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Microencapsulation techniques for cannabinoids: pharmaceutical approaches, technological challenges, and formulation perspectives

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Abstract

Microencapsulation is a widely applied strategy for protecting bioactive compounds by entrapping them within a polymeric or lipid-based shell, thereby enhancing their stability and enabling controlled release. In recent years, the growing number of applications of cannabinoids has driven increasing interest in microencapsulation as a strategy to overcome challenges related to poor aqueous solubility, chemical instability, and limited bioavailability. The aim of this review is to summarize and evaluate commonly employed microencapsulation techniques for obtaining cannabinoid delivery systems.

A systematic literature search was conducted using the PubMed, SCOPUS, EBSCO, and Embase databases, resulting in the selection of over 50 original research articles and reviews. The search strategy employed combinations of keywords including cannabis AND microencapsulation methods, cannabinoids AND microencapsulation techniques, hempseed oil AND spray-drying OR coacervation technology, and cannabis industry AND microencapsulation.

The findings indicate that the most frequently investigated microencapsulation techniques for cannabinoids include spray-chilling, spray-cooling, fluidized-bed coating, liposomal entrapment, extrusion, freeze-drying, coacervation, and emulsification. These techniques differ in their encapsulation efficiency, scalability, particle size distribution, and suitability for specific delivery routes. Overall, microencapsulation has demonstrated significant potential to improve the physicochemical stability of cannabinoids, protect them from environmental degradation, and enable controlled or targeted release.

In conclusion, microencapsulation represents a promising and rapidly evolving approach for the development of advanced cannabinoid formulations, offering innovative solutions for enhanced stability, defined delivery performance, leading to potential of therapeutic applicability.

Key words: cannabinoids, controlled release, encapsulation techniques, microencapsulation, stability enhancement

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Introduction

Microencapsulation is the process of enclosing solid, liquid, or gaseous substances within a polymeric coating to form small particles, microcapsules, which protect the core material and allow controlled release (1). By shielding the core material from environmental damage and preventing unintentional exposure, the polymeric wall acts as a protective barrier. Controlled release of the encapsulated substance occurs at a predetermined site and/or time through polymer dissolution, diffusion, or degradation in response to specific stimuli such as pH, enzymes, or temperature (2).

Microencapsulation has numerous applications in the pharmaceutical, agricultural, food, and other industries, providing products with various applications, such as encapsulated active substances, essential oils, colors, aromas, sweeteners, microorganisms, and other materials (3).

The utilization of microencapsulation in the pharmaceutical industry facilitates the development of drug delivery systems, including sustained-release, targeted delivery, and taste-masking formulations, improving drug efficacy, patient compliance, and therapeutic outcomes (4). The microencapsulation of biologically active compounds such as peptides, proteins, and nucleic acids enhances their stability, bioavailability, and controlled release, paving the way for innovative therapeutic interventions (5). The process of microencapsulation also stabilizes vaccines and biological therapeutics, protecting them from degradation during storage and transportation, particularly in challenging environmental conditions (6).

Food industry has gained advantages from microencapsulation due to the possibility of protecting sensitive flavors from degradation due to exposure to light, oxygen, moisture, or temperature, thereby preserving their quality and extending shelf life. Probiotic-enriched foods can also benefit from microencapsulation techniques primarily designed to protect microorganisms from harsh gastrointestinal conditions, thereby preserving their viability (7).

Singh et al. (2010) define microcapsules as spherical particles containing a core substance, sized between 50 nm and 2 mm, thus accenting the influence of the microencapsulation technique on the microparticle size (4). Microcapsules encompass not just membrane-enclosed particles or droplets, but also dispersion in a solid matrix without a characteristic external wall phase, although the term “capsule” implies a core and shell structure. Their size range distinguishes them from the smaller nanoparticles or nanocapsules. In addition, mononuclear and polynuclear microcapsules can be distinguished by whether the core (nucleus) is divided or not (8). Conversely, microspheres are a class of microparticles that are synthesized as matrix systems, with the core of the particle uniformly distributed and/or dissolved inside a network of polymers. Depending on whether the center of the microsphere is dissolved in a molecular state or suspended in a particulate form, they can be homogeneous or heterogeneous (9).

Microcapsules remain of considerable interest in controlled-release applications due to their relatively simple design and formulation, as well as the inherent advantages of microparticulate delivery systems. These systems enable sustained release from

individual microcapsules while providing improved uniform and reproducible drug delivery (10).

Selecting the right wall material is crucial as it impacts both the stability and encapsulation effectiveness of the microcapsule. The following qualities should be present in the perfect wall material: non-reactiveness with the core material; ability to keep the core sealed inside the capsule; ability to shield the core from external factors as much as possible; exhibiting no undesirable taste when applied in oral formulations; and commercial viability (11). Mixing two or more materials is a common strategy in microencapsulation, as individual wall materials rarely possess all the desired physicochemical properties. A wide range of natural and synthetic polymers have been investigated as encapsulation matrices, including lipids (waxes, paraffin, hydrogenated oils and fats, mono- and diglycerides), polysaccharides (cellulose, chitosan, gum Arabic, alginate, carrageenan), proteins (gluten, casein, gelatin, albumin), and inorganic materials such as calcium sulfate and silicates (12).

The originally produced microcapsules can be finally enclosed in other dosage forms, such as hard gelatin capsules, which may be enteric coated, soft gelatin capsules, or suspended in liquids, all of which allow dispersion of individual microcapsules after release (4, 5).

The techniques used to produce these capsules range from simple blend operations to complex polymeric coatings. The existing methods of microencapsulation can be divided into three major categories: physical methods (spray-drying and freeze-drying), physicochemical methods (complex coacervation, ionic gelation and electrostatic layer-by-layer deposition), and chemical methods (interfacial polymerization and *in situ* polymerization) (10).

The possibility of the microencapsulation of cannabinoids and technological procedures for obtaining this kind of pharmaceutical forms has not been comprehensively reviewed so far, to the best of our knowledge.

