, the isolation and characterization of these potential impurities (**2** and **3**) are reported.

EXPERIMENTAL

^{1}H NMR spectra were recorded by a Varian 500 MHz spectrometer using TMS as internal standard in DMSO-d_6. ^{13}C NMR spectra were recorded by a Bruker Advance 300 MHz and Varian 500 MHz spectrometer in DMSO-d_6. The IR spectra were recorded in Nujol using Perkin-Elmer Spectrum (ES version) One Fourier transform (FT) IR spectrophotometer. High-resolution mass spectral (HRMS) analysis was performed using electrospray ionization (ESI) method and a Xevo G2 QTOF mass spectrometer. Reagents and solvents were of highest grade and procured from the commercial sources and used as such.

Isolation of 1,1′-dichlorphenamide dimer (2) and 1,3′-dichlorphenamide dimer (3): Compound **4** (100 g, 0.777 mol) was slowly added to chlorosulfonic acid (400 mL) by maintaining the solution at 20-30 ºC. The reaction mass was heated and stirred at 75-80 ºC for 2 h. To this reaction mass, thionyl chloride (222 g, 1.866 mol) was added and stirred for 1 h at 75-80 ºC. The reaction mass was cooled to 10-20 ºC and quenched in a mixture of water (800 mL) and dichloromethane (400 mL). The aqueous layer was separated and extracted with dichloromethane (200 mL). The combined organic extract was washed with ~5% aqueous NaCl solution (300 mL). The organic layer was separated and concentrated under reduced pressure. To this residue, toluene (200 mL) and cyclohexane (300 mL) were added. The precipitated product was collected by filtration, dried to afford as a mixture of compounds **5**, **7** and **8** (228 g, **7** and **8** together ~0.7 to 1.1% by HPLC). To this residue, toluene (680 mL) and PCl_5 (292 g, 1.8 mol) were added uniformly at ambient temperature. The reaction mass was warmed and stirred under a gentle reflux for 90 min. The reaction mass was cooled to ambient temperature, and then toluene (680 mL) and water (1600 mL) were added. The organic layer was separated and washed with ~5% aqueous NaCl solution (3680 mL). The organic layer was concentrated to half of its volume under reduced pressure and cooled to 0-10 ºC. To this concentrated organic layer, 20% aqueous NH_3 (894 g, 13.52 mol) and tetrahydrofuran (450 mL) were added at 0-10 ºC. The reaction mass was stirred for 45 min and water was added to the reaction mass. The organic layer was separated and extracted with 20% aqueous NH_3 (230 mL). The combined aqueous extract was washed with toluene (680 mL). To the washed aqueous layer, carbon (23 g) was added, cooled to 10-15 ºC and stirred for 45 min. The carbon was collected by filtration (filtrate contains **1**) and added tetrahydrofuran, stirred for 2 h at ambient temperature. Again, the carbon was removed by filtration and the filtrate was evaporated completely to afford a mixture of **1**, **2** and **3** (in the ratio of 84.16, 6.79 and 3.67% by HPLC). To this residue, water, 20% aqueous NH_3 and carbon were added and stirred again for 30 min. The carbon was collected by filtration. To this carbon, tetrahydrofuran was added and stirred for 2 h at ambient temperature. After the removal of carbon, the filtrate was evaporated completely to afford a mixture of **1**, **2** and **3** (in the ratio of 20.23, 44.25 and 21.90% by HPLC). To this residue, water and aqueous NH_3 were added and stirred for 1 h at ambient temperature. The undissolved solid was collected and dried to afford crude **2** (79.28% by HPLC). The pure product was isolated by preparative HPLC as a white powder (98.08% by HPLC). The filtrate was evaporated completely to afford crude **3** (45.79% by HPLC). The pure product was isolated by preparative HPLC to afford **3** (a white powder, 94.44% by HPLC).

