PHARMA SOLUTIONS
WHITEPAPER • APRIL 2022

Unlock advanced CBD formulations with lipid-based systems

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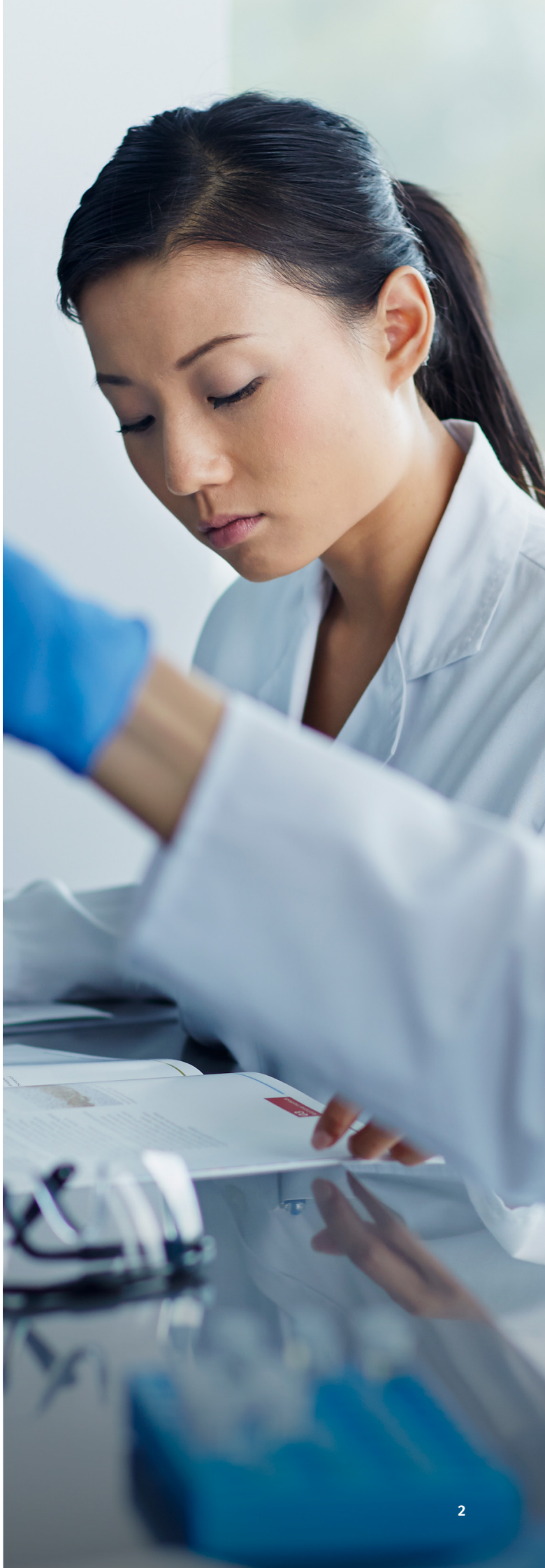

Executive summary

Cannabidiol (CBD) has substantial therapeutic potential, in addition to low toxicity.

But its development as an effective drug product for pharmaceutical use is challenged by factors such as low and variable bioavailability. In order to enhance the performance of CBD-based drugs, it is paramount to understand and overcome the inherent challenges when developing therapies including CBD, particularly when the ingredient will be delivered through the oral route.

This whitepaper explores the issue of CBD's oral bioavailability, and the benefits of lipid-based systems for optimized CBD formulation.

Make a difference with CBD-based therapies

The CBD pharmaceuticals market holds huge growth potential – powered by renewed scientific interest in the medical use of CBD in a variety of health areas, including CNS (central nervous system) diseases, pain disorders, cancer, and more.

CBD is the second most prevalent cannabinoid found in the cannabis plant, after THC (tetrahydrocannabinol). Unlike THC though, it does not produce a psychoactive, 'high', effect and is generally well-tolerated, with a favorable safety profile. The medical community has been aware of CBD for many years. However, it was not until the discovery of the endocannabinoid system (ECS) – which is thought to regulate several physiological functions and numerous health/disease states – in humans in the late 1980s that the potential of CBD as a therapeutic ingredient was explored.

Mounting scientific evidence demonstrates the beneficial medical potential of CBD in a wide variety of therapeutic areas

Bioavailability: a key consideration in CBD formulation

Oral drug delivery is the most common route for drug administration, and the preferred route for many patients and formulators alike.

However, drug developers can face several challenges related to CBD's oral bioavailability – creating new opportunities to optimize CBD-based formulations and enable the molecule to fulfill its full potential as a therapeutic agent.