The aim of this review is to summarize and evaluate the most commonly employed microencapsulation techniques for cannabinoid delivery systems. This review was conducted using a structured literature search of the following databases: PubMed, SCOPUS, EBSCO, and Embase. Original research articles and review papers published in English were considered. The selection focused on studies describing micro- and nanoencapsulation techniques applied to cannabinoids, cannabis extracts, or hemp-derived oils, with emphasis on pharmaceutical formulation, stability, bioavailability, and controlled release. After removing the duplicates and carefully reviewing the retrieved articles, the selection narrowed to 25 publications, and their findings are presented in this review.

Commonly used techniques for microencapsulation of bioactive compounds

Diverse microencapsulation techniques offer a wide range of possibilities when designing new microencapsulation systems. The available polymers, as well as the employed technique, are selected according to the properties of the core material, the application of the microcapsule, the size of particles needed, release characteristics of the

microcapsule, and the cost of production (13). Most commonly applied microencapsulation techniques include:

- The *air suspension technique,* also referred to as the *Wurster process*. It is performed by dispersing the solid, particulate core material in a supporting air stream with a simultaneous spray-coating of the suspended particles. The particles are suspended using an upward stream of moving air in the coating chamber and recirculated in this chamber to receive an increment of the coating material during each cycle. The supporting air stream also aids in the rapid drying of the drug. Only solid materials can be used as a core material in this technique, and the final product size ranges from 35 to 5000 μm (14).
- The *Coacervation / Phase separation* method includes forming three separate phases, deposition of the coating polymer around the core, and finally the formation of a rigid coat by thermal or cross-linking techniques. The cross-linking may result in simple coacervation comprising of one macromolecule, and complex coacervation of several macromolecules (Figure 1). This is a low-cost method, and is usually used for encapsulating flavor oils (15). This process can occur only within a limited pH range, concentration of colloid, or electrolyte, and can be used for the encapsulation of both solids and liquids to provide microcapsules sized from 2 to 5000 μm (13).

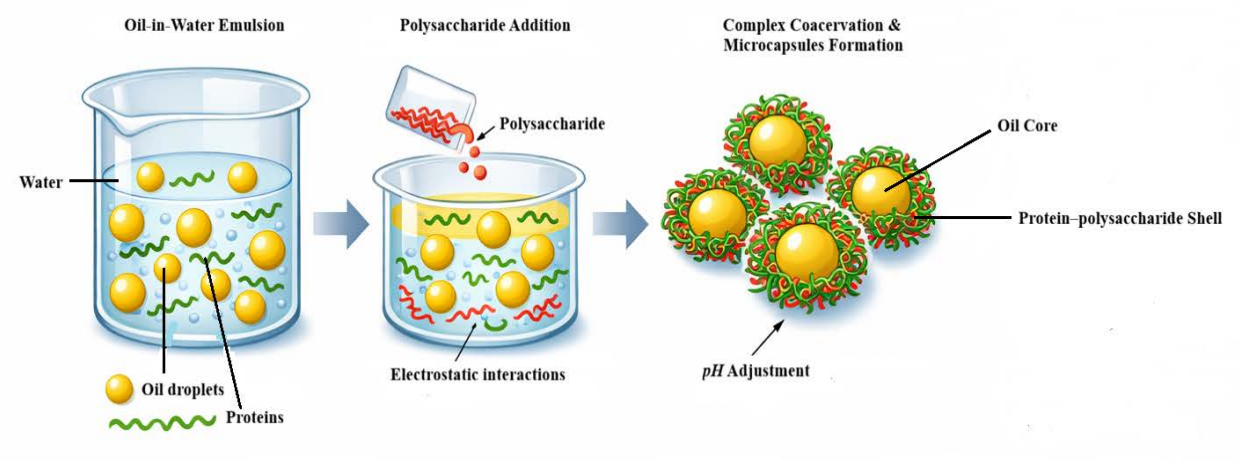

Figure 1. Schematic representation of protein-polysaccharide complex coacervation in the oil microencapsulation process

Oil droplets are first dispersed in an aqueous phase containing proteins, resulting in the formation of an oil-in-water emulsion. Subsequent addition of a polysaccharide leads to electrostatic interactions between oppositely charged biopolymers, which, under appropriate pH conditions, induce complex coacervation. This process results in the formation of a protein-polysaccharide coating surrounding the oil core. The obtained microcapsules provide enhanced physical stability of the system and effective protection of the encapsulated oil against oxidative degradation.

Slika 1. Šematski prikaz kompleksne koacervacije proteina i polisaharida u procesu mikroinkapsulacije ulja

Kapljice ulja se najpre disperguju u vodenoj fazi koja sadrži proteine, čime se formira ulje-u-vodi emulzija. Naknadnim dodatkom polisaharida dolazi do elektrostatičkih interakcija između suprotno naelektrisanih biopolimera, što pri odgovarajućim pH uslovima indukuje kompleksnu koacervaciju. Ovaj proces rezultira formiranjem protein-polisaharidnog omotača oko uljanog jezgra. Dobijene mikrokapsule obezbeđuju poboljšanu fizičku stabilnost sistema i efikasnu zaštitu inkapsuliranog ulja od oksidativne degradacije.

- The *spray-drying* method is performed by the initial formation of emulsion, solution, or suspension of the core and coating material. The preparation is then nebulized in a drying chamber with circulating hot air for the evaporation of the coating material and encapsulation of the core (Figure 2). The large-scale production of microcapsules can be done at a low cost using this method. However, the relative limitation of this microencapsulation method is that it can only produce microcapsules of around 600 μm, and these may not often be uniform in size (16).