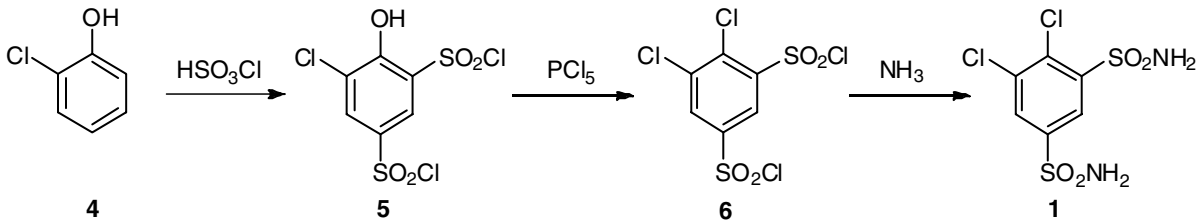
1,1′-Dichlorphenamide dimer (2): IR (Nujol, ν_{max}, cm^{-1}): 3393 (NH_2), 2923 (C-H), 1463 (C=C), 1377 (S=O), 722 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.41 (d, 1H, J = 2 Hz), 8.68 (d, 1H, J = 2.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 126.04, 132.75, 135.45, 136.11, 138.77, 144.17; HRMS (ESI, QTOF) for $C_{12}H_8N_2O_6S_3Cl_4$ $(M-H)^+$: *m/z* calcd. (found): 510.8220 (510.8479).

1,3′-Dichlorphenamide dimer (3): IR (Nujol, ν_{max}, cm^{-1}) 3370 (NH_2), 2922 (C-H), 1463 (C=C), 1377 (S=O) 722 (C-Cl). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.37 (d, 1H, J = 2.5 Hz), 8.45 (s, 2H), 8.65 (d, J = 2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 126.90, 132.79, 133.02, 133.50, 135.62, 135.67, 135.81, 137.52, 138.71, 144.03; HRMS (ESI, QTOF) for $C_{12}H_8N_2O_6S_3Cl_4$ $(M-H)^+$: *m/z* calcd. (found) 510.8220 (510.8470);

RESULTS AND DISCUSSION

A literature review revealed a sole method [19] for the synthesis of dichlorphenamide (**1**) (**Scheme-I**) and involves chlorosulphonation of *o*-chlorophenol **(4)** with chlorosulfonic acid to produce a crude product merely of 5-chloro-4-hydroxybenzene-1,3-disulfonyl chloride **(5)**. This crude product **5** is treated with PCl_5 at 120-140 ºC to produce 4,5-dichlorobenzen-1,3-disulfonylchloride **(6)**. Treatment of compound **6** with aqueous NH_3 produced crude dichlorphenamide (**1**) which was recrystallizated with aqueous isopropyl alcohol.

During the synthesis of dichlorphenamide (**1**), 1,1′-dichlorphenamide dimer (**2**) and 1,3′-dichlorphenamide dimer (**3**) were identified as process related impurities. The formation of these



