

COMMENTARY

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Commentary on “time-dependent selected reaction monitoring-based GC-MS/MS method for estimation of genotoxic impurities in a new antibacterial agent: alalevonadifloxin mesylate”

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Abstract

The references cited in this article to justify the analysis of alkyl mesylates in alalevonadifloxin mesylate (ALA) are considered totally inappropriate since they all present evidence showing that such esters are *not* formed during the synthesis of a sulfonic acid salt using an alcohol as solvent. Relevant mechanistic and kinetic data, first published over a decade ago, demonstrate that no alkyl-sulfonate impurities are produced when an equimolar amount of methanesulfonic acid is added to the base form of a drug substance dissolved in ethanol (or a similar alcohol solvent), and so confirmatory assay data should not be required.

Keywords: Mesylate salt, Alkyl mesylates, Side-reaction

Introduction

We are writing to raise serious concerns over about the misleading citation of references in the above article by Ahirrao et al., *Journal of Analytical Science and Technology* volume 11, Article number: 22 (2020) (Ahirrao et al. 2020).

“Synthesis of ALA involves the use of methanol, ethanol, and isopropanol as solvents at various staged of synthesis and during purification. Though possibility of reaction between the methane sulfonic acid and the alcohols is ruled out in the formation of AMs (Teasdale et al. 2010; Snodin and Teasdale 2015; Snodin 2019), it is regulatory mandate to estimate levels of AMs in the drug substance.”

Commentary

We wish to point out that none of the articles supports the notion that undesired reactions between methanesulfonic acid (MSA) and alcohols during the synthesis of a mesylate-salt drug substance result in the formation of alkyl-mesylate impurities. All three publications strongly contradict the false belief that alkyl mesylates can be formed by a side-reaction during sulfonic-acid-salt synthesis using an alcohol solvent. When an equimolar amount of MSA is added to the base form of an API a proton-transfer reaction from acid to base occurs. These reactions are diffusion-controlled and so base protonation is essentially instantaneous leading to complete neutralization of added sulfonic acid. There is therefore no scope for alcohol protonation which is a necessary prerequisite for an ester-forming side-reaction; protonation of the alcohol requires very strongly acidic conditions, i.e., pH << 1. Moreover, sulfonic-acid salts can be recrystallized using ethanol (or a similar alcohol) as a solvent without any production of ethyl-sulfonate impurities. To generate alkyl sulfonates at neutral pH in such a system, the mechanistically impossible

This comment refers to the article available at <https://doi.org/10.1186/s40543-020-00214-w>.

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nucleophilic displacement of hydroxide ion by sulfonate anion would need to occur.

It is also noteworthy that Ahirrao et al., in common with many others developing assay methods for alkyl sulfonates, provide no assay data on alkyl mesylates in commercial samples of ALA drug substance or drug product. We believe that such information is necessary to support or refute the hypotheses employed to justify the development of the GC-MS/MS assay. There is one recent exception to this normal pattern (Jin et al. 2019); these researchers actually applied their assay method for 15 sulfonate esters to commercial samples of three drug products: phentolamine mesylate, amlodipine besylate, and tosylloxacin tosylate. None of esters was detected in any of the drug products under investigation.

Conclusions

We consider that Ahirrao et al. have cited our articles in an extremely misleading fashion wrongly implying that these publications provide a justification for the development of highly sensitive assays for alkyl-mesylate impurities. We recommend revision of this article by means of an author correction in order to provide a truly evidenced-based understanding of the risk of alkyl-mesylate contamination of mesylate-salt drug substances.

Acknowledgements

Not applicable

Authors' contributions

Initial draft by DJS; review and comments by AT and DPE. The authors read and approved the final manuscript.

Funding

Not applicable: no external funding was provided to support the preparation of this short article. We, the authors, declare that we have no financial or other conflicts of interest and that no external funding was provided to support the preparation of this short article.

Availability of data and materials

See cited references.

Competing interests

Not applicable

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Received: 9 August 2020 Accepted: 23 October 2020

Published online: 10 November 2020

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