CANNABIDIOL DELIVERY THAT IS ON THE "TIP OF THE TONGUE"

In this article, Zdravka Misic, PhD, Innovation Project Manager at dsm-firmenich, explores how formulation expertise can be applied to overcome the low bioavailability of cannabinoids and how innovation in orally disintegrating tablets is driving progress for cannabidiol-based therapeutics.

Cannabinoid-based early drug development – particularly the cannabidiol (CBD) category – is gaining increasing attention and investment due to its undeniable innovation potential. However, the low bioavailability of cannabinoids makes formulation challenging, especially when developing solid oral dosage forms, which are still preferred by patients. Consequently, to date, innovation in drug delivery in the CBD space has been limited, with most cannabinoid therapies reliant on oil-based oral solutions for administration.

This has prompted the question, "How can patient-centric CBD-based therapies with improved efficacy, compliance and patient acceptability be achieved?" The answer may be presented by orally disintegrating tablets (ODTs) – a promising dosage form for the delivery of a wide range of APIs – which hold significant potential for delivery of CBD-based therapies.

UNDERSTANDING CBD FORMULATION TO DATE

Cannabinoids have sparked intense interest among the scientific community thanks to their potential to offer wide-ranging therapeutic benefits for human health. Among these compounds, CBD stands out for its therapeutic benefits owing to its non-intoxicating nature. Progress in CBD research has revealed its capacity to potentially treat multiple medical conditions, with emerging evidence related to neurological disorders, such as central nervous system (CNS) diseases, mood disorders, cancers and even sleep disorders (e.g. insomnia). In view of this, CBD holds significant promise in addressing unmet patient needs.

Despite pioneering advancements, CBD-based drug development is still in its early stages and comes with some challenges. Enhancing the bioavailability of CBD and unlocking its complete therapeutic potential for patients is one noteworthy opportunity. The low bioavailability of the molecule – as little as 6% in humans[1] – may sometimes necessitate doses above 300–400 mg per day to achieve a substantial therapeutic effect.[2] Consequently, patients are required to administer large quantities of cannabinoid-based medications, typically in the form of oil-based oral solutions, to attain beneficial outcomes. However, this approach can be unpleasant and introduce potential complications, such as unwanted adverse effects like diarrhoea.

Enhancing the bioavailability of CBD would help to mitigate these challenges and, while progress is being made, much of the research in this field is still focused on oil-based oral solutions. This is fuelling the exploration of more patient-centric and convenient dosage forms for CBD-based therapies in clinical trials – one of those being ODTs.

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ODTs: A POTENTIAL GAME CHANGER FOR CBD-BASED THERAPIES

ODTs represent an innovative dosage form for drug delivery, offering benefits that cater to varying patient needs and preferences due to their user-friendly and convenient form. Designed to dissolve quickly in the mouth without water, they are easy to administer on-the-go and, therefore, facilitate better patient compliance. This makes ODTs an appealing drug delivery system for patients who have difficulty swallowing pills or tablets, such as older adults, or those seeking more

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Figure 1: Sleep disorders are an underserved therapeutic area that could greatly benefit from an improved delivery method for CBD-based therapeutics.

> "ODTs are absorbed in the mouth, thereby bypassing the gastrointestinal tract and avoiding first-pass metabolism – the breakdown of the API in the gut or liver."

treatment flexibility. The swift dissolution and absorption of the API into the bloodstream makes ODTs particularly beneficial for health conditions requiring immediate effect, such as insomnia and other sleep disorders.

ODTs are absorbed in the mouth, thereby bypassing the gastrointestinal tract and avoiding first-pass metabolism – the breakdown of the API in the gut or liver. This allows for faster absorption of the API into the bloodstream and rapid onset of action. For this reason, they are an attractive option for drugs that do not absorb easily in the stomach and those with limited bioavailability due to first-pass metabolism, such as CBD. Cannabinoids, like CBD, can be affected by incomplete absorption in the gut and undergo extensive first-pass metabolism in the liver (up to 75% for CBD).[1]

The versatility and effectiveness of ODTs has led to their use across multiple therapeutic settings, from alleviating pain via analgesic medications to providing relief from allergies through antihistamines and facilitating fast-acting treatment during acute episodes in patients with psychiatric disorders. Given the persistent challenge of CBD bioavailability and delivery for drug developers, ODTs are emerging as an extremely promising avenue for cutting-edge CBD formulation.

