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Medicinal cannabis delivery systems: A perspective

Diego E. Boldrini[1,2]*, and Olivia V. López[1,3]

[1]Pilot Plant of Chemical Engineering, National University of the South, National Scientific and Technical Research Council, Bahía Blanca, Buenos Aires, Argentina

[2]Department of Chemical Engineering, National University of the South, Bahía Blanca, Buenos Aires, Argentina

[3]Department of Chemistry, National University of the South, Bahía Blanca, Buenos Aires, Argentina

Abstract

In recent years, cannabis derivatives have been proposed for the treatment of various medical conditions, including pain, inflammation, epilepsy, sleep disorders, multiple sclerosis, anorexia, schizophrenia, neurodegenerative diseases, nausea, and cancer. While the benefits of cannabis derivatives, primarily cannabinoids, have been demonstrated and continue to be studied, their use presents various challenges associated with their low water solubility, rapid metabolism, erratic and poor bioavailability, and erratic pharmacokinetics, which directly affect their efficacy. In this context, a great deal of research is being carried out to overcome these drawbacks by designing delivery systems capable of improving solubility/bioavailability, potency, and efficacy, while addressing the purity and quality issues required by the pharmaceutical industry. This article aims to critically review the major trends and challenges in designing controlled-release cannabinoid delivery systems and their potential application in the pharmaceutical industry.

Keywords: Cannabis; Cannabinoids; Drug delivery systems

***Corresponding author:**
Diego E. Boldrini
(dboldrini@plapiqui.edu.ar)

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1. Introduction

Cannabis plant (*Cannabis sativa* L.) is one of the oldest plants cultivated for food, fiber, and medicine. Native to western Asia, it can grow in all habitats, from sea level to temperate zones and alpine foothills. Cannabis has been used for thousands of years to treat conditions such as asthma, epilepsy, fatigue, glaucoma, insomnia, nausea, pain, and rheumatism.[1] First botanically classified in 1753 by Carl Linnaeus, *C. sativa* L. is an annual plant belonging to the *Cannabaceae* family. Later, in 1785, Jean Baptiste Lamarck discovered another species which he named *Cannabis indica*. At present, the Missouri Botanical Garden recognizes 13 species, namely *C. sativa*, *C. indica*, *Cannabis americana*, *Cannabis chinensis*, *Cannabis erratica*, *Cannabis foetens*, *Cannabis generalis*, *Cannabis gigantea*, *Cannabis intersita*, *Cannabis kafiristanica*, *Cannabis lupulus*, *Cannabis macrosperma*, and *Cannabis ruderalis*.[2] Chemical composition of these species has been widely studied, and approximately 500 compounds have been identified, including cannabinoids, terpenes, flavonoids, alkaloids, stilbenes, phenolic amides, and lignanamides.[3-5]

Cannabinoids are the most abundant and exclusive metabolites of these species and the most important because they are capable of interacting with an entire system of endogenous receptors (endogenous cannabinoid system). In addition, they are terpenophenolic in nature and are generally concentrated in the resin produced in the plant's trichomes, especially in the female inflorescences. There are around 70 known terpenophenolics, of which tetrahydrocannabinol (THC) is the most studied.[3] Cannabinoids are synthesized and accumulated as cannabinoid acids, and it is not until the drying and storage process that the acids are gradually decarboxylated until they reach their final form, such as THC or cannabidiol (CBD).[6] Around 120 terpenes have also been identified in these plant species.[3,7] These metabolites are responsible for the flavor of the different varieties. Some of these terpenes are pharmacologically active and could produce synergistic effects with cannabinoids.[8] Flavonoids are aromatic compounds and can be found in free form or conjugated with a glucoside. More than 20 of these metabolites are produced,[3,7] mainly found in the plant leaves, and some studies suggest that they modulate the action of cannabinoids.[8] Other chemical components also present in the plant are alkaloids, although they are found in lower proportions. These are nitrogenous compounds that usually present biological activity at low doses and can be derived from amino acids. Due to the low concentration of alkaloids present in these species, their pharmacological evaluation is difficult. Finally, it also contains stilbenoids, lignanamides, and phenolic amides. Stilbenoids are phenolic compounds which are presumed to have certain pharmacological activities, such as antibacterial, antifungal, anti-inflammatory, antineoplastic, neuroprotective, cardio- and vasculo-protective, and antioxidant effects. Phenolic amides have also been reported to have cytotoxic, anti-inflammatory, antineoplastic, and analgesic activities, whereas some lignanamides have shown cytotoxic activity.[3]

