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REVIEW

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Nanoformulations as a strategy to overcome the delivery limitations of cannabinoids

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Abstract

Medical cannabis has received significant interest in recent years due to its promising benefits in the management of pain, anxiety, depression and neurological and movement disorders. Specifically, the major phytocannabinoids derived from the cannabis plant such as (−) trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), have been shown to be responsible for the pharmacological and therapeutic properties. Recently, these phytocannabinoids have also attracted special attention in cancer treatment due to their well-known palliative benefits in chemotherapy-induced nausea, vomiting, pain and loss of appetite along with their anticancer activities. Despite the enormous pharmacological benefits, the low aqueous solubility, high instability (susceptibility to extensive first pass metabolism) and poor systemic bioavailability restrict their utilization at clinical perspective. Therefore, drug delivery strategies based on nanotechnology are emerging to improve pharmacokinetic profile and bioavailability of cannabinoids as well as enhance their targeted delivery. Here, we critically review the nano-formulation systems engineered for overcoming the delivery limitations of native phytocannabinoids including polymeric and lipid-based nanoparticles (lipid nano capsules (LNCs), nanostructured lipid carriers (NLCs), nanoemulsions (NE) and self-emulsifying drug delivery systems (SEDDS)), ethosomes and cyclodextrins as well as their therapeutic applications.

KEYWORDS
cannabidiol, cannabinoids, drug delivery, medical cannabis, nanoformulations, tetrahydrocannabinol

1 | INTRODUCTION

The botanical species Cannabis commonly known as marijuana is among one of the most ancient plants that have been cultivated and utilised by the humans as a fibre, food and medicine (Andre, Hausman, & Guerriero, 2016; Hartsel, Eades, Hickory, & Makriyannis, 2016; Hollister, 2001; Small, 2015). Cannabis species can be classified into two categories, namely, *Cannabis sativa* and *Cannabis indica*. Some taxonomists also add a third species, *Cannabis ruderalis* (Small, 2017). Among these, *Cannabis sativa* has long history of being used as traditional medicine for the management of various diseases. Since 1970, cannabis preparations have been used as palliative therapies to reduce nausea, vomiting, loss of appetite and pain associated with chemotherapy, mood amelioration and insomnia in cancer patients (Ekert, Waters, Jurk, Mobilia, & Loughnan, 1979; Kalant, 2001; Pisanti & Bifulco, 2019). Cannabis is the most widely used illicit drug around the world. Cultivation of cannabis for recreational, industrial and medicinal use was strictly banned in many countries. Because of the strict

regulations, the potential medicinal properties of the plant were remained unexplored until its legalisation in California in 1996 (Ruheel, Gomes, Usman, Homayouni, & Ng, 2021). Since then, more than 30 US states and many other countries including but not limited to Canada, Chile, Colombia, Germany, Austria, Australia, Israel, Portugal, Finland, Spain, Netherlands, Newzeland, Switzerland, United Kingdom, Uruguay and Thailand legalised cannabis for medicinal use (Kumar et al., 2021).

