ART12.11, A NOVEL CANNABIDIOL:TETRAMETHYLPYRAZINE CO-CRYSTAL DEMONSTRATES A UNIQUE PHARMACOKINETIC PROFILE

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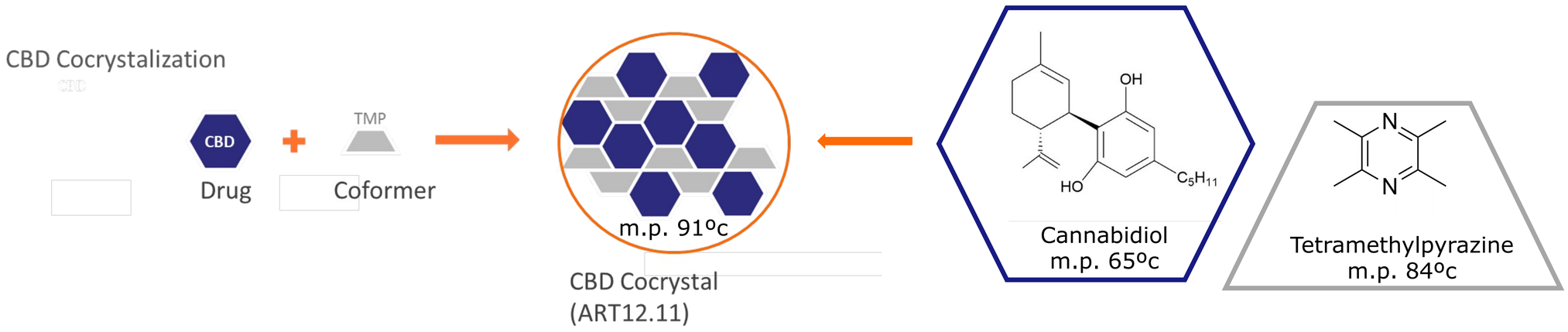
Introduction

The therapeutic utility of cannabidiol (CBD) is often hampered by its physical and pharmacokinetic properties, including high lipophilicity, polymorphism, poor solubility, and poor oral bioavailability. Co-crystallisation is a useful method for overcoming problematic properties of drugs and is a well-established process in drug development. Co-crystals consist of the drug substance (i.e. CBD) and a co-former molecule, which modify the physicochemical properties whilst retaining the intrinsic pharmacological drug activity. Artelo Biosciences have developed a patented cocrystal of CBD with the co-former tetramethylpyrazine (TMP; also called ligustrazine), designated ART12.11. We have previously reported ART12.11 offers improvements in patentability, physicochemical, pharmacokinetic (PK), and pharmacodynamic properties compared to CBD[1].



The aim of the study was to compare the pharmacokinetic profile of an orally administered aqueous suspension of ART12.11 to an orally co-administered aqueous suspension of CBD and TMP

Methods

Male Sprague Dawley rats (n=3) were administered a single dose of either CBD (1 mg/kg intravenously [IV] or 10 mg/kg by oral gavage [PO]), TMP (1 mg/kg IV or 4.3 mg/kg PO), a co-administered mixture of CBD and TMP (1 mg/kg & 1 mg/kg IV or 10 mg/kg & 4.3 mg/kg PO) or ART12.11 (14.3 mg/kg [containing 10 mg/kg CBD and 4.3 mg/kg TMP in a cocrystal] PO). Animals were dosed 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 from both the IV and PO dosed animals. Plasma samples were analysed by LC-MS/MS to provide quantification of the test materials.

Results

When given IV CBD, TMP, and co-administered CBD and TMP showed similar PK profiles for both parent analyte and the major metabolite of CBD and TMP (Figure 1). In the fed state, orally administered ART12.11 led to increased plasma levels of parent CBD, and a major metabolite 7-COOH-CBD when compared to CBD alone or co-administered CBD plus TMP (Figure 2). Both the mean C_{max} and mean $AUC_{0\text{-}t}$ for parent CBD analyte from ART12.11 (83.7 ng/ml; 355 h.ng/ml) were 10–12 times greater than CBD alone (10.2 ng/ml; 28.5 h.ng/ml) and 4–5 times greater than co-administered CBD plus TMP (17.8 ng/ml; 93.3 h.ng/ml).

