British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1370

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 14th APS International PharmSci 2023

Phase stability and polymorphism of a new naproxen salt

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ARTICLE INFO

Received: 09/06/2023
Accepted: 08/07/2023
Published: 30/12/2023

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KEYWORDS: naproxen, polymorphism, phase stability.

SUMMARY

We report on the synthesis and structural characterization of a new naproxen salt. *In-situ* heating X-ray diffraction experiment allows us to determine the phase stability of the various polymorphic phases. Slow heating rate and repetitive scans strategy were essential to probe all phases in presence. Contrary to previously reported absence of polymorphic forms for naproxen salt, this new salt exhibits one metastable dihydrate form and five anhydrous phases. The crystal structures of all phases were determined using the *in-situ* X-ray powder diffraction data.

INTRODUCTION

Sodium naproxen is widely used as a non-steroidal anti-inflammatory active pharmaceutical ingredient (API). The crystal structure of this API has been reported in 1990 [Kim *et al.*, 1990]. This remains the single known polymorph despite three decades of research on this API. Physicochemical stability is a serious problem during new drug development and thus pseudo-polymorphism has been widely investigated for sodium naproxen. So far, four hydrates have been reported and characterized [Bond *et al.* 2014]. So, while the pseudo-polymorphism is rather rich, polymorphism is unusually simple with only one known representative. This is a rather unusual case as polymorphism for APIs tends to be rather rich [Lee, 2014]. Besides the sodium salt, various hydrated naproxen salts of general formula $M[C_{14}H_{13}O_3]_2.xH_2O$ have been reported in the literature: M = Zn (x = 3), M = Ni (x = 10), M = Cu (x = 4) and M = Cd (x =1 and 3) [Wang *et al.*, 2012]. Among all those salts, still no polymorphism has been reported so far. Consequently, we have started to investigate a new salt while searching for possible polymorphism.

MATERIALS AND METHODS

The new salt was synthetized using as starting material the corresponding nitrate and sodium naproxen in aqueous solution. Upon the addition of the nitrate salt in the sodium naproxen salt, a precipitate appears. This new salt has the formula $M[C_{14}H_{13}O_3]_2.2H_2O$. In-situ X-ray powder diffraction experiment was carried out as function of temperature using an Empyrean diffractometer equipped with a focusing mirror, Cu K_α radiation and using a Debye-Scherrer geometry. The new salt was investigated in the range 25-200°C.

RESULTS AND DISCUSSION

The initial *in-situ* investigation of the temperature dependence, as shown in Fig. 1, was suggesting the existence of one dihydrate (x = 2) and 4 polymorphic phases of the anhydrous phase (x = 0) prior to melting around 170°C. The crystal structures of the various phases could be indexed and solved from the *in-situ* powder diffraction data. Repetitive scans at constant temperature were key to obtaining sufficient data quality of phase pure material. Indeed, several phases show major phase coexistence with other

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phases (see phase γ for instance) or very small stability regime (see phase α for instance).

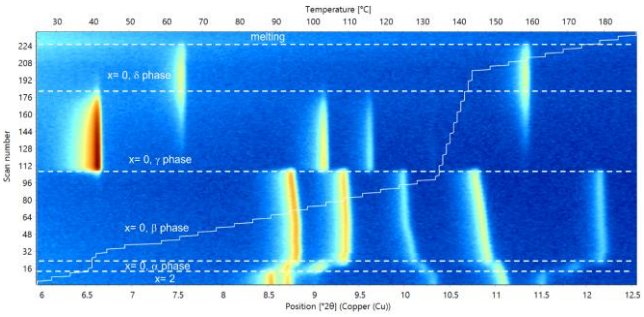

Fig. 1. *Isoline plot of the temperature dependence of a new naproxen salt of general formula* $M[C_{14}H_{13}O_3]_2.xH_2O$ *(dihydrate x = 2, and anhydrous, x = 0) in the temperature range 25 < T < 190°C.*

Upon a closer inspection, an additional phase is observed just before the melting point which is very similar to the δ phase. This ε phase is closely related to the δ phase with similar unit-cell volume and cell parameters. We present in Fig. 2 the temperature evolution of the various phases in presence with their corresponding symmetries and unit-cell volumes.

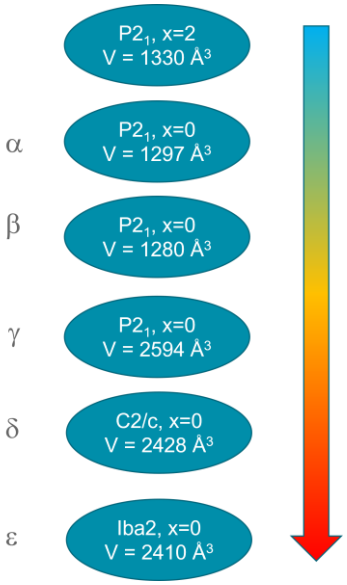

Fig. 2. *Overview of the various polymorphic forms as function of temperature for the new salt* $M[C_{14}H_{13}O_3]_2.xH_2O$ *in the temperature range 25 < T < 170°C.*

CONCLUSIONS

This work demonstrates the relevance of non-ambient in-situ X-ray powder diffraction for phase stability of API. Additionally, we have demonstrating that contrary to previous results naproxen salts exhibit also a rich polymorphism like other API.

ACKNOWLEDGEMENTS

All authors are employees of Malvern Panalytical.

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