Low and variable oral bioavailability remains one of the most significant issues faced by formulators innovating with CBD. Poor bioavailability is the result of incomplete absorption and significant pre-systemic elimination. Furthermore, variability in the molecule's oral bioavailability – related to different absorption rates and high inter- and intra-patient variability – can lead to inconsistent efficacy of the drug and a higher risk of side effects. These factors can significantly affect the therapeutic impact of the drug if not addressed properly.

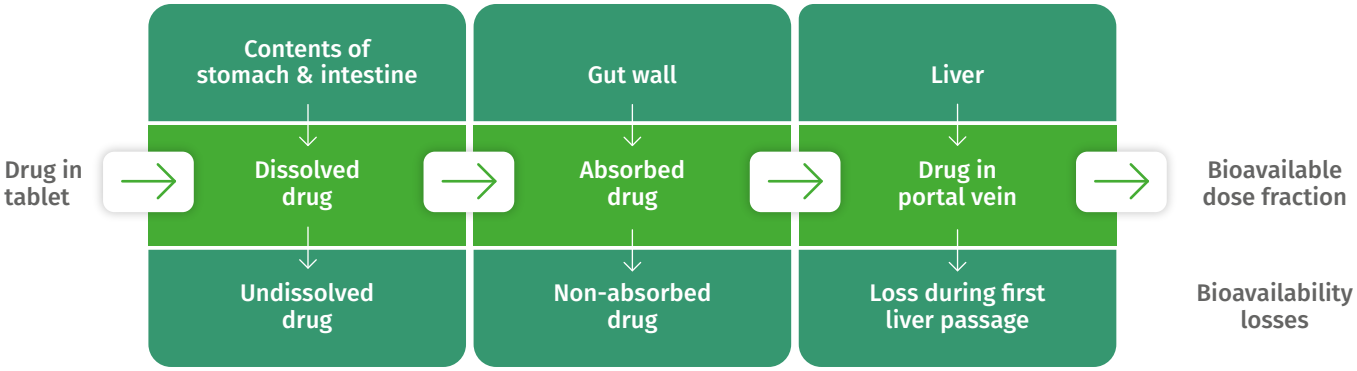

Fig 1. Illustration of drug pharmacokinetics – the movement of a drug through the body.

1 Incomplete gastrointestinal absorption

Cannabinoids, including CBD, have very low solubility in water (12.6 mg/L) and high lipophilicity (logP 6.3), meaning that a significant fraction of the dose may be lost in the gut due to incomplete absorption.

2 Extensive hepatic pre-systemic metabolism

Like any drug, CBD passes through the liver – via the portal vein – when administered orally, and then enters the systemic circulation where it travels to its site(s) of action. Most molecules undergo some extent of first pass metabolism in the liver – a phenomenon whereby the concentration of a drug is greatly reduced by enzymatic metabolism before it reaches the systemic circulation. However, CBD is subject to significant pre-systemic metabolism in the liver.

It is estimated that up to 75% of orally absorbed CBD is removed by hepatic metabolism before reaching systemic circulation.[1] This, coupled with the incomplete gastrointestinal absorption of the molecule, means that the absolute oral bioavailability of CBD after intake is thought to be about 6%.[1] As such, the active ingredient needs to be consumed in a large quantity to have any real therapeutic effect.

To prevent a CBD-based solution not reaching market because of its compromised absorption and extensive metabolism in the liver – and therefore poor bioavailability – it is therefore vital that a higher percentage of the dose is able to reach the blood circulation, from which it can travel to the site(s) of action.

CBD is classified as:

BCS class 2 drug: A poorly water-soluble and highly permeable pharmaceutical.

BDDCS class 2 compound: A poorly water-soluble drug that is eliminated by metabolism.

3 Impact of food on bioavailability

The absorption of BDDCS class 2 medications generally increases when co-administered with a high-fat meal. As individuals have different diets and eat at different times, this can lead to even further variability in the oral bioavailability of CBD and an increased potential for adverse effects. This has been demonstrated in healthy individuals and patients with refractory epilepsy, where a four-fold increase in bioavailability was observed in individuals where CBD was administered with a high-fat diet, compared to those who fasted.[2, 3, 4]

To limit the bioavailability variability of CBD, this BDDCS class 2 drug should function as close as possible to a class 1 substance – namely eliminating or minimizing food effects on the extent of absorption.

The **absolute oral bioavailability of CBD** after intake is thought to be about **6%.**[1]

The impact of drug-drug interactions

Because CBD behaves as a high hepatic clearance compound when administered orally, drug-drug interactions affecting its metabolism are likely.