Scheme-I: Reported preparation of dichlorphenamide **(1)**

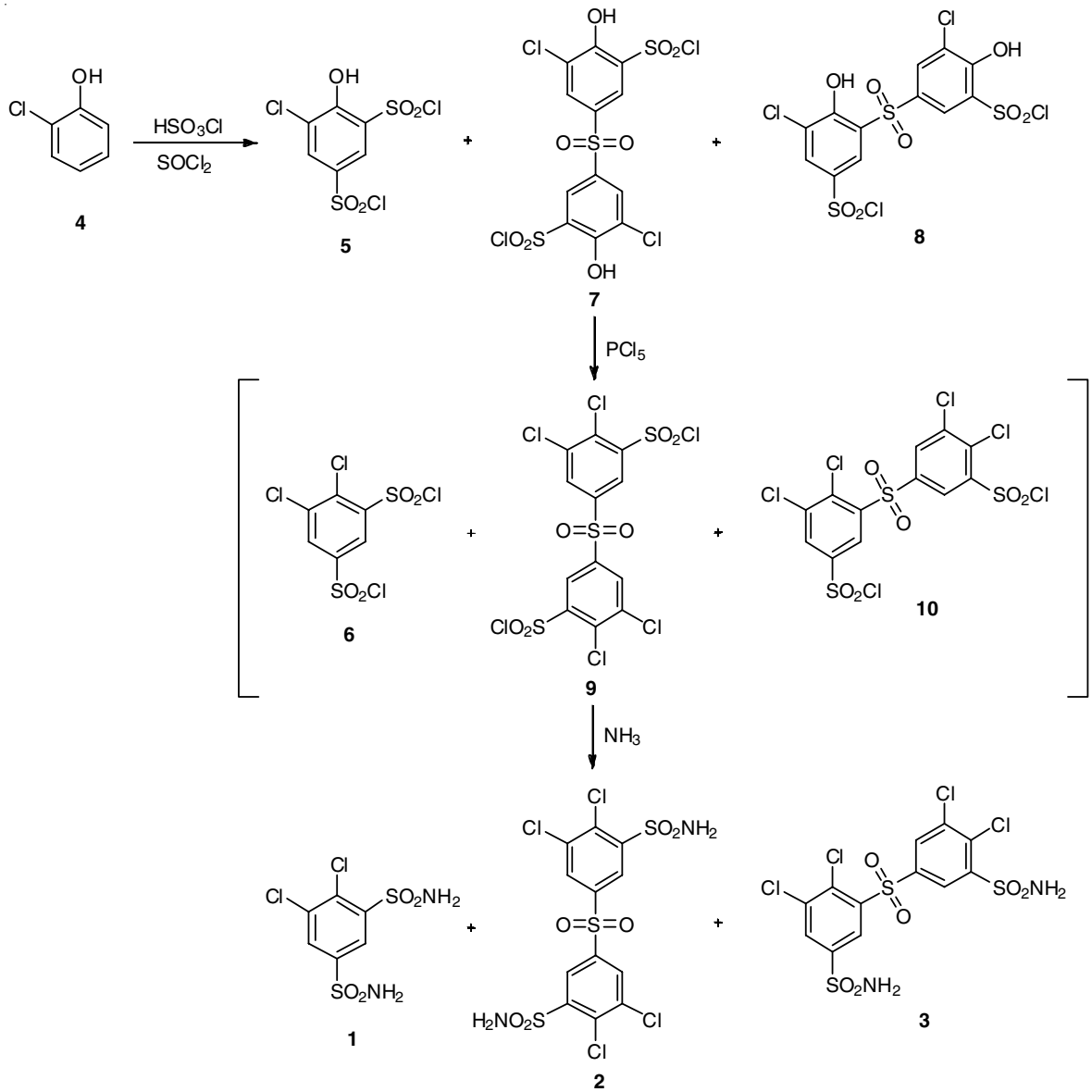
dimer impurities were identified by LC-MS. The LC-MS analysis predicted two impurities with same *m/z* 512 amu. During the routine manufacturing process of dichlorphenamide (**1**), 1,1′-dichlorphenamide dimer (**2**) was formed at a level of ~0.1-0.2% and 1,3'-dichlorphenamide dimer (**3**) was formed at a level of ~1.0-1.2%.

It was believed that these impurities may be originated during the chlorosulfonation reaction of **4** and further carried forwarded to further steps. Further **5** reacts with **4** in the same reaction conditions with a loss of one hydrochloric acid molecule and subsequent chlorosulfonation to afford **7**. Dimer **7** reacts in a similar way as **5** with PCl_5 and aqueous NH_3, is considered as a route cause for the contamination of 1,1'-dichlorphenamide dimer (**2**) in dichlorphenamide (**1**) (**Scheme-II**).

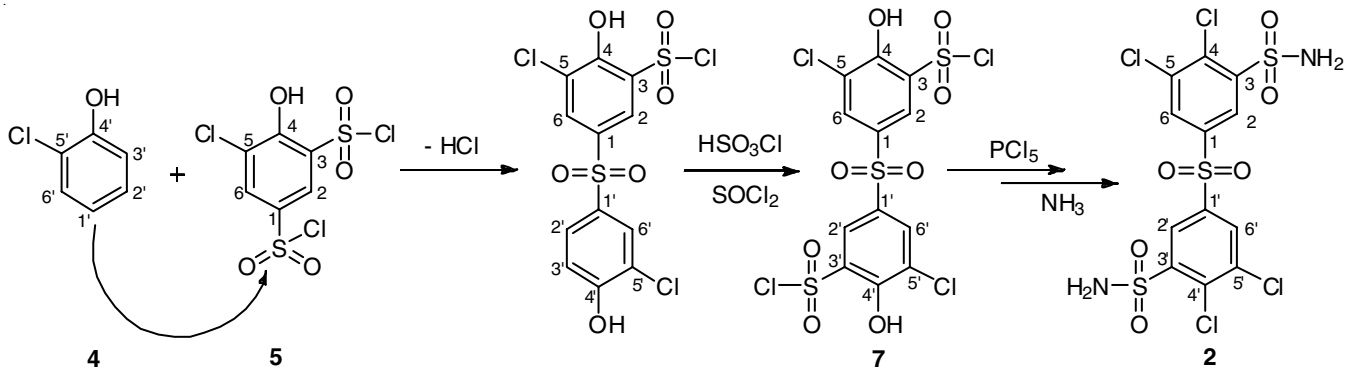
The synthesis of **2** involves reaction of **4** with one of the chlorosulfonyl groups of **5** in presence of chlorosulfonic acid and thionyl chloride at 75-80 ºC to afford **7**. Further, this product was reacted with PCl_5 in toluene under reflux temperature and then with 20% aqueous NH_3 in tetrahydrofuran at 0-10 ºC to afford crude **2**, which was further purified to get pure **2**. The plausible mechanism for compound **2** is shown in **Scheme-III**.