2. Medicinal cannabis delivery systems

Given the low bioavailability of cannabinoids, their clinical use is limited. In this sense, the pharmaceutical industry is focused on improving this point to optimize the different formulations. At present, a wide variety of cannabis products are commercially available to be administered in several routes, namely oral, transdermal, pulmonary, and transmucosal administration. Various release systems have been proposed for each administration route to increase their efficacy. Table 1 shows the main advantages and disadvantages of each route of administration.

2.1. Oral administration

Although oral administration of cannabinoids has been shown to have poor bioavailability, mainly due to poor absorption and degradation in the stomach or pre-systemic metabolism in the liver, various formulations have been proposed to counteract this disadvantage. For example, several encapsulation systems have been proposed to protect cannabinoids, such as micelles, soft capsules, and tablets.[9-11] Another alternative to improve oral bioavailability is the combination with lipids, which has been shown to increase the cannabinoid absorption rate. In the case of long-chain triglycerides, it has also been shown that this combination can cross the liver, reducing the possibility of pre-systemic metabolism.[12] Cyclodextrins or their derivatives have also been proposed to form inclusion complexes that significantly increase cannabinoid solubility.[13] Another approach to improve cannabinoid solubility is their derivatization, known as prodrugs. An example is the CBD/naproxen combination developed by Claritas Pharmaceuticals (USA), which is being tested

Table 1. Main advantages and disadvantages of oral, transdermal, pulmonary, and transmucosal administration of cannabis products

Route of administration	Advantages	Disadvantages
Oral	Patients prefer oral administration for its simplicity.	This route causes slow and erratic absorption and degradation by stomach acids. Bioavailability is reduced by the pre-systemic metabolism in the liver.
Transdermal	Transdermal delivery bypasses the first-pass metabolism effect, resulting in increased drug bioavailability. Besides, it can provide continuous drug release. Topical application is suitable for localized pathologies.	Local irritation and limited skin penetration of drugs.
Pulmonary	Highly effective, rapid distribution to the central nervous system, and higher systemic bioavailability.	Inhaling harmful combustion products can cause bronchitis and chronic coughing. Vaporization systems and nebulization formulations lack practicality.
Transmucosal	Transmucosal delivery bypasses the first-pass metabolism effect, resulting in increased drug bioavailability.	The use of transmucosal excipients may cause mouth ulcers. The bioavailability of intranasal delivery systems could be improved.

in various pathologies.[14] Although the aforementioned formulations partially counteract the difficulties associated with oral administration of cannabinoids, there are other routes of administration that could increase efficacy through more direct uptake and transport of the drug into the bloodstream, also avoiding hepatic metabolism. These alternative administration routes are described in sections 2.2, 2.3, and 2.4.

