Better Delivery of Cannabidiol

Subjects: Others
Contributor: Saoirse O'Sullivan

Cannabidiol (CBD) has substantial therapeutic potential, but its development as an effective drug by the pharmaceutical industry is hindered by intrinsic characteristics such as low bioavailability, low water solubility, and variable pharmacokinetic profiles. Potential avenues to overcome these issues with CBD include self-emulsifying drug delivery systems, improved crystal formulations and other solid-state delivery formulations, which are mostly in the pre-clinical or early clinical stages of development.

Keywords: cannabidiol ; pharmacokinetics ; bioavailability ; therapeutics

1. Introduction

Cannabidiol (CBD) is a phytocannabinoid used globally for a variety of indications, but with few approved medicinal applications. Purified CBD is only licensed in treatment-resistant, rare paediatric forms of epilepsy [1][2][3][4][5]. In order to be successfully utilised as a medicine, it is paramount to identify and overcome the inherent challenges that face CBD's effective delivery, particularly through the oral route, which is the most preferred route for drug delivery by patients and drug developers. Some of the most significant issues with oral CBD include poor bioavailability, variable pharmacokinetics profiles, and possible polymorphisms [6], which may have unintended consequences of less predictable efficacy, increased side effects and drug–drug interactions with higher doses.

2. Novel CBD Medical Products in Development

2.1. Self-Emulsifying Drug Delivery Systems

Methods to increase oral CBD bioavailability have included self-emulsifying drug delivery systems (SEDDS). These involve mixtures of oils, surfactants, and solvents that produce nano or micro sized droplets when they come into contact with an aqueous solution such as in the gut [6]. The small nature of the droplets increases the surface area available for drugs to be dissolved and absorbed. For example, soft gelatin capsules containing CBD developed by Satipharm, based on an advanced self-nanoemulsifying technology, have demonstrated greater bioavailability (about 31–34% higher compared to a reference oromucosal spray), solubility, and faster time to peak plasma concentrations in humans [7][8][9]. However, inter-individual variations were still high. This formulation has been proven safe and effective in a paediatric population with treatment-resistant epilepsy [1]. Another group recently reported a 4.4-fold increase in C_{max}, enhanced bioavailability, and shorter T_{max} with a SEDDS-CBD formulation based on VESIsorb® technology compared to a control CBD oil [6]. VESIsorb® is a novel lipid-based delivery system which self-assembles on contact with an aqueous phase into a colloidal delivery system, which solubilises the drug and improves diffusion and absorption and thus bioavailability [10]. In rats, another approach of a nano-emulsion (NE) formulation has been tested. CBD-NE oil drops increased absorption and bioavailability (21% higher) compared to a control CBD oil [11]. However, there may be practical (stability, complex formulations, safety of excipients, scalability) and economic (cost of formulation, patentability) issues with this method of increasing oral CBD bioavailability.

Although the methodology is not clear from publicly available information, Echo Pharmaceuticals and Ananda Scientific are also investigating formulations which claim to enhance bioavailability and consistency in PK profiles by increasing CBD's water solubility; Ananda's Liquid Structure™ Enhanced CBD and Echo Pharmaceutical's Arvisol, using their lipophilic compound delivery technology Alitra®. Both compounds are in preclinical or early clinical phase 1 development .

Another encapsulated form of CBD is APH-1501 (produced by Aphios), which are time-released capsules in which CBD is encapsulated in biodegradable polymer nanospheres as a lyophilised powder. This CBD is awaiting phase 2 testing in opioid addiction.

2.2. Solid-State Delivery Formulations

Solid-state oral delivery allows for 100% of the drug to reach the GI tract and has the potential to improve PK characterisation [12][13]. CBD delivered via this route would also further avoid local side effects associated with use of Sativex oromucosal spray (1:1 CBD:THC) or GI discomfort or pain associated with the vehicle itself in oral liquid formulations [14]. Current investigated solid-dose oral formulations of CBD include a 200 mg CBD tablet by Columbia Care called BeneCeed™, which will be used in a UK clinical trial. Elsewhere, a patent by GW pharmaceuticals lists a solid-state CBD as a potential clinical consideration in the treatment of inflammatory bowel disease [15]. Whilst dosing in this fashion ensures a consistent dose, formulations of this nature do not necessarily address problems associated with poor bioavailability.

2.3. Improved Single Crystal Structures

Some researchers claim to have improved the single crystal form of CBD. For example, one patent listed describes a crystalline CBD of a novel form, including (*R*,*R*)-(−)-crystalline cannabidiol [16]. This crystalline form was shown to possess a melting point of 37–50°C, compared with a melting point of 66–67 °C for CBD. Intramolecular crystal lattice binding between ions within a crystal affects its melting point and reductions in lattice energies may increase aqueous solubility [17]. PureForm CBD™ is described as a molecularly identical, non-hemp-based CBD that has been developed using their InterMolecular Stacking Technology to improve solubility and stability [18]. There is no further publicly available information on these products.

