ALTASCIENCES

CASE STUDY

Rapid Development of a Liquid-filled, Hard-Shell Capsule Formulation of Cannabidiol

INTRODUCTION

Cannabidiol (CBD) has shown promise for addressing a number of ailments, including epilepsy, anxiety, pain, and inflammation. The pharmaceutical industry is now working toward developing reliable products that will deliver the best outcomes for patients, and solve the many unmet health needs within the population. As an integrated early phase drug development solution company offering a flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services, Altasciences can quickly implement formulation development and clinical manufacturing to address the urgent need for CBD and other next generation formulations.

STUDY OVERVIEW

Altasciences' client, Emyria, presented the challenge of developing several oral formulation candidates for CBD from scratch for a new over-the-counter (OTC) product in Australia. Nine liquid-filled, hard-shell capsule (LFC) formulations were designed, manufactured, and compared *in vitro* via a standard dissolution assay at Altasciences' CDMO site in Philadelphia, PA.

The assay was able to distinguish the speed and completeness of dissolution among the nine early formulations. Three candidates were selected by the client for a pharmacokinetic (PK)/toxicokinetic analysis in dogs, and 3,000 capsules of each formulation containing 50 mg of CBD were manufactured.

One capsule of each formulation and a 50-mg CBD solution (Epidiolex) were dosed in eight beagles in a crossover study over four weeks at Altasciences' preclinical research facility in Scranton, PA. PK analysis confirmed good correlation between *in vitro* dissolution and *in vivo* PK data. The best formulation developed dramatically outperformed the commercial product Epidiolex in both C_{max} and AUC.

Most importantly, the entire project from the design of formulations through development of analytical methods, prototype manufacturing and characterization, test article manufacturing of three candidates, design of animal study and testing protocols, bioanalytical method development and analysis, and reporting of data **was completed in just over three months**.

This was possible because of the close program coordination across three Altasciences sites and the oversight of a single dedicated project manager.

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OBJECTIVE

To create alternative oral formulations that may match or improve upon the PK profile of oral CBD in the fastest and most cost-effective manner possible.

METHODS

Altasciences' CDMO facility in Philadelphia, PA, proposed a broad range of novel prototype formulations for both powder-filled and liquid-/semisolid-filled, hard-shell HPMC capsules. All selected excipients were suitable for oral use with a previous use history, as found on the FDA Inactive Ingredient Database (IID).

Step One — The liquid-/semisolid-filled hard capsule excipients were chosen for their ability to solubilize CBD, low melting temperatures, and their potential to increase absorption of the CBD.

Step Two — The excipients were tested for their ability to fully solubilize the CBD. Once dissolved, the warm CBD solutions were filled into HPMC hard capsules (50 mg of CBD/capsule), capped, and banded. One of the formulations did not fully dissolve an ingredient and was eliminated from consideration.

Step Three — The amount of CBD in each capsule formulation was determined by HPLC using a stability-indicating method developed in parallel with prototype design and manufacturing, and subsequently validated.

Step Four — Lead prototypes for a dog PK study were selected based on the following criteria:

- Stability of CBD to the manufacturing process (heat)
- Dissolution rate and completeness in simulated fasted dissolution media (FaSSIF)
- Ease of manufacturing
- Appearance

Step Five — The dissolution of dosage forms was monitored by measuring CBD levels in FaSSIF media by HPLC over three hours. Based on the results, two of the formulations were selected.

THE STUDY

Based on these results and other factors, such as cost and availability of excipients, Emyria selected three formulations for their crossover PK studies in beagle dogs at Altasciences' preclinical testing site in Scranton, PA. Epidiolex (100 mg/mL solution in sesame oil/ethanol, GW Pharma) was included in the study for comparison.

Male beagle dogs (eight males/treatment for Treatments 1 to 4) were used in this study. Animals were allocated to four different treatment groups receiving 50 mg of CBD in four different formulations. The same eight animals were used for each treatment, and treatments were separated by a minimum seven-day washout period.

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Twelve serial blood samples (~3 mL per sample timepoint) per treatment were obtained from each dog via direct venipuncture of a jugular vein using blood collection tubes containing K_2-EDTA as the anticoagulant at pre-dose and at 10 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose timepoints.

Plasma was separated and analyzed for CBD using a qualified LC-MS/MS bioanalytical method developed by Altasciences' laboratories in Laval, Québec, Canada. Non-compartmental analysis (NCA) of plasma concentration data was conducted using Phoenix® WinNonlin®, version 8.0.

All animals that were administered 50 mg of CBD in four different treatment groups were systematically exposed to CBD following a single oral administration, with variability between the individual animals within each treatment group being observed.

RESULTS

The mean CBD C_{max} and AUC_{last} observed in Treatment 4 were 2.5- and 4.1-fold higher than the mean values observed following the oral administration of CBD oil (Epidiolex) in Treatment 1. The mean CBD C_{max} observed in Treatments 2 and 3 were generally similar to the mean C_{max} in Treatment 1, while the mean AUC_{last} values were approximately two-fold higher than the mean AUC_{last} of Treatment 1.

CONCLUSION

The results of the study confirmed expectations that an improved formulation with potentially better pharmacodynamics was possible using suitable, FDA-acceptable excipients in a capsule format.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.