2.2. Transdermal administration

Dermal formulations can be transdermal (for systemic effects) and topical (for localized effects on the skin). Transdermal drug administration has the advantage of avoiding the first-pass metabolism effect. In addition, a sustained release is achieved over time, preventing the adverse effects of high drug concentrations. Topical application suits localized symptoms associated with peripheral neuropathic pain, dermatological disorders, and arthritis. However, this administration route has several disadvantages such as limited skin penetration of drugs and local irritation. Particularly, cannabis is highly lipophilic, a property that hampers its release through the skin. In this sense, numerous researchers have developed synthetic cannabinoid prodrugs to obtain more skin-permeable products and demonstrated the efficiency of this strategy.[15,16]

2.3. Pulmonary administration

Since ancient times, cannabis has been consumed in the form of cigarettes, both for recreational and therapeutic purposes. Its compounds have very high bioavailability, reaching a maximum concentration in plasma after approximately 7.5 min. In addition, this concentration can remain constant for about 4 h with rapid distribution to the central nervous system. Unfortunately, this route of administration has the problem of being able to cause conditions such as bronchitis and chronic cough associated with the harmful products generated during smoking.[15] One method that can mitigate these adverse effects is the use of vaporization, which involves heating cannabis to the temperature at which cannabinoids are vaporized, below the combustion temperature. This avoids the formation of harmful compounds associated with the combustion process.[17]

2.4. Transmucosal administration

Through transmucosal administration, drugs can be rapidly absorbed into the bloodstream due to the vascularity of the oral mucosa. This route of administration is non-invasive and has the advantage of being able to bypass the first pass through the liver. In this way, pre-systemic metabolism is avoided. Although the oral route is the most commonly used intramucosal route of administration, there are other more effective administration modes such as intranasal, oral transmucosal, and rectal routes. In this context, a multitude of cannabis products have been developed to be administered by this route, such as sublingual disintegrating thin films, sprays, orally disintegrating tablets, buccal mucoadhesive tablets, films and patches, chewing gum, and lozenges.[15] These formulations have been shown to increase the bioavailability of cannabinoids, but have not been developed with the ability to release cannabinoids at sites of interest such as tumors or disease sites, and also show various adverse effects. In this context, there is currently a growing interest in the development of nano-formulations of cannabis compounds for cancer therapy, pain management, and treatments for various other pathologies.

3. Trends, perspectives, and conclusion

The usefulness and efficacy of a drug delivery system depend on several factors such as solubility, half-life, metabolism, distribution, and ease of use. In this regard, many novel proposals have been developed in recent years to improve the performance of the above-mentioned systems. Particularly, nanotechnology is an example of a novel proposal for medicinal cannabis delivery systems. Nanoparticles have been extensively studied in controlled release systems. Their main attributes are: (i) improved encapsulation efficiency and increased drug solubility; (ii) presence of surface functional groups that improve stability and internalization; (iii) increased bioavailability, improved pharmacokinetics, and minimal clearance from the body; and (iv) controlled drug release properties. Examples of nanoparticle-based delivery systems for cannabinoids are nano-emulsions, dendrimers, micelles, liposomes, and biodegradable polymers. As mentioned above, the delivery of cannabinoids in lipids has several advantages which, in combination with nanotechnology, make it highly attractive in the design of delivery systems. In this context, systems based on nanomicelles, nanoemulsions, and nanostructured lipid carriers have been proposed. Another alternative is the formation of self-emulsifying delivery systems, which can improve the bioavailability, dissolution, and stability of cannabinoids. These systems consist of mixtures of solvents, surfactants, and oils with the ability to spontaneously disintegrate upon contact with an aqueous phase, such as the fluids present in the gastrointestinal tract. On the other hand, polymer-based drug delivery systems have also been proposed to modulate the release of cannabis compounds. In particular, poly(lactic-co-glycolic acid) has been widely studied for encapsulating cannabis-based compounds due to its biocompatible and biodegradable properties.[15] The use of nanotechnology

to develop cannabis-based formulations has shown to have several advantages over other formulations, such as increased efficacy, tumor targeting, and reduced systemic toxicity. However, each proposed formulation has been studied or has remarkable performance for a specific type of cannabinoid. In this sense, further developments using nanotechnology applicable to a specific cannabinoid or group of cannabinoids are needed, accompanied by appropriate pre-clinical and clinical studies.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

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Ethics approval and consent to participate

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