This is because the enzymes involved in metabolizing CBD as it passes through the liver – namely CYP450 enzymes – are also involved in the metabolism of other compounds or drugs. Competitive binding for these enzymes between drugs can lead to large inter-individual differences in the efficacy of CBD in patients receiving the same dose of the drug.[5] Plus, there is an increased risk of adverse effects due to the drug-drug interactions that may occur.[6]

To avoid the risk of these drug-drug interactions, it is therefore important to reduce the first-pass effect of CBD – simply increasing the absorption of the drug will not suffice.

Optimize your CBD formulation with lipid-based systems

There is potential for the development of novel CBD formulations associated with greater and more consistent bioavailability, less susceptibility to food effects and reduced variability in clinical response.

An optimal formulation strategy will address the challenge of bioavailability at all stages:

- Improve dissolution in the gut
- Increase the absorption across the gut wall
- Reduce the extent of first-pass metabolism.

Optimizing the bioavailability of CBD means that a smaller quantity of the drug is needed to be effective, thereby reducing dosage for the patient, limiting the risk of side effects associated with drug-drug interactions and lowering the cost in use.

The benefits of lipid-based systems

Lipid-based systems – including liposomes or lipid nanoparticles – are a natural way to improve the bioavailability of molecules with low water solubility, like CBD.

This well-established technology works by transporting active ingredients through the gastrointestinal tract, into the lymphatic or blood circulation and to the target area(s) in the body without the drug degrading. Because the ingredient inside the lipid-system is protected until it reaches its target, this method results in greater bioavailability and therapeutic efficacy.

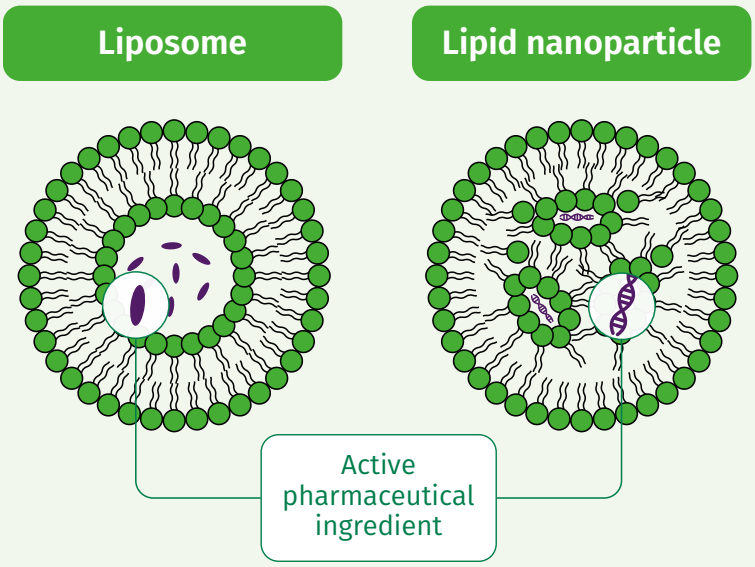

Fig 2. Lipid encapsulation and liposomal delivery of fat-soluble actives are well-established strategies for enhancing the bioavailability of poorly soluble compounds because they protect the active ingredient until it reaches its site(s) of action in the body.

Think CBD. Think DSM.

The CBD market is full of promise, but it's a difficult space to navigate alone.

To help customers realize the full potential of CBD – and inspire the creation of bespoke, purpose-led drug products that benefit global patient health – DSM has created a platform that facilitates early-stage drug development and novel scientific discoveries in this rapidly evolving field of research.

We also offer an industry-leading nutritional lipids portfolio, which meets the highest safety and quality requirements for use in a range of pharmaceutical applications.

Our CBD offering includes:

A high quality ingredient
THC-free CBD, pharma-grade API

Customized solutions
Custom CBD manufacturing capabilities upon request, plus formulation, technical and application support

Expert services
Quality, regulatory and scientific expertise in early-stage drug development and beyond

Where others see APIs, we see unlimited CBD potential

Advanced formulation expertise and technical capabilities

We have more than 70 years of experience in producing and securing the supply of APIs; bringing the passion and unique innovation expertise and capabilities needed to succeed in the pharmaceutical market. Currently, we're exploring multiple avenues and technologies in CBD formulation for improved oral bioavailability.

Enter the CBD market with confidence.

Partner with DSM to explore the potential of CBD as a novel therapeutic ingredient. **Contact one of our experts** today to learn more.

Contact us

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