Cannabis plant contains more than 500 bioactive compounds of those over 120 phytocannabinoids were identified (ElSohly, Radwan, Gul, Chandra, & Galal, 2017; Izzo et al., 2020; Izzo et al., 2020; Reekie, Scott, & Kassiou, 2017). It is believed that cannabinoids are responsible for the pharmacological effects of cannabis. Chief among those are (−) trans-Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Hanuš, Meyer, Muñoz, Taglialatela-Scafati, & Appendino, 2016; Lafaye, Karila, Blecha, & Benyamina, 2017). THC is a psychoactive compound that contributes both to cannabis' notoriety as a recreational drug and to its effectiveness as a medicinal product (Banister, Arnold, Connor, Glass, & McGregor, 2019; Nahas, Harvey, Sutin, Turndorf, & Cancro, 2002). THC is used to reduce emesis, stimulate appetite in the treatment of HIV-induced anorexia and for the management of spasticity disorders (Sallan, Zinberg, & Frei, 1975). It has been shown that the biological and psychological effects of THC is mediated through the cannabinoid receptor (CB1 receptor) activation in the central nervous system (Bloomfield, Ashok, Volkow, & Howes, 2016; Turner, Williams, Iversen, & Whalley, 2017). In contrast to THC, CBD is considered as non-psychoactive and is used clinically in combination with THC in the equimolar concentrations (Sativex®) for the management of multiple sclerosis (MS) associated symptoms (Barnes, 2006; Keating, 2017). CBD as a single drug has also attracted significant interest due to its broad range of medicinal properties such as analgesic, antiinflammatory, anxiolytic, antipsychotic, anticonvulsant, antioxidant properties as well as its favourable clinical safety and tolerability profiles (Bonaccorso, Ricciardi, Zangani, Chiappini, & Schifano, 2019; Lattanzi, Brigo, Cagnetti, Trinka, & Silvestrini, 2018; Pinto et al., 2020; Rohleder, Müller, Lange, & Leweke, 2016; Rong et al., 2017; Samanta, 2019). Recently, US FDA approved CBD oil based Epidolex™ for the treatment of Lennox–Gastaut syndrome associated seizure's (Lattanzi et al., 2018; Lattanzi et al., 2020). Further, cannabidiol is also actively being pursued in clinical trials for the management of Parkinson's diseases [NCT03582137], schizophrenia [NCT02088060, NCT02926859] and anxiety disorders [NCT02548559, NCT04286594].

In the last decade, THC and CBD have also attracted remarkable interest for oncology treatment. Due to their palliative benefits in the management of pain associated with radiation treatment, loss of appetite, nausea and vomiting (Aggarwal, 2016; Cyr et al., 2018; Strouse, 2020). Recent reports have demonstrated that phytocannabinoids, show remarkable anticancer properties in preclinical models of different cancers, effecting various stages of tumour progression such as cell proliferation and survival, metastasis and angiogenesis (Bogdanović, Mrdjanović, & Borišev, 2017; Chakravarti, Ravi, & Ganju, 2014; Singh et al., 2021). CBD and THC have been reported to exhibit significant anticancer activities against glioma, leukaemia, prostate, breast, cervical and colon carcinomas, among others (Bala, Rademan, Kevin, Maharaj, & Matsabisa, 2019; Blasco-Benito et al., 2018; Dumitru, Sandalcioglu, & Karsak, 2018; Kampa-Schittenhelm et al., 2016; Kisková, Mungenast, Suváková, Jäger, & Thalhammer, 2019; López-Valero et al., 2018; Lukhele & Motadi, 2016; Roberto, Klotz, & Venkateswaran, 2017; Singh et al., 2021). Moreover, several clinical trials are being pursued for CBD and its combination with chemotherapeutic drugs for the treatment of gastrointestinal malignancy, multiple myeloma (NCT03607643) and glioblastoma (NCT03246113, NCT03529448 and NCT03687034).

1.1 | Limitations to use of cannabinoids

Despite the diverse medicinal properties, the therapeutic efficacy of phytocannabinoids in humans is greatly hindered because of their physico-chemical properties including poor water solubility and stability (Fairbairn, Liebmann, & Rowan, 1976; Pacifici et al., 2018). The phytocannabinoids are prone to degradation under the influence of heat, light and storage. For instance, Drooge et al showed that rapid degradation of THC within a few hours when it is exposed to air and it is accelerated at elevated temperatures. Complete degradation of THC was reported within 40 days of exposure at 20°C (van Drooge et al., 2004). Similarly, Mazzetti et al. observed auto-oxidation of CBD samples within 30 days of storage at ambient temperatures; the amount of oxidation was more prevalent in solutions and in exposure to light (Mazzetti, Ferri, Pozzi, & Labra, 2020).

