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Short communication

Gas chromatographic assay determination of methocel (methylcellulose) across different excipient grades (E5 LV, E4M, K15M, etc.)

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Introduction

Hydroxypropyl Methylcellulose (HPMC), commercially known as Methocel, is a semi-synthetic cellulose derivative (ether) widely used as a pharmaceutical excipient due to its excellent film-forming, thickening, and controlled-release properties.

Structurally, HPMC is derived from cellulose, in which part of the hydroxyl groups are chemically substituted with methoxy ($–OCH_3$) and hydroxypropyl ($–OCH_2CHOHCH_3$) functional groups. These functional characteristics are largely governed by the type and extent of chemical substitution on the cellulose backbone.

Therefore, quality control of Methocel requires accurate determination of the content of these substituent groups. The physicochemical and functional properties of Methocel are strongly dependent on the type and degree of substitution (DS and MS) of these functional groups along the cellulose backbone (Deshmukh et al., 2017).

Variations in substitution levels define different viscosity grades and performance characteristics, such as E5 LV, E4M, E15 LV, K15M, and A15C, which are widely used in pharmaceutical formulations. Because of this structural variability, accurate determination of methoxy and hydroxypropoxy content is essential for quality control.

Gas chromatography coupled with flame ionization detection (GC-FID), based on chemical cleavage and derivatization of ether substituents, is a standard pharmacopeial method (USP) for assay determination of cellulose ethers (Vlad Robert et al., 2025).

Materials and methods

The determination of Methocel content was performed according to the United States Pharmacopeia (USP) method using a GC-FID. The chromatographic analysis was carried out on a DB-1 capillary column (30 m × 0.53 mm × 3 µm).

The reagents used in the analysis included adipic acid, hydroiodic acid (HI, 55–57%), octane, and o-xylene, all obtained from Merck. Sample preparation and derivatization were performed in accordance with the USP procedure.

The prepared samples were injected into the GC-FID system under optimized conditions, and quantification was performed based on the chromatographic response of the analytes. The assay results were calculated in compliance with USP requirements (Johnson, 2024).

The analytical method is based on the acid-catalyzed cleavage of ether linkages in cellulose ether

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derivatives using concentrated hydroiodic acid (HI) at elevated temperatures, resulting in the formation of volatile alkyl iodides and the regeneration of hydroxyl groups on the polymer backbone. Substituents are quantitatively transformed into measurable alkyl iodides:cIodomethane (CH_3I) from methoxy substitution and Iodopropane (C_3H_7I) from hydroxypropoxy substitution

These compounds are highly volatile, chemically stable under GC conditions, and exhibit strong FID response, making them suitable analytical markers for substitution quantification.

Results and discussion

The optimization of key reaction parameters for the GC-FID determination of Hydroxypropyl Methylcellulose (HPMC) demonstrated a significant influence on the accuracy and reproducibility of the assay.

Hydroiodic acid (HI), used for ether bond cleavage, was found to be critical for complete derivatization. At concentrations below 55%, incomplete cleavage resulted in underestimation of substitution values. In contrast, concentrations above 57% led to overly aggressive reaction conditions, causing partial degradation of the polymer matrix and formation of secondary artifacts. Optimal performance was achieved within the USP-recommended range of 55–57%.

Reaction temperature also showed a strong effect on assay outcomes. Temperatures below 130 °C resulted in incomplete conversion and reduced formation of alkyl iodides due to slower reaction kinetics. Temperatures above 130 °C led to degradation of the cellulose backbone, formation of secondary by-products, and partial loss of volatile alkyl iodides. Maintaining the reaction at 130 ± 2 °C ensured efficient cleavage and consistent analyte formation, whereas temperatures exceeding this range promoted degradation of the cellulose backbone and loss of volatile compounds.

Adipic acid, acting as an auxiliary acidifying agent, improved the reproducibility and completeness of the reaction. However, excessive amounts increased the viscosity of the reaction mixture, which complicated phase separation and introduced minor chromatographic interferences.

Overall, optimization of these parameters ensured accurate, precise, and reproducible GC-FID determination of HPMC in accordance with USP methodology.

Conclusion

Optimization of reaction conditions and accurate control of HI concentration, reaction temperature, and adipic acid amount are essential to prevent incomplete cleavage or polymer degradation, both of which significantly affect analytical accuracy.

The analytical method confirms that substitution levels in tested Methocel grades comply with pharmacopeial specifications and highlights the critical role of precise analytical control in ensuring excipient quality and performance in pharmaceutical applications.

References

Deshmukh, K. et al., 2017. 2.1.8 Hydroxypropyl Methylcellulose. In Biopolymer Composites in Electronics. https://www.sciencedirect.com/topics/chemistry/hydroxypropyl-methylcellulose

Johnson, A., 2024. Hypromellose and Other Cellulose Type Assays by Gas Chromatography. https://hpcimedia.com/images/zz_Manufacturing%20Chemist/Butterworth%20Laboratories/03_Hypromellose-and-Other-Cellulose-Type-Assays-by-Gas-Chromatography-Whitepaper-April-2024-Final-Version.pdf

Vlad Robert, A. et al. 2025. Hydroxypropyl Methylcellulose—A Key Excipient in Pharmaceutical Drug Delivery Systems. Pharmaceutics 17(6), 784. https://doi.org/10.3390/pharmaceutics17060784