2.4. Cocrystal Engineering as a Potential Solution for CBD Oral Delivery

Interest and progress in the concept of cocrystallisation have expanded over recent years and is becoming a well-established process in drug development. Cocrystals consist of the API and one or more unique crystalline co-formers which modify the material properties whilst retaining the intrinsic pharmacological drug activity. Cocrystallisation is a useful method for overcoming problematic properties of drugs by increasing the bioavailability, solubility, dissolution rate, physical form, melting point, tableting, stability, or permeability of drug substances [19][20][21]. Further advantages of crystal preparations include the potential for numerous co-molecules including preservatives, other APIs, and pharmaceutical excipients, as well as providing the opportunity to address intellectual property issues by extending API life cycles and fulfilling patent eligibility criteria [22].

Entresto™ is an example of a drug–drug cocrystal containing monosodium sacubitril and disodium valsartan used to treat chronic heart failure that has obtained FDA approval. PK studies demonstrated a mean relative bioavailability of 161% in the cocrystal form of valsartan compared to reference valsartan tablets [23]. The cocrystal demonstrates high solubility and medium permeability. Suglat® is another marketed cocrystal, comprised of the sodium glucose cotransporter 2 (SGLT2) inhibitor ipragliflozin and L-proline, approved in Japan for the treatment of diabetes mellitus. The third cocrystal currently on the market is Depakote®, an anti-convulsant drug, which is comprised of valproate sodium with valproic acid [24].

Artelo Biosciences have developed a cocrystal with CBD that was designed to take advantage of cocrystal properties and help alleviate some of the problems with CBD delivery. This cocrystal uses the co-former tetramethylpyrazine (TMP; also called ligustrazine), a plant-derived compound from the Ligusticum species that is widely used in Chinese medicine. TMP may offer increased efficacy and bioavailability, by acting synergistically and changing the physiochemical properties that are associated with ineffective absorption. ART12.11 (CBD:TMP cocrystal) is currently in the nonclinical phase of pharmaceutical development targeted towards post-traumatic stress disorder (PTSD), inflammatory bowel disease (IBD), stroke and rare diseases, and has been recently granted a composition of matter patent in the US.

2.5. Other Delivery Systems and Formulation in Development

An oral capsule developed by Lexaria Bioscience Corp called “TurboCBD” claims to result in increased circulating CBD levels compared to control CBD, and contains American ginseng, ginkgo biloba, and organic hemp oil, produced using DehydraTECH™ delivery technology [25].

Preveceutical’s “Sol-Gel” is exploring an intranasal CBD formulation to increase bioavailability and is currently in the pre-clinical stage. Zynerba Pharmaceuticals have progressed a permeation-enhanced CBD gel “Zygel” for transdermal application to phase 2 trials [26]. Botanix pharmaceuticals are exploring a number of gel formulations for transdermal application in indications such as acne, psoriasis and dermatitis that are in early clinical development.

Kalytera are also exploring inflammatory skin conditions using an L-valine-ester derivative of CBD for topical delivery, which is in pre-clinical stages. Kalytera are also developing a bi-sulphate derivative of CBD for oral delivery which claims to be water soluble, a bi-phosphate CBD derivative aimed for intra-tracheal delivery via a novel aerosolised formulation,

and an intravenous (IV) formulation. GW Pharmaceuticals list an IV formulation in phase 1 trial for neonatal hypoxic-ischemic encephalopathy (NHIE).

A sublingual formulation by Diverse Biotech Inc., and an oral liquid by Emerald Health Pharmaceuticals containing a pure synthetic CBD are both in early clinical phases.

Complexation of CBD with cyclodextrins (CD) has also been investigated as a potential method to increase the water solubility and subsequently improve the bioavailability of sublingually delivered CBD. Mannila and colleagues demonstrated precipitation complexation of CBD and β-CD at a 1:2 ratio could increase the water solubility of CBD and increase the dissolution rate [88]. The authors noted sublingual delivery of the CBD/β-CD complex produced superior bioavailability compared to oral dosage forms of CBD in rabbits. However, in this study, CBD delivered in an ethanol solution sublingually was comparable to sublingual delivery of the CBD/β-CD complex. Two formulations of CBD and CDs are currently in development by Medexus pharmaceuticals and Vireo health LLC. These companies propose complexes of CBD and CDs will increase the aqueous solubility and subsequently improve bioavailability. However no clinical studies have been performed using these exact formulations to date.

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