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Overcoming the Analytical Challenge of Non-Biological Complex Drug Analysis by Process Control Drug Discrimination via Comprehensive Chromatographic and Mass Spectrometric Approaches

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Medication errors are the leading cause of preventable patient harm. Globally, about 5% of patients are affected by medication-related harm, with 25% of these harms being life-threatening. Often, these errors are caused by orthographic or phonetic properties of medications. Look-alike, sound-alike errors are further aggravated by the availability of both foreign and local drugs sharing similarities in regulatory requirements and areas of application as well as the drug's complexity.

The relatively new drug group of non-biological complex drugs (NBCDs) covers complex synthetic medications and has gained significant medicinal, economic, and regulatory interest lately. Tentatively, also bituminosulfonates (BSs), obtained by sulfonation of shale oil distillates, are allocated toward the NBCD category. Their shale oil-based origin results in high isomeric and isobaric complexity and therefore cannot be fully described by physicochemical analytical means. These BSs are listed in the European Pharmacopeia (Ph. Eur.) by the brand name Ichthammol and are used for treating various dermatological diseases. Simultaneously, the Chinese Pharmacopeia (ChP) also lists a drug with dermatological application named Ichthammol. However, the ChP describes Ichthammol as a product of vegetable oil-based origin. Despite the origin differences, the Ph. Eur. and ChP share comparable bulk parameters defined in the corresponding monographs for Ichthammol.

To tackle the high error potential by unintended substitutions, we investigated Ichthammol matrices compliant with the Ph. Eur. as well as with the ChP in a comprehensive approach utilizing FT-ICR MS to resolve the isobaric complexity and comprehensive two-dimensional GC coupled to high-resolution ToF MS for isomeric information. We achieved an in-depth chemical description of different Ichthammol matrices by tracing compounds throughout the manufacturing process with high confidence in our results even without suitable standard reference materials for the Ph. Eur. compliant Ichthammol. For ChP compliant Ichthammol matrices, our results allowed confident conclusions about the manufacturing process without investigating process intermediates. Finally, we were able to transfer this information from these state-of-the-art methods to LC triple quadrupole MS, an approach that qualifies for routine differentiation between shale oil-based Ichthammol matrices derived from different distillation cuts and between Ichthammol samples derived from starting materials with different origins.

With this work, we present an approach to overcome the analytical challenges of NBCD analysis. By achieving detailed molecular-level information from state-of-the-art investigations we were able to differentiate between various Ichthammol matrices. These sophisticated results were then transferred into a routinely usable analysis method, which in the next step can be implemented into a regulated pharmaceutical environment.

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