Another impurity, 1,3′-dichlorphenamide dimer (**3**) might be originated during the preparation of **5** from **4**. Reaction of **4** with chlorosulfonic acid leads to the formation mono sulfonated compound *i.e.* 5-chloro-4-hydroxybenzenesulfonyl chloride (**11**) and further chlorosulfonation of **11** in presence of chlorosulfonic acid to afford **5**. During the formation of **5**, there may be a chance to form dimer **8** by the addition of **11** with **5** and loss of one hydrochloric acid molecule. Similarly, dimer **8** reacts with PCl_5 and aqueous NH_3 considered as a route cause for the contamination of 1,3'-dichlorphenamide dimer (**3**) in dichlorphenamide (**1**) (**Scheme-II**).

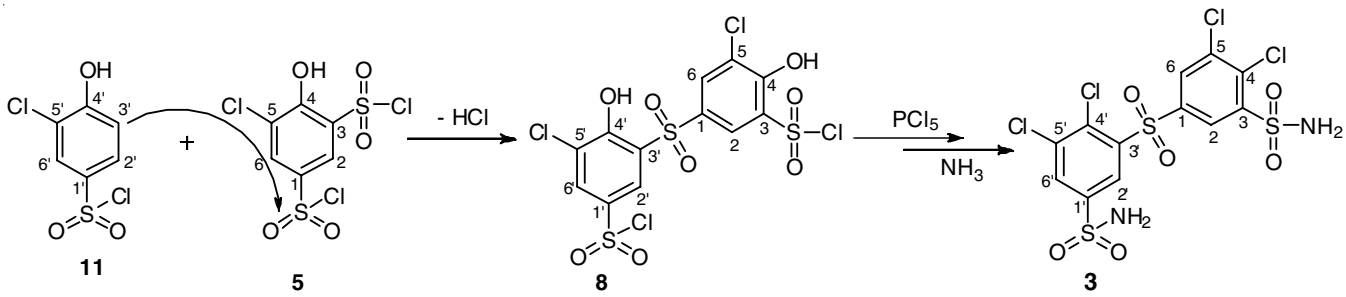
The synthesis of **3** involves reaction of **5** with monosulfonated compound (**11**) in presence of chlorosulfonic acid and thionyl chloride at 75-80 ºC to afford **8**. Further, this product



Scheme-II: Preparation of 1,1'-dichlorphenamide dimer (**2**) and 1,3'-dichlorphenamide dimer (**3**)



Scheme-III: Plausible mechanism of 1,1'-dichlorphenamide dimer (**2**)



Scheme-IV: Plausible mechanism of 1,3'-dichlorphenamide dimer **(3)**

was reacted with PCl_5 in toluene under reflux temperature and then with 20% aqueous NH_3 in tetrahydrofuran at 0-10 ºC to afford crude **3**, which was further purified to get pure **3**. The plausible mechanism for compound **3** is shown in **Scheme-IV**.

Conclusion

Isolation, identification and characterization of potential impurities *viz*. 2,3-dichloro-5-(3,4-dichloro-5-sulfamoyl-phenyl)sulfonyl-benzenesulfonamide (**2**) (1,1′-dichlorphenamide dimer) and 2,3-dichloro-5-(2,3-dichloro-5-sulfamoyl-phenyl)sulfonyl-benzenesulfonamide (**3**) (1,3′-dichlorphenamide dimer) of dichlorphenamide drug had been successfully demonstrated. In addition, the possible pathways for the formation of these impurities were also described. The synthesis of these impurities not only helps in obtaining good quality of the drug substance but also helps in establishing the impurity profile of dichlorphenamide by understanding the cause of its origin. Our efforts to synthesize these dimeric impurities have proved to be beneficial for generic pharmaceutical industry.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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