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The Development and Validation of a Stability-Indicating Assay and Related Substances Method for Morphine Sulfate Tablets by HPLC

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INTRODUCTION

The analysis of prolonged release Morphine sulfate tablets for assay and related substances requires the use of multiple methods [1] and analytical techniques, including thin-layer chromatography (TLC). This work aimed to consolidate these methods into a single approach, and ensure that the final method was robust and stability-indicating. Validation was then performed in accordance with ICH Q2.

Morphine sulfate tablets are manufactured by Custom Pharma at four dose strengths: 10, 30, 60 and 100mg. The tablets are coated with an Opadry® aqueous film coat, with each dose being coated a different colour. The coating is designed to ensure a steady release of Morphine *in vivo* over an 8 hour period.

Included in this project was an investigation into developing a sample extraction for whole tablets, where previously grinding was the only option. Finally, the scope of the method was extended to ensure it could be used to perform content uniformity testing of the two lowest dose strengths.

MATERIALS AND METHODS

The LiChrospher HPLC column used in the original method was routinely causing failures in the system suitability due to falling plate numbers. This is a standard silica stationary phase that has been in use for many years across the industry. A more robust column was required to prevent premature stationary phase degradation, and a Phenomenex Gemini® C18 was selected.

An Agilent 1100 HPLC system equipped with a quaternary pump, chilled autosampler and variable wavelength detector was used throughout this project. An isocratic mobile phase combining an acetate buffer at pH 4.85 with Acetonitrile was applied. Development work was performed to optimise the chromatography and resolution on the Gemini® column for all known components whilst minimising the total runtime.

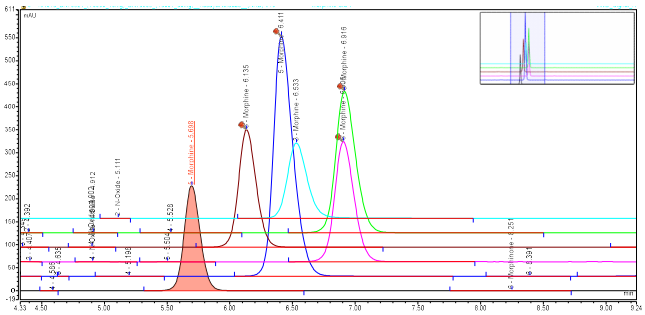

Fig.1. Optimisation of Morphine sulfate chromatography

Finally, the sample preparation and extraction procedure was improved such that whole tablets could be tested without the coloured coating causing any specificity problems. This required the inclusion of a solid phase extraction step for one dose only to remove a specific colouring agent.

RESULTS AND DISCUSSION

The validation of the developed method met all of the required acceptance criteria. A suitable limit of quantitation was shown for the three named impurities: Morphine n-oxide, Pseudomorphine and Codeine.

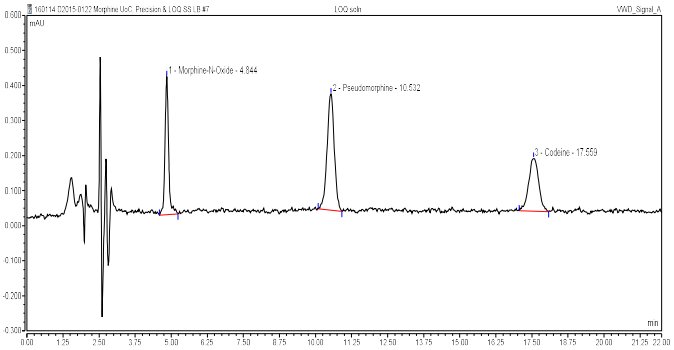

Fig.2. Injection of LOQ solution containing known impurities

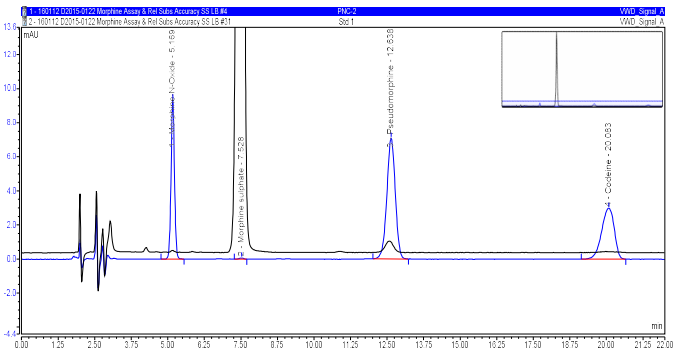

Fig.3. Excellent baseline resolution for Morphine sulfate and known impurities

CONCLUSIONS

A single method has been successfully developed and validated to ensure that the testing of Morphine sulfate tablets is accurate, precise and specific. This method can be used in place of both the TLC and non-robust HPLC methods previously used. The regulatory requirement to test content uniformity has also been addressed.

ACKNOWLEDGMENTS

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REFERENCES

[1] Prolonged-release Morphine tablets, *British Pharmacopoeia 2016*