The phytocannabinoids (THC and CBD) are categorised as Biopharmaceutics Classification System class II drugs with high lipophilicity (logP of ∼6.3 and ∼6.97 respectively) and low water solubility (12.6 and 28.0 mg/L respectively) and PKa of 9.29 and 10.6 respectively (Cherniakov et al., 2017; Cherniakov, Izgelov, Domb, & Hoffman, 2017; Stella et al., 2021). These physiological properties of cannabinoids are responsible for poor, erratic and variable absorption profiles. Oral formulations of THC exhibit poor bioavailability (6%–10%) due to instability in the acidic gastric pH and also undergo extensive hepatic first-pass metabolism by CYP450 enzyme (CYP3A4 and CYP2C9) to an equally potent 11-OHTHC metabolite that further metabolises to inactive THC-COOH (Grotenhermen, 2003). It is reported that P-glycoprotien (P-gp) mediated excretion of THC from the enterocytes limits the absorption (Bonhomme-Faivre, Benyamina, Reynaud, Farinotti, & Abbara, 2008). Similar to THC, CBD also has low oral bioavailability in humans ranging between 9% and 13% because of its low water solubility and excessive first pass metabolism to 7-OH metabolite by CYP enzymes (CYP3A4 and CYP2C19) which accounts for 75% loss of drug that reaches systemic circulation (Millar, Stone, Yates, & O'Sullivan, 2018; Nelson et al., 2020).

Oral formulations of cannabinoids are poorly permeable in gastrointestinal tract and cause irritation and therefore alternatives routes of administrations such as pulmonary, rectal, sublingual and intravenous injections were explored (Huestis, 2007; Mahmoudinoodezh et al., 2022). Though the bioavailability of cannabinoids through these was higher compared to oral formulations the poor solubility of

cannabinoids in aqueous media poses challenges for handling and accurate dosing. For instance, intravenous administration of drug can be precipitated at higher doses and nonaqueous solutions, or oils need to be used to solubilise the cannabinoids. In addition, intravenous administration is not desirable because of its invasive nature, risk of infection and the lack of patient compliance. The highest bioavailability reported for cannabinoids is for smoking (2%–56%) which delivers the drugs faster and efficiently to the brain through lungs and blood (Huestis, 2007). However, the absorption of drugs through smoking cannot be controlled due to variability in smoking dynamics. Therefore, it is not favourable as a reliable route of administration which causes uncertainty in dosage delivery. Taking into consideration of these limitations of cannabinoids, novel drug delivery systems need to be developed which can protect the cannabinoids against oxidation and improve the bioavailability and efficacy.

2 | PHYTOCANNABINOID NANOFORMULATIONS

To beat the limitations and improve the poor biopharmaceutical properties, several nanotechnology-based formulation strategies have been applied for effective delivery of cannabinoids. The encapsulation of phytocannabinoids in nanocarriers protect the core cannabinoid compounds from degradation as well as improve the physicochemical stability and bioavailability. Despite of clinical relevance, studies investigating nano formulation of phytocannabinoids have never been reviewed. Therefore, in this comprehensive review we have collated the nano encapsulation approaches that have been applied for phytocannabinoids such as polymeric and lipid-based nano particles (lipid nano capsules (LNC), nanostructured lipid carriers (NLC), self-emulsifying drug delivery systems (SEDDS) and nano emulsions), ethosomes and cyclodextrins (CDs) for distinct pharmaceutical and therapeutic benefits (summarized in Figure 1 and Table 1).

2.1 | Polymeric nanoparticles

Polymeric NPs have shown significant potential as drug delivery vehicles because of their favourable controlled release properties, stability in physiological conditions, biocompatibility, biodegradability, nonimmunogenic, noninflammatory and ability to avoid reticuloendothelial system (Begines et al., 2020; Khalid & El-Sawy, 2017; Soppimath, Aminabhavi, Kulkarni, & Rudzinski, 2001). Drug molecules can be