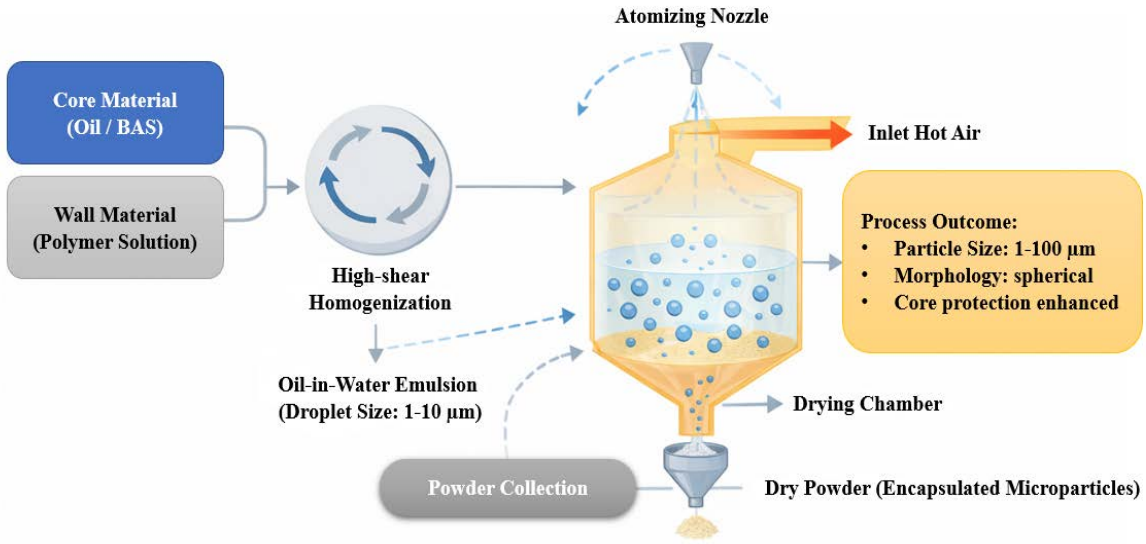

Figure 2. Schematic representation of the spray-drying microencapsulation process
The process involves preparing an emulsion through high-shear homogenization, followed by the atomization of the feed into fine droplets, convective drying with hot air, and the formation of encapsulated microparticles, which are ultimately collected as a dry powder.

Slika 2. Šematski prikaz procesa mikroinkapsulacije sušenjem raspršivanjem
Proces obuhvata pripremu emulzije homogenizacijom pod visokim smicanjem, zatim atomizaciju sirovine u sitne kapljice, konvektivno sušenje toplim vazduhom i formiranje inkapsuliranih mikročestica koje se na kraju sakupljaju kao suvi prah.

- In the *spray-cooling* method, a mixture of core and coating material is nebulized using an atomizer. Following atomization, the droplets enter a chamber with airflow at low temperature to facilitate solidifying the coating material to encapsulate the core. It is one of the cheapest microencapsulation techniques, but has low encapsulation capacity with increased chances of the expulsion of the core during storage (17).
- The *pan-coating* method involves effective coating of solid particles greater than 600 µm in a pan. The coating material is generally applied as a solution or atomized and sprayed over the solid core material in the circulating pan. Warm air is passed over after applying the coating material, in order to remove the coating solvent. It is extensively used in the preparation of controlled release products (18).
- The *solvent evaporation* method consists of dissolving the coating material in a volatile solvent, in which the core material is dispersed. This mixture is agitated to produce a microcapsule. Heating can be used to evaporate the solvent if needed. Using this technique, both liquid and solid core materials can be encapsulated, yielding microcapsules with size 5 to 5000 µm (19).

- The *polymerization* method includes the employment of polymerization techniques to form protective microcapsule coatings *in situ*. This happens due to the monomeric units' reaction that is present at the interface between the core material and the coating material (Figure 3). The liquid or gaseous phase is used as the core material, and thus, the reaction occurs at the liquid–liquid, liquid–gas, solid–liquid, or solid–gas interface (20).

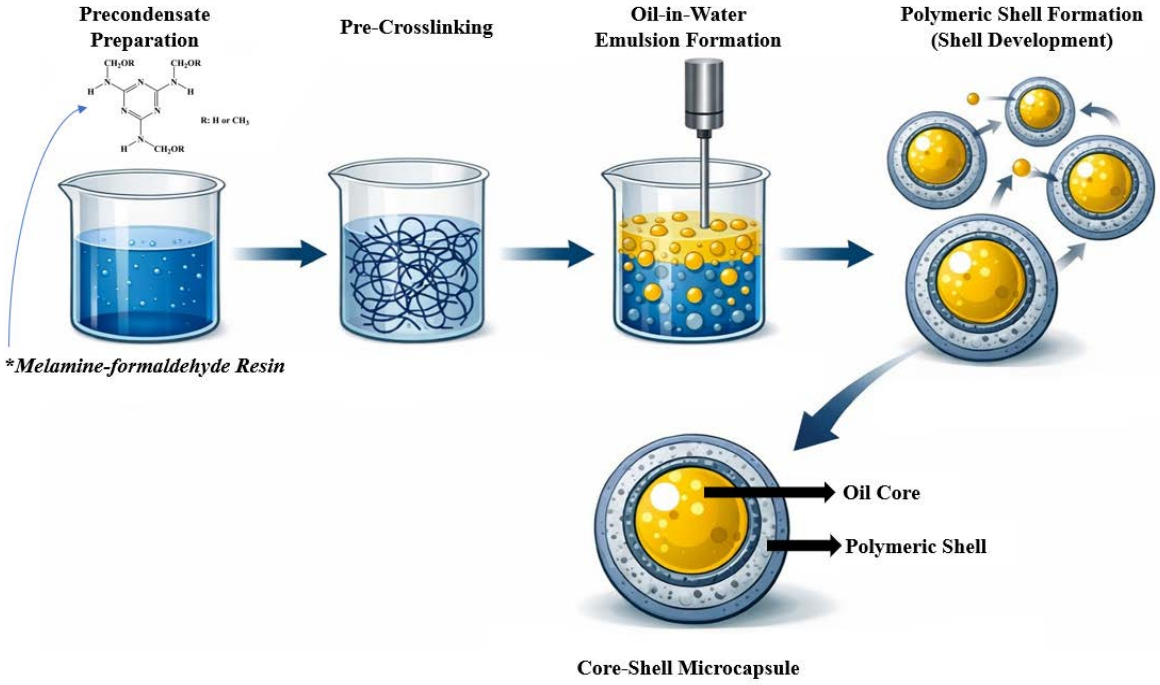

Figure 3. Schematic representation of oil microencapsulation with a bioactive compound via *in-situ* polymerization
The four-step process includes (1) the preparation of the precondensate, (2) pre-crosslinking, (3) formation of the emulsion, and (4) development of the polymeric shell, ultimately yielding core–shell microcapsules with an oil core and a polymeric coating.

