Pharma Solutions

NITRITE CONTENT IN HYDROXYPROPYL METHYLCELLULOSE

Introduction

N-nitrosamines are considered probable or possible carcinogens according to the International Agency for Research on Cancer, an agency within the World Health Organization [1].

Regulatory bodies across the world have requested pharmaceutical companies to evaluate, investigate and control the formation of nitrosamines in drug products [2-4].

A frequently cited mechanism for nitrosamine formation involves the reaction of secondary or tertiary amines (present as functional groups on Active Pharmaceutical Ingredients [API], as degradants or as impurities) with a nitrosating agent like nitrous anhydride [5,6] which can form from the protonation of nitrite under acidic conditions.

Nitrites are found in excipients [7,8], food products [9, 10] and water [11]. One way to control nitrosamine formation is to control the levels of one of (or both) the nitrosating agent or the vulnerable amine.

Excipients that contain low levels of nitrites are a key part of drug product manufacturers' nitrosamine risk mitigation plans. Pharma Solutions at IFF is committed to meeting the needs of formulators and drug product developers. In response to the needs of nitrosamine risk assessments, IFF has developed analytical methods for the measurement of nitrite in excipients such as METHOCEL™ PREMIUM hydroxypropyl methylcellulose.

Materials and methods

METHOCEL™ PREMIUM hydroxypropyl methylcellulose (HPMC) type 2208 (K chemistry) pharmaceutical grade products were sampled for nitrite evaluation due to the use of hypromellose at high concentration in matrix tablet formulations [12]. METHOCEL™ K100 LV, K4M, K15M, K100M and K200M PREMIUM results are shown in Table 1.

Samples were prepared by extracting nitrite from METHOCEL™ with sodium hydroxide solution at 80 °C and analyzed on a Dionex ICS-6000 dual channel anion chromatograph system with conductivity detector using a Dionex IonPac AS19 column and KOH gradient. The method was validated for precision, accuracy, and linearity; the limits of detection (LOD) and quantitation (LOQ) were 8 and 27 parts-per-billion (ppb), respectively. Results expressed in ppb are summarized in Table 1.

Results

As shown in Table 1, nitrite values for mid- and high viscosity K grades were observed between 46 and 286 ppb. Low viscosity METHOCEL™ K100 LV PREMIUM lots showed significantly lower nitrite values, with a maximum value of 59 ppb and 16 out of 35 lots tested below the limit of detection of 8 ppb. METHOCEL™ PREMIUM LV products receive an additional low pH processing step, and the contribution of this step towards reducing the nitrite content is subject to ongoing investigations. While IFF does not currently monitor or control nitrite content in the production of METHOCEL™ K PREMIUM chemistry, the results of the analysis shown in Table 1 suggest IFF's current manufacturing capability produces METHOCEL™ K PREMIUM chemistry products in the range between 50 ppb and 300 ppb nitrite.

Table 1. Nitrite levels for select METHOCEL™ PREMIUM products

		Nitrite (ppb)			
Product	Number of lots evaluated	Mean	Min	Max	Number of lots < LOD
K100 LV	35	29	< 8	59	16
K4M	37	140	88	204	0
K15M	19	82	46	114	0
K100M	33	118	62	230	0
K200M	18	146	82	286	0

Recent studies have highlighted that nitrite content can be variable among excipient suppliers and can impact nitrosamine formation within drug products. Boetzel et al. [7] have assembled a summary of nitrite levels in excipients which showed hypromellose levels can range as high as 5000 ppb, with a mean value of 800 ppb across five suppliers. Schlingemann et al. concluded that reduction of residual dimethylamine (DMA) in metformin API, as well as reduction of nitrite in excipients, is critical for controlling n-nitrosodimethylamine (NDMA) formation in metformin HCl tablets[13]. Their results indicate that setting a process-specific limit for DMA in metformin HCl (59 µg/g) in combination with limiting the nitrite contribution from excipients, particularly HPMC (< about 500 ppb) were key elements in a successful strategy to limit post-optimization NDMA formation towards a target of < 30% of acceptable intake.

IFF's Pharma Solutions team continues to evaluate process and analytical improvements to meet our customers' expectations in the field of nitrosamine-sensitive oral solid dosage forms. Our scientists are open to discussing any challenges and resolution strategies for nitrosamine-related inquiries across our portfolio offerings.

References:

1. World Health Organization, Agents Classified by the IARC Monographs, 2022.
2. U.S. Food and Drug Administration, Control of nitrosamine impurities in human drugs: Guidance for industry. 2021.
3. European Medicines Agency, Nitrosamines EMEA-H-A5(3)-1490, 2021. 2021.
4. Health Canada. Guidance on nitrosamine impurities in medications. 2022.
5. Wainright, T., The Chemistry of Nitrosamine Formation: Relevance to Malting and Brewing. J. Inst. Brew., 1986. 92: p. 49-64.
6. Helmut Bartsch, H.O.a.B.P., Inhibitors of Endogenous Nitrosation: Mechanisms and Implications in Human Cancer Prevention. Mutation Research, 1988. 202: p. 307-324.
7. Boetzel, R., et al., A Nitrite Excipient Database: A Useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products. Journal of Pharmaceutical Sciences, 2022: p. 1-10.
8. Wu, Y., et al., Reactive Impurities in Excipients: Profiling, Identification and Mitigation of Drug–Excipient Incompatibility. AAPS PharmSciTech, 2011. 12(4): p. 1248-1263.
9. Fornal, L., et al., Nitrate and Nitrite Content in Wheat Dried in Internal-Combustion Dryers. Roczniki Nauk Rolniczych, C, 1975. 71(4): p. 37-44.
10. Karwowska, M. and A. Kononiuk, Nitrates/Nitrites in Food—Risk for Nitrosative Stress. Antioxidants, 2020. 9(3): p. 241-257.
11. Nitrate and nitrite in Drinking-water: Background document for development of WHO Guidlines for Drinking-water Quality. 2003.
12. Raymond C. Rowe, P.J.S., Sian C. Owen, Handbook of Pharmaceutical Excipients. 2006: Pharmaceutial Press.
13. J. Schlingemann, C.B., S. Hickert, L. Bourasseau, M. Walker, C. Celdran, et al., Avoiding N-Nitrosodimethylamine Formation in Metformin Pharmaceuticals by Limiting Dimethylamine and Nitrite. International Journal of Pharmaceutics, 2022: p. 121740.

pharma.iff.com

Where science & creativity meet

HO 00432-0 E A 06.2023