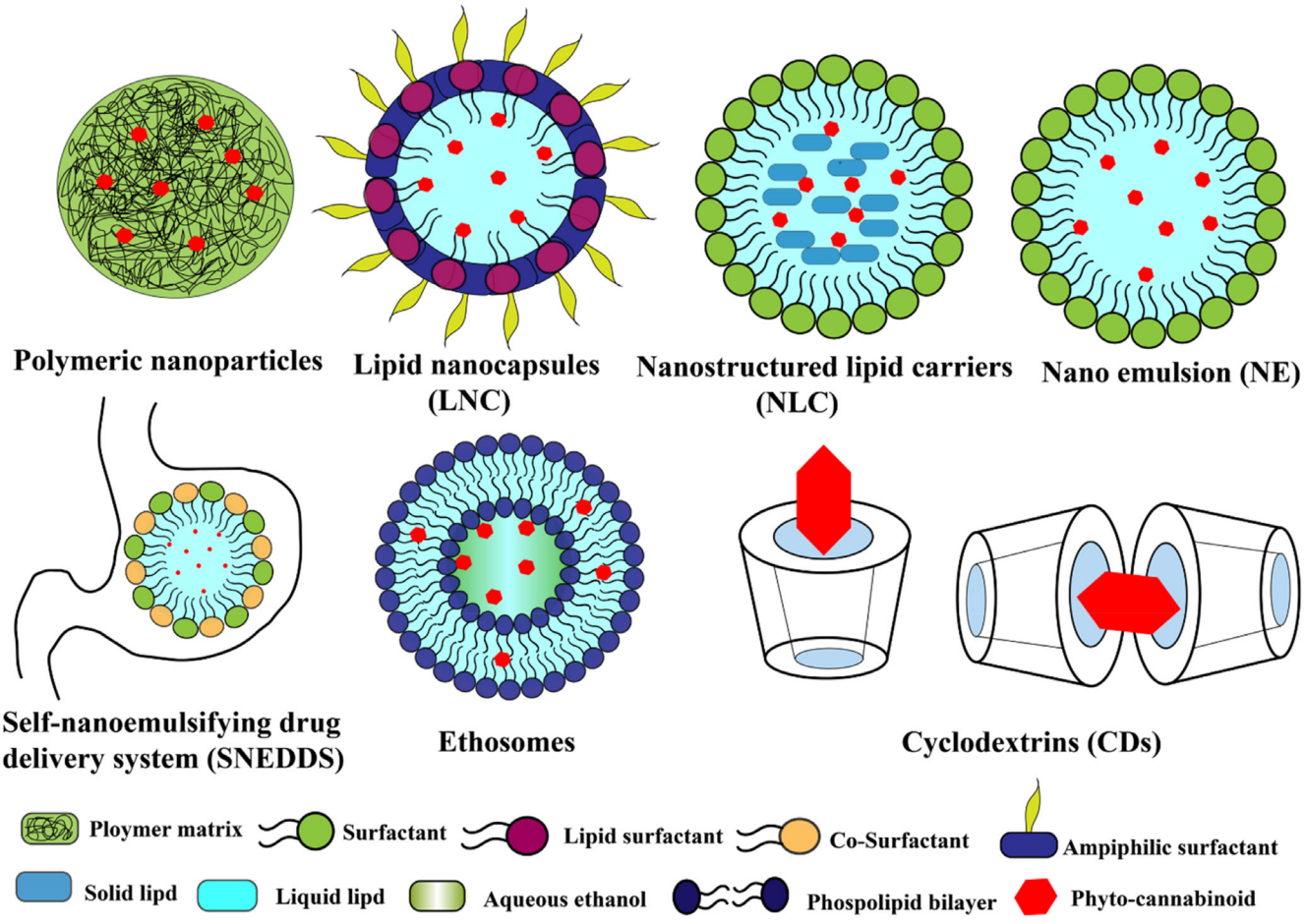

FIGURE 1 Structures of different phytocannabinoid nano drug delivery systems reported in the literature.

TABLE 1 Summary of various nano formulation approaches for delivery of phytocannabinoids.