Slika 3. Šematski prikaz mikroinkapsulacije ulja sa bioaktivnom supstancom putem *in-situ* polimerizacije
Proces u četiri koraka obuhvata (1) pripremu prekondenzata, (2) delimično umrežavanje, (3) formiranje emulzije i (4) razvoj polimernog omotača, što rezultira mikrokapsulama strukture jezgro–omotač sa uljanim jezgrom i polimernim omotačem.

Until the desired release, encapsulation should allow the core to remain separated from the outside environment. As a result, releasing the target component at the right moment and location is a crucial aspect of the encapsulation process that increases its efficacy and broadens its use. The interactions between the wall material and the core are the primary elements influencing the release rates (21). Additionally, other factors can

influence the release, such as core volatility, core-to-wall material ratio, particle size, and wall material viscosity grade (13, 21).

While microencapsulation offers numerous potential applications, this technique is not without limitations. Key advantages and limitations are summarized in Table I.

Table I Overview of microencapsulation strategies for bioactive compounds (BACs) with their advantages and limitations

Tabela I Pregled strategija mikroinkapsulacije bioaktivnih jedinjenja (BAJ) sa njihovim prednostima i ograničenjima

Technique / Method	Principle and process description	Key advantages	Key limitations	References
Spray-drying	An emulsion or solution containing the bioactive compound and wall material is atomized into a heated drying chamber, where rapid solvent evaporation leads to the formation of dry microcapsules.	Highly scalable and cost-effective; continuous operation with high throughput; widely available industrial equipment; significantly improves shelf-life and storage stability of encapsulated compounds.	Exposure to elevated temperatures may cause the degradation of thermolabile bioactives; broad particle size distribution; limited selection of suitable wall materials; potential loss of volatile compounds.	(1, 22, 29)
Freeze-drying (Lyophilization)	The emulsion or dispersion is frozen and subsequently subjected to sublimation under reduced pressure, yielding a porous dry matrix containing the encapsulated bioactive compound.	Operates at low temperatures, preserving heat-sensitive and oxidation-prone compounds; maintains structural integrity and bioactivity; produces powders with excellent rehydration properties.	Time-consuming and energy-intensive process; high capital and operational costs; limited scalability; often results in broad particle size distribution and fragile structures.	(2, 23, 29)
Simple coacervation	The phase separation of one or more polymers (e.g., gelatin, gum Arabic) occurs under controlled conditions, leading to the deposition of a polymer-rich coating around the bioactive core.	Enables good control over capsule size, morphology, and release behavior; mild processing conditions; suitable for sensitive bioactives.	Process complexity and sensitivity to pH, temperature, and ionic strength; difficult scale-up; often requires cross-linking agents and subsequent drying steps; relatively high production costs.	(2, 24, 29)

Ionic gelation	Encapsulation is achieved through ionic cross-linking of polyelectrolytes (e.g., alginate with Ca^{2+} ions), forming hydrogel matrices that entrap bioactive compounds.	Mild, solvent-free process; avoids high temperatures and organic solvents; biocompatible and environmentally friendly; relatively simple implementation.	Formation of heterogeneous particles; high permeability may result in premature release; limited mechanical strength; reproducibility and batch-to-batch variability challenges.	(1, 25, 29)
Solvent evaporation / extraction	The bioactive compound and polymer are dissolved in an organic solvent and emulsified in an aqueous phase; solvent removal leads to polymer solidification and capsule formation.	Particularly effective for hydrophobic bioactive compounds; allows fine control over particle size and morphology; relatively high encapsulation efficiency.	The use of organic solvents raises safety, environmental, and regulatory concerns; potential solvent residues; multi-step process; may result in low loading efficiency for certain compounds.	(5, 26, 29)
Fluidized bed coating	Solid particles are suspended in an upward air stream while a coating solution or melt is sprayed, forming a uniform polymer layer around the core particles.	Suitable for coating relatively large particles; enables continuous processing; good control over coating thickness and uniformity; widely used in pharmaceutical applications.	Requires pre-formed core particles; risk of particle agglomeration; limited applicability to liquid or nano-scale systems; high equipment complexity.	(6, 27, 29)
Extrusion	A mixture of bioactive compound and polymer is extruded through a nozzle into a hardening or gelation bath (e.g., alginate into calcium chloride), forming spherical beads.	Simple and low-cost technique; gentle processing conditions; minimal thermal and mechanical stress; suitable for sensitive bioactives.	Produces relatively large particle sizes; low production rate; limited scalability; not suitable for applications requiring fine or uniform microcapsules.	(6, 28, 29)

Cannabis, Cannabinoids, and products derived from *Cannabis* spp.

The Cannabis plant (*Cannabis sativa* L.), a dioecious annual flowering plant of the Cannabaceae family, is also referred to as hemp. Well-known for its wide range of chemical components, it has been extensively grown primarily for use in food, medicine, and recreational activities (30). Preparations derived from cannabis have been used for a variety of medical purposes, including anxiolytics, antiepileptics, pain relief, and inflammation. They have also been used as adjuvant therapy to alleviate the adverse effects of chemotherapy or as cytotoxic drugs to promote apoptosis or suppress cell growth in many cancer types (31).