ADVANCEMENTS IN CBD-BASED ODTs

One field where CBD-based ODTs hold promise is for the treatment of insomnia. Sleep disorders are a prevalent worldwide concern that can profoundly impact an individual's quality of life and overall wellbeing. Studies have indicated that insomnia affects somewhere between 10% and 30% of the global population, with some estimates reaching as high as 60%.[3] Despite its frequent occurrence and ease of diagnosis, the condition remains extremely challenging to treat. Many prescriptions and over-the-counter (OTC) medications for insomnia exhibit limited efficacy and are often accompanied by undesirable side effects and the potential for dependency or tolerance issues.

To tackle this prevalent yet largely unaddressed problem, CBD has garnered attention as a possible solution due to its promising therapeutic effects in conditions associated with insomnia, such as anxiety and pain. Subsequently, CBD has become a focal point of several sleep disorder trials and, although the science is still emerging, preliminary research is favourable (Figure 1).[4]

To help advance research further in this field, dsm-firmenich has teamed up with Oz Medicann Group Pharma (Sydney, Australia), an innovator in cannabinoid medicines, to investigate the possibilities of a CBD-based ODT for insomnia. In the next phase of clinical trials, the efficacy and dosage level of a Schedule 3 OTC ODT is to be explored. However, it is not just insomnia where these CBD-based ODTs have the potential to transform patient care.

A BRIGHT OUTLOOK AHEAD

There is a myriad of opportunities for groundbreaking CBD developments, presenting a chance to broaden treatment options for patients globally. Currently, over 220 clinical trials are underway to explore the therapeutic capacity of CBD, especially in the realms of CNS diseases, mood disorders and pain management. Despite affecting tens of millions of people worldwide annually, these conditions lack cannabinoid-based therapies for their treatment.

CBD science is particularly robust and established in CNS disorders, which encompass a broad category of neurological conditions, including epilepsy and Parkinson's disease. The molecule's favourable safety profile, along with its anti-convulsant effects and neuroprotective properties, have propelled research in this area, leading to the introduction of CBD-based treatments on the market.

Further research currently being initiated includes trials exploring the role of CBD as an immunomodulatory agent. The API's immunomodulatory and anti-inflammatory properties make it a compelling therapeutic compound for diseases characterised by excessive inflammation, such as chronic diseases or inflammatory conditions. Moreover, cannabinoid research does not stop at CBD. Investigations related to minor cannabinoids, such as those found in lower concentrations in the cannabis sativa plant, including cannabinol and cannabigerol, are also underway and anticipated to become a growing focus for innovation.

THE KEY TAKEAWAY

ODTs represent a patient-friendly dosage form that prioritises convenience, efficacy and ease-of-use, ultimately enhancing the overall treatment experience for patients across various healthcare settings. With this in mind, ODTs could revolutionise CBD delivery in a way that places patient centricity and elevated care at the forefront.

ABOUT THE COMPANY

As innovators in nutrition, health and beauty, dsm-firmenich reinvents, manufactures and combines vital nutrients, flavours and fragrances for the world's growing population to thrive. With its comprehensive range of solutions, including natural and renewable ingredients and renowned science and technology capabilities, dsm-firmenich works to create what is essential for life, desirable for consumers and more sustainable for the planet. As a purpose-led partner in the pharmaceutical industry, dsm-firmenich remains at the forefront of leading-edge cannabinoid research; driving forward the next frontier of medicine and helping drug developers realise the full therapeutic potential of these unique compounds. dsm-firmenich is a Swiss-Dutch company, listed on the Euronext Amsterdam, with operations in almost 60 countries and revenues of more than €12 billion (£10.3 billion) annually. With a diverse worldwide team of nearly 30,000 employees, the company brings progress to life for billions of people every day, everywhere.

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Zdravka Misic, Innovation Project Manager at dsm-firmenich, holds a PhD in Pharmaceutical Sciences from the University of Basel (Switzerland). She started her career as a formulation scientist at Teva in 2004. In 2009, she moved to Switzerland to ETH Zürich as an ESKAS (Swiss Government Excellence Scholarships for Foreign Scholars) scholarship holder. Dr Misic joined dsm-firmenich in 2014 and, since then, has worked as a Principal Pharmaceutical Scientist on developing new delivery systems for dsm-firmenich's products and collaborated closely with marketing in presenting them to customers. She also leads external collaborations with academic partners (including the International University of Applied Sciences and ETH Zürich) and established CDMOs within the pharmaceutical industry. Since January 2024, Dr Misic has switched to the position of an Innovation Project Manager, dedicated to pharma innovation projects in the specific development of new oral solid CBD formulations with enhanced bioavailability.