Type of formulation	Drug	Size of nanoparticles	Dose	Route of administration	Status of investigation	Outcome	Ref
Polymeric							
PLGA NPs-coated with PEG, chitosan (CS)	THC	290–780 nm	5 mg/kg	Peritumoral injection	In vitro *and* In vivo	• Controlled drug release • Improved in vitro anticancer activity • Lower toxicity on normal cells • 1.5-fold reduction of tumour volume over free THC	Martin-Banderas et al. (2015)
PLGA NPs-coated with PEG, CS	THC	259–434 nm	25–150 μM	–	In vitro	• Controlled drug release • Improved cell uptake • Improved antiproliferative efficacy at high incubation periods (120 h).	Martín-Banderas et al. (2014)
PLGA	CBD	228–236 nm	100 μM	Topical	In vitro *and* In vivo	• Controlled drug release for 96 h • CBD-NPs showed higher in vitro cytotoxicity's compared to free drug • Slightly higher in vivo tumour growth inhibition compared to CBD	Fraguas-Sánchez et al. (2020)
Lipid based NPs							
Lipid nanocapsules (LNCs)	CBD	20–60 nm	29–615 μM	–	In vitro	• CBD in LNCs showed lower cytotoxicity on U373 cells over the free drug • CBD- loading in LNCs resulted in reduced IC_{50} values	Aparicio-Blanco, Sebastián, Benoit, and Torres-Suárez (2019)
Nanostructured lipid carriers (NLCs)	THC	250 nm	–	–	In vitro	• Formulations were physically stable for 1 year • Improved mucoadhesive properties	Hommoss, Pyo, and Müller (2017)
Nanostructured lipid carriers (NLCs)	CBD	177 nm	5 mg/kg	Intra nasal and oral	In vitro *and* In vivo	• Enhanced mucoadhesive properties • Improved antinociceptive activity	Matarazzo et al. (2021)
Nano dispersions	CBD	277 nm	–	–	In vitro	• Improved physical and chemical stability	di Bello, Bloise, Mazzetto, and Mele (2017)

TABLE 1 (Continued)

Type of formulation	Drug	Size of nanoparticles	Dose	Route of administration	Status of investigation	Outcome	Ref
Nano emulsion	CBD	35 nm	50–100 mg/kg	Oral	In vivo	• Improve intestinal absorption, • Reduction of mean Tmax (faster absorption)	Nakano, Tajima, Sugiyama, Sato, and Sato (2019)
Self-nanoemulsifying drug delivery (SNEDDS)-Pronanolipospher (PNL)	THC and CBD+piperine or curcumin or resveratrol	30–65 nm	15 mg/kg (CBD) 20 mg/kg (THC)	Oral	In vivo	• Increased solubility • Reduction of phase I metabolism • Improved oral bioavailability	Cherniakov, Izgelov, Barasch, et al. (2017), Cherniakov, Izgelov, Domb, and Hoffman (2017)
SNEDDS-PNL	THC-CBD (1:1) +(piperine)	30–50 nm	10 mg (CBD), 10.8 mg (THC)	Oral	Clinical	• Increase in Cmax (increasing plasma concentration • Increased bioavailability for both THC and CBD	Cherniakov, Izgelov, Barasch, et al. (2017), Cherniakov, Izgelov, Domb, and Hoffman (2017)
SNEDDS-PNL	THC: CBD (1:1)	–	–	Oromucosal spray	Clinical	• Increase in Cmax (increasing plasma concentration) and reduction of Tmax (faster absorption) values for both CBD and THC compared to Sativex®,	Atsmon et al. (2018)
SEDDS	CBD as hemp extract	40–50 nm	25 mg	Oral	Clinical	• Increased Cmax (increasing plasma concentration, • Enhanced bioavailability • Faster absorption (reduction of Tmax)	Knaub et al. (2019)
SNEDDS	CBD	41–674 nm	19.3 mg/kg	Oral	In vivo	• Faster absorption (reduction of Tmax) • Increased Cmax (increasing plasma concentration)	Kok et al. (2022)
SNEDDS	THC and CBD	50 nm	15 mg/kg (CBD, 20 mg/kg (THC)	Oral	In vivo	• Improved bioavailability	Izgelov, Shmoeli, Domb, and Hoffman (2020)
SNEDDS	CBD as cannabis extract	–	40 mg	Oral	Clinical	• Improved Cmax (increasing plasma concentration) and AUC	de Prá, Vardanega, and Loss (2021)
Ethosomes	CBD	–	200 mg	Topical	In vivo	• Enhanced skin permeation • Improved antiinflammatory activity	Lodzki, Godin, Mechoulam, Gallily, and Touitou (2003)