The main classes of *Cannabis* spp. constituents include terpenoid compounds such as cannabinoids, monoterpenes, flavonoids, and even some alkaloid structures. Most of them are produced by secretory cells in innate trichomes localized in the female inflorescences (32).

Δ9-Tetrahydrocannabinol (THC) is the most abundant cannabinoid in drug chemotypes, constructed from a tricyclic 21-carbon structure without nitrogen and two chiral centers in the trans configuration. Obtaining the active form of THC is performed through decarboxylation of THCA and transformation of the carboxyl group to hydroxy radical (33).

Psychotropic effects are primarily associated with Δ9-tetrahydrocannabinol (THC), whereas cannabidiol (CBD) is considered non-psychoactive. This happens when THC activates cannabinoid receptors by decreasing the neural mechanisms that drive receptor control and limit the release of neurotransmitters, resulting in a psychotropic impact. THC is a CB1 agonist and a weak CB2 partial agonist (32, 33).

Unlike THC, CBD is a strong non-psychoactive component that has not been shown to have any intoxicating effects (28). CBD inhibits excitotoxicity and modifies cellular activity by binding to CB1, CB2, and 5HT1A receptors (34). Numerous illnesses, including neurological and metabolic disorders, have been linked to CBD's anti-inflammatory and antioxidant qualities (35).

According to the *Biopharmaceutics Classification System (BCS)*, pharmacologically active cannabinoids intended for oral use are classified as Class II, due to their very low water solubility and high lipophilicity; CBD (12.6 mg/L, logP 6.3, pKa 9.29) and THC (28.0 mg/L, logP 6.97, pKa 10.6) (36).

Oral cannabidiol (CBD) shows low and highly variable systemic exposure that depends strongly on formulation, dose and fed/fasted status, rather than a single fixed value. Many reviews and human studies report very low absolute oral bioavailability for unformulated CBD (commonly cited ~6%) (37). However, alternative formulations (lipid vehicles, self-emulsifying drug delivery systems, nanoparticles, oral solutions) and administration with food, especially high-fat meals, can markedly increase CBD, $C_{max,}$ and AUC by several-fold (36, 37). The low and variable oral exposure is owed to CBD's high lipophilicity and poor aqueous solubility, instability to oxidation/photodegradation under some conditions, limited dissolution in the gastrointestinal tract, and substantial presystolic (intestinal and hepatic) metabolism. Tissue distribution is extensive and the

plasma–tissue ratio also depends on dose and formulation. Therefore, estimates are not recommended (33, 36, 37). Although long-term CBD usage is reported to be clinically well-tolerated, its lability makes it difficult for formulation development and subsequent efficient delivery. In this line, encapsulating methods are regarded as a promising approach for CBD formulation and delivery (38).

One of the main challenges in addressing cannabis formulations is that, unlike conventional bioactive compound formulations, cannabis contains a complex mixture of active pharmaceutical ingredients (39).

One of the oils with the highest nutritional content is hempseed oil, which is extracted from *Cannabis sativa* L. seeds. It contains two polyunsaturated fatty acids (PUFAs), which are regarded as important for balanced nutrition, linoleic acid and linolenic acid in a ratio of 3:1 (40). It is also promoted due to its valuable composition of highly unsaturated oil, minerals, and vitamins. The nutritional quality and health benefits of hempseed oil result in its increasing inclusion in the food, nutraceutical, and cosmetic industries (41).

Hempseed oil is sensitive not only to higher temperatures, but also to oxidation, which decreases the quality of the product. In order to stabilize hempseed oil and prevent it from oxidation, one of the effective approaches is freeze-drying. Combined with microencapsulation of hempseed oil, freeze-drying can provide oxidation stability and maintain the nutritional value, especially regarding PUFAs. As a result, its shelf life can be extended allowing hempseed oil to be applied in a wide range of food and skin care products (40, 41).

Other bioactive compounds found in cannabis include terpenoids and flavonoids, which can influence its physicochemical characteristics. The color of cannabis oil results from the flavonoid content, whilst terpenoids contribute to its distinct flavor and odor. There are notable differences between these two classes of compounds in various cannabis chemotypes (42). Despite the potential bioactivity of flavonoids and terpenoids, very little is known about the physiological and pharmacological impact of these compounds in humans. This is especially true when regarding the *environmental effect*, which refers to the collective interaction of cannabis's active and inactive metabolites to affect the active components' receptor potency. The entrainment effect alone is thought to have a greater influence on the subjective perception or therapeutic effects of cannabis than non-cannabinoids (43).

Microencapsulation methods for cannabinoids: characteristics and applications

Among various available delivery methods, oral, intravenous, transdermal, or rectal, due to its ease of dosage, oral administration is the most popular method of administration; nonetheless, the bioavailability of cannabis is lower than that of other routes of administration (44, 45). Studies have shown that if cannabis is contained in emulsions, liposomes, or polymeric particles, bioavailability can be improved (45).

There are several cannabinoid preparations that are available for oral use, including *Marinol*® (which contains *dronabinol*, or synthetic THC), *Cesamet*™ (which contains

nabilone, a synthetic cannabinoid similar to THC), including few other formulations that are based on balanced ratios of THC/CBD, encapsulated in different matrices that are in advanced stages of clinical studies (46).

Marinol®, was developed in the United States by Unimed/Solvay Pharmaceuticals, FDA-approved in 1985 for chemotherapy-induced nausea, vomiting, and AIDS-related anorexia, and is classified as a Schedule III controlled substance with moderate abuse potential (46, 47). *Cesamet*™, a fully synthetic THC analogue developed by Eli Lilly and marketed by Valeant Pharmaceuticals, received FDA approval the same year for chemotherapy-induced nausea in patients unresponsive to conventional therapy and is a Schedule II substance, reflecting higher abuse potential (48). Both drugs are authorized in select European, Canadian, Australian, and New Zealand markets under strict prescription frameworks. Globally, dronabinol and nabilone are regulated under the 1961 UN Single Convention on Narcotic Drugs, which permits medical use while strictly controlling manufacture and distribution (49).