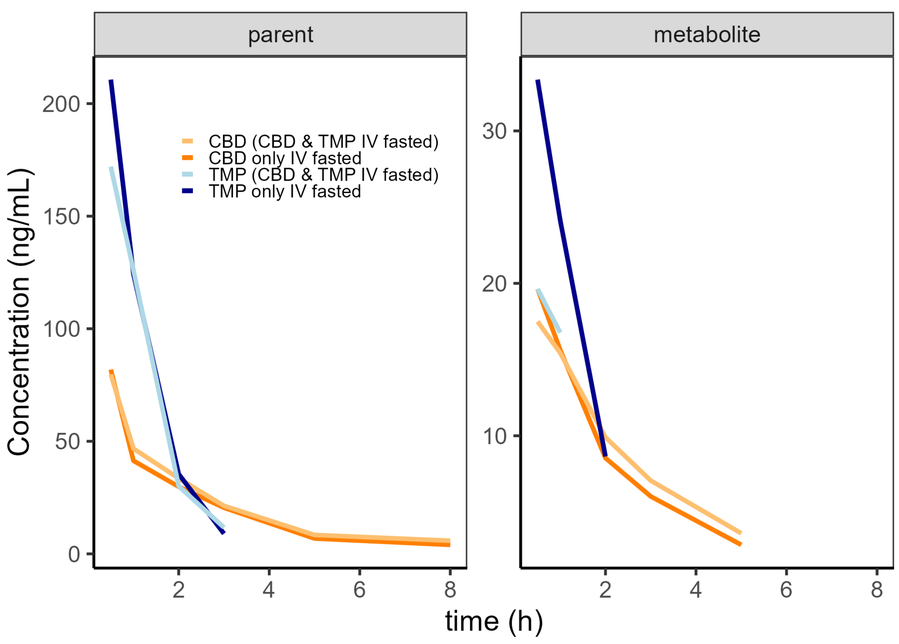


Figure 1. 8-hour PK profiles of CBD and TMP parent and 7-COOH-CBD and TMP-OH metabolite analytes from IV administration of CBD (1 mg/kg) compared with CBD & TMP co-administration (1 mg/kg & 1 mg/kg) in the fasted state.

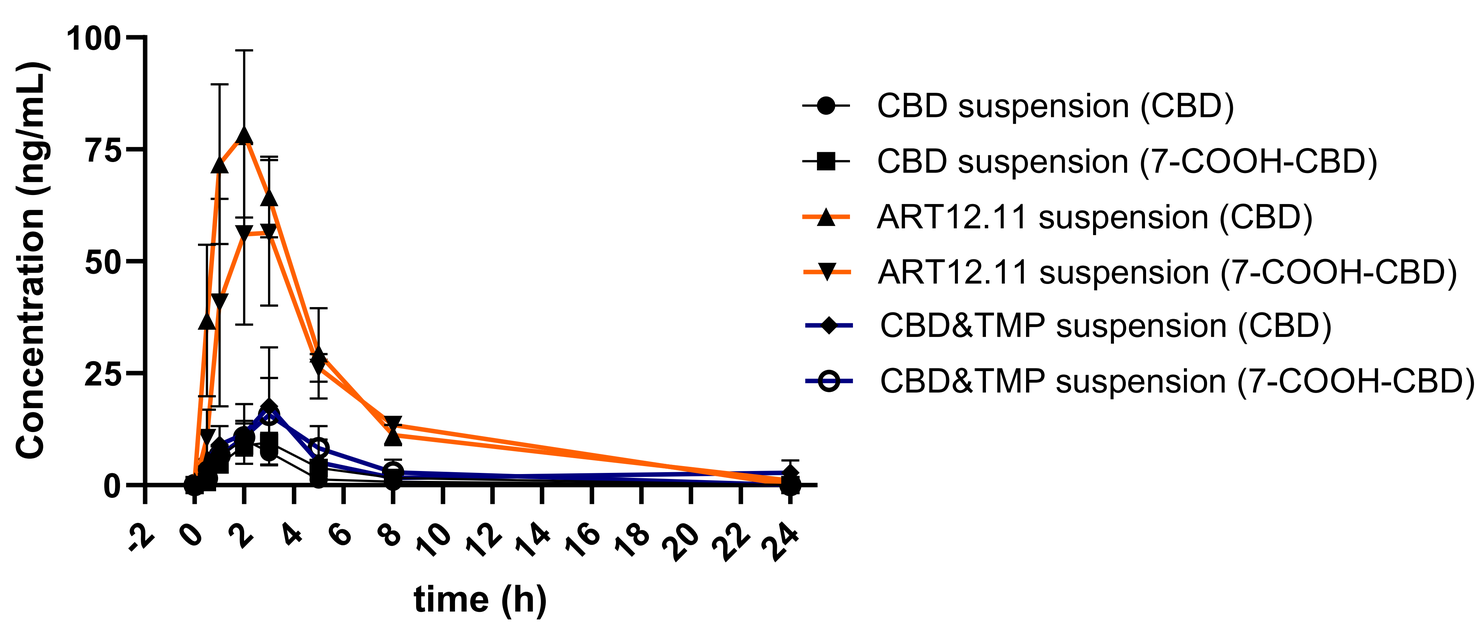


Figure 2. 24-hour PK profiles of CBD and 7-COOH-CBD analytes from PO administration of ART12.11 in the fed state (10 mg/kg CBD/4.3 mg/kg TMP) compared with a CBD suspension (10 mg/kg) or co-administration of CBD (10 mg/kg) and TMP (4.3 mg/kg).

Conclusions

The unique pharmaceutical properties that co-crystallisation provides translates into greatly increased exposures of CBD and a major metabolite 7-COOH-CBD from ART12.11 compared to CBD alone. The uplift observed is not due to systemic drug-drug interactions between CBD and TMP as demonstrated by their consistent IV PK profiles whether delivered as a single agent or co-administered together. Furthermore, the increased CBD and 7-COOH-CBD exposures observed from ART12.11 upon oral dosing cannot be replicated by co-administering an equimolar equivalent dose of CBD and TMP. These results are supportive of further development of ART12.11 co-crystal as an effective approach to dosing CBD in an oral solid dosage form.

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

Disclosures; AY, SOS, MO, WW are all paid employees of Artelo Biosciences Limited. AY owns stock in Artelo Biosceince Inc.

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