

N-nitrosamine risk assessments for oral dosage forms: Nitrite content in the microcrystalline cellulose (MCC) produced by Asahi Kasei Corporation.

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INTRODUCTION

The effects of N-nitroso compounds on human health (particularly their role in gastric cancer) are well known.¹ Certain N-nitrosamines are described as highly probable human carcinogens. They are usually formed by the reaction of secondary or tertiary amines with a source of a nitrosating agent, typically derived from nitrite.^{2,5}

Oral excipients are considered as a potential risk factor during the drug product assessment.³ Being an excipient manufacturer, Asahi Kasei Corp. (Japan) is focused on mitigating the risk and providing information about the safe use of excipients.

In most cases, the nitrite contribution is dominated by the highest formula % excipients. Thus, the fillers/diluents which are typically used in larger proportions should be considered as a potential risk factor.⁴

MCC is widely used in pharmaceutical development and is one of the most common fillers /diluents contributed to oral solid dosage form formulations, usually present in much higher concentration compared with other excipients.⁶ So, the high nitrite content in MCC can be a significant risk for nitrosamine formation and consequently patient health.

Boetzel R. et al presented the results of eight excipients including their origin and different batches along with the correspondent statistics for the nitrite level. The evaluation of these results also showed the differences between various suppliers and between batches. In this study, the nitrite content in MCC from nine suppliers showed a spread from 0.04µg/g to 2.4µg/g, with a mean of 0.70 µg/g⁴

The aim of this investigation was to test the nitrite and nitrate content in the excipients produced by Asahi Kasei Corp. (Japan) to provide scientifically based data for N-nitrosamine risk assessment in oral formulations.

MATERIALS AND METHODS

Materials. MCC grades as **Ceolus™** KG-1000, KG-802, UF-711, UF-702, PH-101, PH-102 (Asahi Kasei Corp., Japan)

Ion chromatography method (IC) developed by Asahi Kasei in collaboration with TOYO Inspection Center (Japan).

Test methodology: Suppressed ion chromatography
 Column: Anion Exchange Chromatography Column (4.6mm I.D×15cm)
 Mobile phase: Sodium Carbonate / Sodium Hydrogen Carbonate eluent solution
 Flow rate: 1.0 mL/min
 Oven temperature: 40°C
 Sample injection volume: 30-100µL
 Detector: UV-VIS detector (Wavelength 210 nm)

The LOD (Limit of Detection) is 0.008µg/g.

Table 1. Nitrite and Nitrate content (µg/g) in the MCC products of Asahi Kasei Corp. (Japan).

MCC grade	Number of lots tested	Nitrite (µg/g) Maximum value	Nitrate (µg/g) Average value
CEOLUST™ PH-101	11	0.011 (6/11 lots show N.D.)	0.071
CEOLUST™ PH-102	10	0.012 (6/10 lots show N.D.)	0.082
CEOLUST™ KG-802	8	< 0.008 (all lots show N.D.)	0.106
CEOLUST™ KG-1000	6	< 0.008 (all lots show N.D.)	0.112
CEOLUST™ UF-702	6	< 0.008 (all lots show N.D.)	0.092
CEOLUST™ UF-711	7	< 0.008 (all lots show N.D.)	0.109

RESULTS

The nitrite and nitrate content of Ceolus™ KG-1000, KG-802, UF-711, UF-702 and PH-101 and PH-102 was determined by ion chromatography method and systemized in **Table 1**. In accordance with the used quantification method, the LOD of nitrites comprised 0.008µg/g. In the majority of tested batches of MCC grades Ceolus™ PH-101 and PH-102 the nitrite content was lower than LOD (0.008µg/g). In all tested batches of grades Ceolus™ KG-802, KG-1000, UF-702, UF-711 the nitrite level has not been detected. At the same time, the nitrate level was very low and didn't exceed 0.112 µg/g.

Being an MCC/Ceolus™ manufacturer, Asahi Kasei Corp. can explain the achieved results by process features. To minimize the appearance of undesirable impurities, secondary and tertiary amines, as well as quaternary ammonium salts or amide solvents are not used in the manufacturing process of products. Furthermore, sodium nitrite esters or nitrite, reagents or catalysts are not used.

CONCLUSION

Ceolus™ demonstrated a very low level of nitrite and nitrate (lower than 0.012 and 0.112 µg/g, respectively) that can allow mitigating nitrosamine formation in the drug products with secondary or tertiary amines.

Obtained results justified with Asahi Kasei Corp.'s manufacturing process features allow to do the evidence-based choice of MCC-grades with low nitrite content for the formulation of oral dosage form formulations with low nitrosamine-associated risk.

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