These preparations are claimed to be effective; however, the development of new medicines is concentrated on full-spectrum compositions, rather single-compound preparations. In order to lessen some of the side effects that THC may have and to improve the analgesic and anti-inflammatory qualities of cannabis, these products also include cannabinoids and other important plant components (50). Enhancing the stability of cannabis by averting component interactions and degradation is one of the main advantages of microencapsulation.

Microencapsulation effectively isolates individual particles by preventing direct contact through the formation of a continuous coating matrix. The core material is completely encapsulated and physically separated from the external environment, representing a significant functional advantage of this technology (50).

Importantly, when appropriate wall materials and encapsulation techniques are employed, microencapsulation can preserve the physicochemical and functional properties of the encapsulated core components without inducing undesirable alterations (50).

This literature review resulted in summarizing the most commonly explored microencapsulation techniques for cannabinoids intended for medical purposes. Their characteristics, used materials and suitable reference are given in Table II.

In the cannabinoid-based preparation industry, using encapsulation procedure may increase manufacturing efficiency. Research has shown that oxygen, heat, pH, light, and other harsh environmental elements can all drastically change the physicochemical properties of cannabinoid-based preparations (50, 51).

Table II Commonly used methods for cannabinoid microencapsulation and their characteristics

Tabela II Najčešće korišćene metode mikroinkapsulacije kanabinoida i njihove karakteristike

Microencapsulation method	Encapsulation / Wall materials	Core material and particle characteristics	Reported particle size and morphology	Reference
Vibration nozzle microencapsulation (VNM)	Chitosan-coated alginate	Full-spectrum cannabis crude oil encapsulated in spherical hydrogel particles	Mean particle size: 460 ± 260 μm; Sphericity index: 0.5 ± 0.3	(52)
Spray-drying microencapsulation	Chitosan (via ionic gelation)	*Cannabis sativa* and *Cannabis indica* methanolic extracts	Particle size range: 1.45–11.0 μm	(29, 53)
Combined spray-drying and emulsification	Maltodextrin combined with hemp, pea, or rice proteins (carrier matrices)	Hempseed oil (HSO) emulsions stabilized with plant protein carriers	Particle size < 20 μm; smallest particles obtained with rice protein microcapsules	(2, 54)
Combined coacervation and spray-drying	Pea protein isolate–sugar beet pectin complex (coacervate shell)	Hempseed oil (HSO) encapsulated within spray-dried coacervates	Hollow particles with irregular and incomplete morphology; Structural defects associated with increased lipid oxidation	(24, 55)
Ionic gelation (sodium alginate method)	Sodium alginate cross-linked with calcium chloride	Cannabidiol (CBD) and deoxycholic acid (DCA) microcapsules	Spherical capsules; Mean diameter: 400 ± 50 μm	(25, 56)
Emulsification method	Soy protein isolate (SPI) or whey protein isolate (WPI) with sucrose ester (SE) emulsifier	Cannabis oil-in-water emulsions stabilized by protein-emulsifier systems	SPI-SE emulsions: 4.26 ± 0.41 μm (0% SE) to 2.98 ± 0.30 μm (1.5% SE); WPI-SE emulsions: 5.85 ± 0.16 μm (0% SE) to 2.74 ± 0.18 μm (1.5% SE)	(14, 57)

The emulsification method is easy to produce on a large scale and may be mixed into various matrices, such as meals and beverages. They are frequently used to encapsulate hydrophobic medicines, including cannabis. However, employing emulsions prevents the regulated release of bioactive chemicals (57). Alternatively, in response to particular stimuli (such as pH, temperature, chemical, and biological conditions), microgels enable the regulated release of bioactive substances. Because of its affordability and biocompatibility, alginate, a naturally occurring polysaccharide with varying polymer topologies at different pH levels, has been utilized extensively in encapsulation processes, and its ability to design microgels that enable intestinal delivery of bioactive compounds (56). However, the addition of other polymers, such as chitosan, agarose, zein, poly-L-lysine or polyethyleneimine, is often required to obtain microgels with improved characteristics or release properties (52, 53).

In the realm of medicinal cannabis, preparations, full-spectrum oral formulations are becoming more and more researched due to the potential synergistic interaction among cannabinoids and other plant bioactive substances (BASs) (51). The study of Villate et al. (2023), aimed at the formulation of an edible product of pharmaceutical quality, the vibration nozzle microencapsulation (VNM) method was suggested for encapsulating a full-spectrum extract utilizing chitosan-coated alginate. The microcapsules' characteristics were assessed, such as *in vitro* gastrointestinal release, long-term stability under three distinct storage settings, added to their physicochemical characterization (52). The synthetic microcapsules had an average size of 460 ± 260 μm and an average sphericity of 0.5 ± 0.3, and their primary contents were cannabinoids of the type Δ^9-tetrahydrocannabinol (THC) and cannabinol (CBN). The microcapsules' cannabinoid profile was preserved by simple storage at 4°C in the dark. Furthermore, the fast intestinal release of cannabis resulted in a medium-high bioavailability (57–77%) of medicinally significant substances, according to the performed *in vitro* tests. The microcapsules' complete characterization suggests that they might be utilized to create oral full-spectrum cannabis formulations (52).

Phupaboon et al. (2022), examined methods of the microencapsulation of the bioactive components extracted from the leaves of three cannabis species: *Cannabis sativa* L., *Cannabis indica* L., and *Mitragyna speiosa* K. Two techniques were employed to extract bioactive compounds: maceration extraction with methanol and microwave extraction. The antioxidant capacity and total polyphenol content (TPC) and total flavonoid content (TFC) produced by microwave extraction were shown to be substantially stronger and greater than those obtained using the maceration extraction method ($p < 0.05$). Additionally, the ionic gelation capabilities of chitosan were used to encapsulate the isolated chemicals by the use of the spray-drying approach. The physical properties of chitosan-coated extracts were analyzed using a scanning electron microscope (SEM), the microparticle size ranged from 1.45 to 11.0 μm. For microencapsulated *M. speiosa, C. indica,* and *C. sativa,* the encapsulation efficiency of bioactive substances was reported to be 99.7, 82.3, and 54.6%, respectively (53).

