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Assay at low ppm level of dimethyl sulfate in starting materials for API synthesis using derivatization in ionic liquid media and LC–MS

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ABSTRACT

Dimethyl sulfate (DMS) is frequently used in pharmaceutical manufacturing processes as an alkylating agent. Trace levels of DMS in drug substances should be carefully monitored since the compound can become an impurity which is genotoxic in nature. Derivatization of DMS with dibenzazepine leads to formation of the *N*-methyl derivative, which can be retained on a reversed phase column and subsequently separated from other potential impurities. Such derivatization occurs relatively slowly. However, it can be substantially speed up if ionic liquids are used as reaction media. In this paper we report the use of 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide (IL1) and 1-butyl-4-methylpyridinium tetrafluoroborate (IL2) as reaction media for the derivatization of DMS with dibenzazepine. It was determined that the stoichiometry between the substrate and DMS may be 1:1 or 2:1, in relation with the nature of the reaction media. An (+)ESI-MS/MS approach was used for quantitation of the derivatized product. Alternatively, DMS derivatization may be carried out with pyridine in acetonitrile (ACN). The *N*-methylpyridinium derivative was separated by hydrophilic interaction liquid chromatography (HILIC) and detected through (+)ESI-MS (in the SIM mode). In both cases, a limit of quantitation (LOQ) of 0.05 μg/ml DMS was achievable, with a linearity range up to 10 μg/ml. Both analytical alternatives were applied to assay DMS in 4-(2-methoxyethyl)phenol, which is used as a starting material in the synthesis of metoprolol.

1. Introduction

Dimethyl sulfate (DMS) is commonly used as an alkylating agent in organic synthesis. In vivo and in vitro tests carried out on DMS have demonstrated the carcinogenic potential of the compound [1,2]. The issue of genotoxic impurities has rapidly acquired increased attention from the pharmaceutical industry [3,4] and the corresponding regulatory bodies [5,6]. Quantitation of trace levels of DMS in complex matrices is challenging due to their reactivity and increased polar characteristics. Experimental tools used for control and analysis of alkyl esters of alkyl and aryl sulfonic acids in active pharmaceutical ingredients have been recently reviewed [7]. Earlier approaches dealt with gas chromatographic (GC) analysis by direct sample injection [8,9] with a FID or MS detection. The major drawback of such an analytical solution relates to the frequent need for cleaning the inlet port to avoid formation of ghost peaks produced by thermal degradation of the matrix deposited on the internal surface of the liner. Isolation of DMS from the matrix through different techniques prior to injection in the GC can be considered as a practical solution to the above mentioned problem. Liquid–liquid extraction of DMS with methyl *t*-butyl ether has been used for aqueous soluble active pharmaceutical ingredient (API) intermediates with satisfactory results [10].

Another important approach for the determination of DMS is through derivatization. For example, the reaction of DMS in aqueous media with sodium thiosulfate leads to formation of methylthiocyanate, which can be directly analyzed by head-space GC–MS [11]. Formation of the methylisothiocyanate byproduct was observed only in minor amounts. Pentafluorothiophenol was also used to act as a methylation substrate for DMS, allowing analysis of the derivative by head-space GC–MS [12]. 2-Mercaptopyridine was successfully used for derivatization of DMS. The fluorescence product was determined by RPLC and detected by fluorescence [13]. Alternatively, trialkylamines (more precisely triethylamine, in the case of DMS) were used as derivatization reagents for alkylating compounds [14]. A quantitative derivatization was obtained after heating at 50–60 °C for 1 h. The resulting quaternary ammonium ion was subsequently separated from the reaction mixture

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derivatization process and the produced quantitative results. As expected, less sensitivity was obtained when making derivatization in ACN for 24 h, although precision and accuracy are not substantially affected (the reaction rate is slow; consequently, differences between periods used for completion of the methylation process are not inducing major experimental errors). One can observe that different substrate: DMS stoichiometry is obtained in IL1 and IL2. As the slope of the linear regression doubles when derivatization is produced in IL2 compared to IL1, it seems obvious that in IL2 the stoichiometry between the substrate and DMS is 2:1 instead of 1:1. The high sensitivity obtained when assaying the *N*-methyl pyridinium derivative is due to the existence of the target compound being in an ionic state in solution. In such conditions, the MS tandem detection may be avoided, and replaced by the single MS-SIM operating mode.

Three different production batches of 4-(2-methoxyethyl) phenol were analyzed through the two alternative methods (derivatization with dibenzazepine in IL2 for 30 min at 120 °C followed by the RPLC separation and MS/MS detection, and derivatization with pyridine in ACN for 30 min at 80 °C followed by the HILIC separation and MS-SIM detection). Both methods found no detectable levels of DMS in one batch. For the other two batches, the RPLC method determined 0.52 ± 0.05 μg/ml (mean ± standard deviation) and 1.2 ± 0.13 μg/ml DMS concentration levels in 4-(2-methoxyethyl)phenol. The HILIC approach yields results of 0.61 ± 0.05 μg/ml and 0.98 ± 0.12 μg/ml (number of replicate determinations was 5). Determined values fall reciprocally within the ±20% limits, which can be considered as acceptable. Additionally, the same methods were used to assay the residual DMS in metoprolol tartrate resulting from the synthesis process of the former 4-(2-methoxyethyl)phenol batches. It should be noted that metoprolol tartrate is not soluble in IL2 and consequently DMS was extracted from the solid material in IL2 through sonication (15 min). In all cases DMS was not detectable. It clearly appears that the intrinsic reactivity of the analyte does not leave it untransformed upon the chemical and physical production stages of the synthesis process.

4. Conclusions

Assay of DMS at low μg/ml levels in 4-(2-methoxyethyl)phenol (starting material for metoprolol synthesis) was possible through applying two analytical alternatives: (a) derivatization with dibenzazepine in ionic liquids at 120 °C for 30 min, followed by a RPLC separation and (+)ESI-MS/MS detection; (b) derivatization with pyridine in ACN at 80 °C for 30 min, followed by a HILIC separation and (+)ESI/MS (SIM) detection. Both alternatives behave similarly. Depending on the nature of the ionic liquid used as a reaction medium, the stoichiometry between the substrate and DMS may be 1:1 or 2:1. Validation of the data obtained through this method recommends both analytical approaches as reliable tools for assaying DMS in different chemical environments.

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