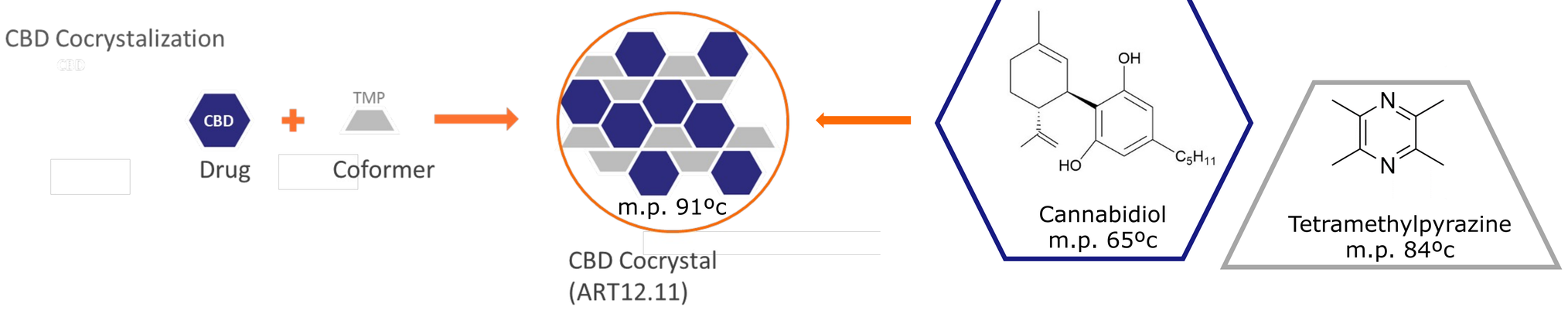
ART12.11, AN AQUEOUS SUPSENSION OF A NOVEL CANNABIDIOL:TETRAMETHYLPYRAZINE CO-CRYSTAL, DEMONSTRATES A PHARMACOKINETIC PROFILE COMPARABLE WITH EPIDIOLEX® IN RATS

Andy Yates, Alison Wilby*, William G Warren, Myles Osborn, Saoirse E O'Sullivan

Artelo Biosciences Limited, Mereside, Alderley Edge, UK & *Seda Pharmaceutical Development Services, Cheadle, Stockport, UK

Introduction

Cannabidiol (CBD) is available as an approved medicine Epidiolex®, an oily oral solution of CBD in ethanol and sesame oil used for controlling seizures in orphan childhood disorders. However, the wider therapeutic utility of CBD in treating non-orphan, adult diseases is hampered by its physical and pharmacokinetic properties, including high lipophilicity, polymorphism, poor solubility, and poor oral bioavailability. Artelo Biosciences have developed a patented (out to 2038) co-crystal of CBD with the co-former tetramethylpyrazine (TMP; also called ligustrazine) in a 1:1 molar ratio, designated ART12.11. We have previously reported ART12.11 offers improvements in physicochemical (e.g. melting point [m.p.]), pharmacokinetic (e.g. PK in dogs), and pharmacodynamic properties compared to CBD[1].



The aim of the study was to compare the pharmacokinetic profile of orally administered aqueous suspension of ART12.11 to an oily oral solution of CBD in ethanol and sesame oil (Epidiolex®-like formulation) in rats.

Methods

Male Sprague Dawley rats (n=3) were administered a single dose of either; aqueous suspension of CBD (10 mg/kg PO); CBD Epidiolex®-like formulation (10 mg/kg PO); or an aqueous suspension ART12.11 (14.3 mg/kg (containing 10 mg/kg CBD and 4.3 mg/kg TMP) PO) in the fed and fasted state. Serial blood samples were taken prior to dosing and at 30 minutes and 1, 2, 3, 5, 8, and 24 h. Plasma samples were analysed by LC-MS/MS.