Phupaboon et al. (2022) presented that it is possible to provide high retention concentration of bioactive components using this method, thus preserving valuable BASs including TPC, TFC, with preserved antioxidant capability (53).

Kurek and Pratap-Singh's (2020) investigated the characteristics of emulsions and spray-dried microcapsules made from hempseed oil utilizing a combination of maltodextrin with hemp protein, pea, and rice as carrier materials. There were two different degrees of oil content in the microcapsules: 10% and 20%. Every sample's viscosity decreased as the amount of oil added increased (54). Based on the *Power Law* model, the consistency index of the produced emulsions was determined. At 10% oil loading, the values for hemp and rice protein were found to be the lowest (9.2 ± 1.3 mPa·s) and the highest (68.3 ± 1.1 mPa·s), respectively. The range of emulsion stability was 68.2 ± 0.7% to 88.1 ± 0.9%. High L* values (from 74.65 ± 0.03 to 83.06 ± 0.03) and low a* values (–1.02 ± 0.015 to 0.12 ± 0.005) that characterize the color features of the microcapsules indicated that the materials were able to coat the hempseed oil's greenish color in an acceptable manner (54).

Microcapsules containing rice protein showed the highest encapsulation effectiveness, whereas the ones containing hemp protein showed the lowest. The oxidative stability of hempseed oil was inhibited by the combination of proteins and maltodextrin. With hempseed oil microencapsulated with a pea protein-maltodextrin combination and 10% oil loading, it was shown that the oil release profile is well suited to the Higuchi model, exhibiting the lowest oil release rates and highest oxidative stability (54).

Rheological studies of the microcapsules showed that the samples varied in viscosity and in response to an increase in shear rate. The viscosity of the sample decreased as the oil loading increased. Each and every sample had a moisture content that was appropriate for dry items. In terms of encapsulation efficiency, hemp protein proved ineffective (57). The plant protein-maltodextrin microencapsulation of hempseed oil effectively reduced oxidation by restricting the oil's peroxide value (PV) and thiobarbituric acid assay (TBA) to 5 meq/kg and 1 mg MDA/kg, respectively, for all samples. Rice protein microcapsules were produced with a particle size of less than 20 μm and approximately 80% encapsulation efficiency at 10% oil loading, while pea protein microcapsules presented the highest oxidative inhibition and the lowest release rate constant at 10% oil loading (54).

Pea protein isolate (PPI) – sugar beet pectin (SBP) coacervate complex was used to obtain microcapsules loaded with spray-dried hempseed oil (HSO), and the effects of coacervation formation at pH (3.5 and 2.5) using wall/core ratio (1:1, 2:1, and 4:1) were observed (55). In general, both the phase behaviors and viscoelastic properties of PPI-SBP coacervates were influenced by the wall/core ratio. The pH of the coacervation formation had a significant impact on the coacervate structures, which in turn influenced the oxidative stability of HSO, oil distribution in microcapsules, spray-drying efficiency, and encapsulation efficiency. PPI-SBP complex coacervates showed denser structure at pH 3.5 due to increased electrostatic contact, but FTIR analysis and rheological

characteristics showed that a softer structure forms at pH 2.5. The spray-dried microcapsules exhibited much higher encapsulation efficiency than the pH 3.5 microcapsules owing to the homogenous large pore size and smooth interior surface of the liquid coacervates generated at pH 2.5 (55). However, the reduced electrostatic contact strength between PPI-SBP resulted in a partially fractured PPI-SBP network generated by the spray-drying process, which limited the oxidative stability of HSO in PPI-SBP microcapsules prepared at pH 2.5. Scanning Electron Microscopy (SEM) and Confocal Laser Scanning Microscopy (CLSM) analysis showed presence of hollow particles and incomplete particle formation providing conditions for the lipid oxidation of the encapsulated HSO, therefore compromising its stability. This research confirmed that higher surface oil percentage of microcapsules, lower encapsulation efficacy, and lower oxidative stability of HSO are associated with lower wall/core ratios (55).

The widely used encapsulation approach using sodium alginate was used by Majimbi et al. (2021). They formulated microcapsules containing CBD and examined the amount of CBD present in the plasma and brain samples of a wild-type mice. Moreover, they investigated the blood-to-brain dynamics of CBD in combination with a permeability enhancer by co-administering deoxycholic acid (DCA) and CBD capsules (56). Namely, they used the ionic gelation process to create microcapsules containing either DCA or CBD, with formulations of 1.5% sodium alginate and 100 mM calcium chloride. The resulting spherical microcapsules had particle size 400 ± 50 μm and it was determined that CBD microcapsules have 2% drug loading and a 23% encapsulation efficiency. The obtained formulations of CBD were given to wild-type C57BL/6J mice that were randomly assigned to treatment in three groups consisting of three to four mice each: 1) CBD capsules, 2) CBD capsules + DCA capsules, and 3) CBD oil as a control. The mice that were given CBD, and CBD + DCA capsules presented plasma CBD concentrations that were 40% and 47% higher, respectively. The mice treated with CBD capsules in combination with DCA capsules exhibited significantly higher brain CBD concentrations compared with those receiving CBD capsules alone, with increases of 48% and 25%, respectively. Compared to the mice given CBD capsules and bare CBD oil, whose concentration of CBD reached maximum an hour after treatment, the mice given CBD capsules and DCA capsules presented a 300% increase in availability of CBD at 0.3 hours (56).

Moreover, this research has shown that the encapsulation of CBD in medium-viscosity sodium alginate may provide protection against light-induced oxidation, acidic digestion, and degradation, hence improving absorption through the gastrointestinal tract and cumulative plasma bioavailability. It is important to note that the addition of bile acid (DCA) can increase the uptake of CBD by up to 40 times within the brain and prolongs its retention, albeit statistically not significantly (56). This adds to DCA's potential to promote the neuroprotective efficacy of oral CBD administration, especially for the treatment of neurodegenerative disorders.

