1. Introduction

Nitrosamine risk assessment and control have become an integral part of pharmaceutical drug product development and quality evaluation. Initial reports of nitrosamine contamination were linked with the drug substance and its manufacturing process. Subsequently, the drug product and aspects of the formulation process have shown to be relevant, including the presence of nitrite in excipients and the active ingredient. Accurate knowledge on the presence and distribution of nitrite in excipients has become an important goal, both to pharmaceutical manufacturers and health authority regulators, as it is a key piece of information used in the risk assessment for nitrosamine formation in the drug product. Only limited validated information on nitrite levels in excipients has been available until now. This has driven the creation of a database to store and share such validated information. The database, maintained by Lhasa Limited, constitutes a central platform to hold the data donated by the pharmaceutical company members on the nitrite concentrations in common excipients measured with validated analytical procedures. As such, 678 data points on 79 excipients, from different lots, and suppliers have been collected in the Nitrites in Excipients Database [1,5].

The article by Hu et al [2] called our attention, since the nitrite measurements reported are considerably higher than those observed in our experience. In the interest of reporting nitrite levels that are fully accurate, we would like to discuss the findings with the article authors.

2. Discussion

In their article, the authors present results for dimethylamine (DMA) and nitrite from the analysis of seven pharmaceutical samples, i.e., five drug products containing the APIs Diphenhydramine HCl (2x), Ranitidine HCl, Losartan potassium and Metformin HCl, as well as for the undiluted APIs Losartan potassium and Metformin HCl. The undiluted APIs were sourced from a life science company and may therefore not be fully equivalent to pharmaceutical grade API in terms of quality, purity, and impurity profile.

Metformin hydrochloride of pharmaceutical quality is synthesized at commercial scale from dimethylamine (DMA) hydrochloride (HCl) and cyanoguanidine in organic solvent, followed by a solvent exchange to water, filtration and crystallization(s), and finally centrifugation and drying. Nowhere is nitrite added intentionally to the process, and neither organic solvent, DMA HCl nor cyanoguanidine are known to introduce relevant amounts of nitrite. The process water is typically obtained from city water, in which nitrite is commonly restricted to max 1 μg/g and actual values are below 0.1 μg/g. Our own analyses of 36 commercial batches Metformin HCl with Ph.Eur. quality detected 0.01–0.06 μg/g nitrite using the Griess reaction followed by HPLC separation and detection by UV. In comparison, the authors claim to detect 27.0 μg/g and 6.86 μg/g nitrite in one batch Metformin HCl of non-pharmaceutical quality and one batch Metformin tablets, which typically contain ca. 90–95% API of pharmaceutical quality and single digit concentrations of excipients such as povidone and microcrystalline cellulose and max 1% magnesium stearate. Using validated methods, we have measured the following maximum nitrite concentrations in the indicated number of samples from a variety of suppliers (2021.3.0 version of database),

| Component                  | Max nitrite (μg/g) | Percentage of formulation | Max nitrite contribution (μg/g API) |
|----------------------------|-------------------|---------------------------|-----------------------------------|
| Metformin HCl              | 0.06              | 0.9                       | 0.05                              |
| Povidone                   | 2.3               | 0.045                     | 0.10                              |
| MCC                        | 2.4               | 0.045                     | 0.11                              |
| Magnesium stearate         | 6.1               | 0.01                      | 0.06                              |
| Max total nitrite concentration in the tablet (μg/g tablet) | 0.33             |                            |                                   |
| Max total nitrite concentration in the tablet (μg/g API) | 0.36             |                            |                                   |

Making a worst-case calculation for a typical Metformin tablet formulation the maximum expected nitrite concentration based on our data would be:

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This value is 20 times lower than the 6.86 μg/g claimed by the authors. Likewise, assuming correctness of our data for povidone, MCC and magnesium stearate, the Metformin API used for producing the tested thors. Likewise, assuming correctness of our data for povidone, MCC and data of max 0.06 nitrite may have been used to quench residual NaN₃ used in the synthesis reagents likely to be contaminated with nitrite. Losartan is an exception, as included in the study, i.e., Diphenhydramine and Ranitidine and could not we tested may contain higher nitrite concentrations. Therefore, their statement is not valid.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Declaration of interests statement

The authors declare the following conflict of interest: The authors Joerg Schlingemann, Sebastian Hickert, Giorgio Blom, and Leonardo Allain are employed by companies that manufacture pharmaceuticals subject to regulations regarding maximum nitrosamine limits.

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