Results

In both the fed and fasted state the aqueous suspension of ART12.11 led to higher plasma levels of both parent CBD and 7-COOH-CBD metabolite compared to the aqueous suspension of CBD.
In the fasted state, orally administered ART12.11 had a lower C_{max} of parent CBD compared to the Epidiolex®-like formulation, but similar 7-COOH-CBD levels (Fig 1A), and similar overall exposure ($AUC_{0-t)}$ to either parent (C) or major metabolite (D). In the fed state, orally administered ART12.11 demonstrated similar plasma levels of parent CBD and 7-COOH-CBD to the Epidiolex®-like formulation (Fig 1B), and similar AUC_{0-t} (Fig 1C, D). When comparing the ratio of 7-COOH-CBD metabolite to CBD parent (M:P ratio), in the fasted state, the CBD aqueous suspension had a ratio of approximately 1.8 (1.8 x metabolite/parent), ART12.11 had a ratio of 0.8 and CBD in the Epidiolex®-like formulation had a ratio of 0.4 (with a reference value of 0.2 for CBD delivered intravenously (i.v)). In the fed state, these ratios were 1.8 (CBD aqueous solution), 0.7 (ART12.11) and 0.5 (Epidiolex®-like formulation). Differences in M:P ratios are likely to be driven by differences in CBD absorption (gut versus lymphatic system; affected by feeding) and first pass metabolism.

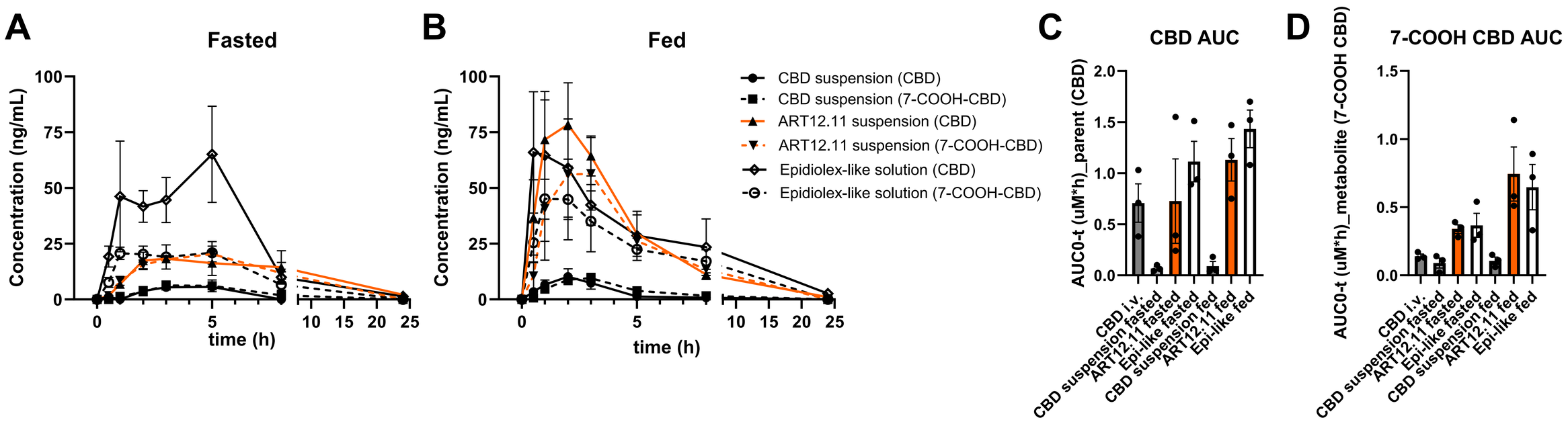


Figure 1. 24-hour PK profiles of CBD and 7-COOH-CBD analytes from PO administration of ART12.11 (10mg/kg CBD/4.3mg/kg TMP) compared with an Epidolex®-like formulation (10mg/kg) in fasted and fed rats.

Conclusions

The unique pharmaceutical properties of ART12.11 translates into increased exposures of CBD and a major metabolite 7-COOH-CBD comparable to an Epidolex®-like formulated CBD. ART12.11 was delivered as an un-optimised aqueous suspension formulation and these results support further solid-dosage form development of ART12.11 targeting similar or greater exposures compared to Epidolex® liquid. The data highlight the importance of the formulation and drug substance used in relation to metabolite formation. Ongoing research at Artelo will now focus on developing an optimised clinical formulation of ART12.11 for future studies.

Reference 1 Jones et al. (2023) A novel cannabidiol:tetramethylpyrazine (CBD-TMP, ART12.11) co-crystal improves the efficacy and bioavailability of cannabidiol to induce anxiolytic and anti-depressant effects. Poster Presentation at Society for Neuroscience Nov 11-15th 2023

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