During the microencapsulation of cannabis oil, Zhang et al. (2022) investigated the effects of various emulsifiers, such as whey protein isolate (WPI)-sucrose ester (SE)

(WPI-SE) and soy protein isolate (SPI)-sucrose ester (SE) (SPI-SE) to various properties of microcapsules obtained via the emulsification method. Adsorption kinetics data demonstrated that sucrose ester (SE) can lower the emulsion's zeta potential, particle size, and interfacial tension. The results of the interfacial protein concentration indicate that SE can alter the interfacial film strength and replace the protein at the oil–water interface in a competitive manner (57). The emulsion structure of both emulsion systems achieved maximum value when the concentration of SE is 0.75% (w/v), and the modulus of elasticity (G') of the emulsion prepared with SPI-SE is high, according to the results of the viscoelastic properties. All of the emulsions display shear thinning behavior, according to the viscosity results, following the Ostwald-de Waele model. By adding SE to the emulsions in both emulsion systems, the emulsion may be stabilized and its oil–water interface composition and strength can be altered (57).

The associated properties of the emulsion can be altered by the protein-SE composite emulsifier. When added to an emulsion, SE can decrease the potential and size of the particles, raise surface pressure and viscosity, and support the stability of the emulsion during microencapsulation. The adsorption quantity of SPI at the interface is more than that of WPI at the same concentration of SE, suggesting that the interfacial layer created by SPI is robust. While SE can substitute for some proteins, lowering the strength of the interfacial coating, it can also raise the emulsion's G' within an acceptable range of SE concentration (0–0.75%), making the emulsion more practical (57).

The stability of the emulsion can be increased by adding the right amount of sucrose ester, and stable emulsions are ideal for creating premium microcapsules. Thus, the microcapsules' quality can be raised by appropriately adding sucrose ester. The microcapsules made using SPI-SE and WPI-SE as emulsifiers have an excellent look and high entrapment efficiency at the level of 0.75% SE, suggesting that the emulsion's properties have some influence on the microencapsulation effect. The findings of Zhang's research offer some theoretical justification for the choice of suitable emulsifiers for the production of oil microcapsules with the required performance and process control (57).

Conclusion

Recent advancements in extraction and purification techniques have enabled the production of higher-purity cannabinoids for medical applications, as well as for the cannabis-based product industry. Despite these improvements, the stabilization and protection of the obtained bioactive substances (BASs) from oxidation, UV light, and other detrimental environmental factors remain a significant challenge.

To address this, various microencapsulation technologies have been employed, including spray-drying, emulsification, coacervation, ionic gelation, and vibration nozzle microencapsulation. These methods have been shown to enhance the bioavailability of major cannabinoids and improve their uptake in the brain. Furthermore, microencapsulation protects cannabinoids from oxidative and gastric acid degradation, leading to more effective absorption and bioavailability of the formulations.

Although microencapsulation is a well-established approach for protecting bioactive compounds, it is also a promising strategy for improving cannabinoid stability and bioavailability, opening new avenues for research and potential therapeutic applications.

Declaration of Competing 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.

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Author contributions

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Tehnike mikroinkapsulacije za kanabinoide: farmaceutski pristupi, tehnološki izazovi i perspektive formulacije

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Kratak sadržaj

Mikroinkapsulacija predstavlja široko primenjivanu strategiju za zaštitu bioaktivnih jedinjenja njihovim inkapsuliranjem u polimerni ili lipidni omotač, što vodi ka poboljšanju njihove stabilnosti i omogućava kontrolisano oslobađanje. Poslednjih godina, rastuća primena kanabinoida u proizvodima podstakla je povećano interesovanje za mikroinkapsulaciju kao pristup za prevazilaženje izazova povezanih sa njihovom niskom rastvorljivošću u vodi, hemijskom nestabilnošću i ograničenom bioraspoloživošću. Cilj ovog preglednog rada je kritička analiza i evaluacija najčešće korišćenih tehnika mikroinkapsulacije u sistemima za isporuku kanabinoida.

Sistematska pretraga literature sprovedena je u bazama podataka PubMed, SCOPUS, EBSCO i Embase, pri čemu je identifikovano oko 50 originalnih i preglednih naučnih radova. Strategija pretrage obuhvatala je kombinacije ključnih reči: *cannabis AND microencapsulation methods*, *cannabinoids AND microencapsulation techniques*, *hempseed oil AND spray-drying OR coacervation technology*, i *cannabis industry AND microencapsulation*.

Rezultati ukazuju da najčešće ispitivane tehnike mikroinkapsulacije kanabinoida uključuju hlađenje raspršivanjem (engl. *spray-chilling*), očvršćavanje raspršivanjem (engl. *spray-cooling*), oblaganje u fluidizovanom sloju, lipozomsku inkapsulaciju, ekstruziju, liofilizaciju (engl. *freeze-drying*), koacervaciju i emulzifikaciju. Ove tehnike se razlikuju u pogledu efikasnosti inkapsulacije, skalabilnosti, raspodele veličine čestica i pogodnosti za specifične puteve primene.

U celini, mikroinkapsulacija pokazuje značajan potencijal u unapređenju fizičko-hemijske stabilnosti kanabinoida, njihovoj zaštiti od degradacije izazvane spoljašnjim faktorima i omogućavanju kontrolisanog ili ciljanog oslobađanja. Zaključno, mikroinkapsulacija predstavlja obećavajuću i brzo razvijajuću strategiju u razvoju naprednih formulacija kanabinoida, nudeći inovativna rešenja za poboljšanu stabilnost, efikasniju isporuku i širu terapijsku primenu.

Ključne reči: kanabinoidi, kontrolisano oslobađanje, tehnike inkapsulacije, mikroinkapsulacija, poboljšanje stabilnosti