Abbreviations: CBD, cannabidiol; CBG, Cannabigerol; DTX, Docetaxel; PCT, Paclitaxel; PLGA, poly (lactic-co-glycolic acid); THC, Tetrahydrocannabinol.

loaded in the polymeric nano particles either by entrapment of the drug within the polymer matrix (noncovalent) or covalent conjugation to the polymer. This allows encapsulation of wide range of hydrophilic, hydrophobic drugs along with high molecular weight compounds (macromolecules, proteins and vaccines) which make the polymeric nana particles ideal for co-delivery. Despite of these advantages batch-batch consistency at industrial scale limits the applications of these NPs (Begines et al., 2020). Different types of biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) and poly (ε-caprolactone) (PCL), have been used for the encapsulation of phyocannabinoids cannabinoids.

2.1.1 | PLGA nanoparticles

PLGA is widely used polymer for designing nano drug delivery carriers due to its biodegradability to nontoxic lactic acid and glycolic acid. Several types of formulations based on PLGA have been explored for delivery of cannabinoids (Kulhari et al., 2016; More et al., 2021) L. Martín-Banderas et al engineered PLGA NPs encapsulated with THC using nanoprecipitation technique suitable for oral administration (Martín-Banderas et al., 2014). The surface of the nanoparticles was further functionalised with chitosan (CS) and polyethylene glycol (PEG) for controlled drug release, increased cellular uptake and enhanced anticancer activity (Martín-Banderas et al., 2014). In vitro studies demonstrated the higher cellular uptake of THC loaded PEG-PLGA NPs. Colon cancer cells treated with free THC showed higher cytotoxicity compared to THC encapsulated PLGA NPs at lower incubation times (96 h) which may be due to insufficient release of THC from the NPs. Interestingly, the nanoformulations exhibited greater cytotoxic effect over the free drug at higher incubation times (t > 120 h) which correlates with the amount of released drug (approximately 70%) from the NPs. The same authors synthesised PLGA NPs encapsulated with THC using Vitamin E as an antioxidant in the nanoformulation to protect THC from oxidation. The average diameter of the PLGA NPs were 290 nm which was increased after functionalisation with PEG (590 nm), CS (745 nm) and PEG–CS (790 nm). The formulations demonstrated higher THC encapsulation efficiencies (95%). Encapsulation of THC in PLGA NPs resulted in controlled drug release that can be speeded up or slowed down upon coatings with PEG and CS, respectively. Surface functionalisation of PLGA NPs with PEG improved vehiculization of THC and reduced protein adsorption. Incorporation of Vitamin E resulted in 67% improvement in stability of THC compared to Vitamin E free formulations. THC-loaded PEGylated PLGA NPs showed significant anticancer activity against murine (LL2) and human lung (A-549) cancer cells while the NPs had minimum effect on human lung (MRC-5) fibroblast cells which indicates the selective cytotoxicity towards the lung cancer cell lines. Further in vivo studies in C57BL/6 mice bearing LL2 lung tumour showed that NPs treatment resulted in 1.5-fold reduction of tumour volume compared to control and free THC.

Recently, Fraguas-Sánchez et al. synthesised CBD loaded PLGA NPs (CBD-NPs) to overcome its stability and administration challenges and improve its anticancer effects against ovarian cancer cells (Fraguas-Sánchez et al., 2020). The synthesised CBD-NPs were spherical with average particle diameter of 240 nm and zeta potential of −16.6 ± 1.2 mV. The CBD entrapment efficiency in NPs was above 95%. The NPs were stable physically for at least 90 days without any significant changes to the particle size. The CBD encapsulated in NPs was released 100% over 96 h. Cellular uptake studies in epithelial ovarian cancer cells (SKOV-3) revealed that, the CBD-NPs were internalised within 2–4 h of incubation. The CBD-NPs displayed lower IC_{50} values compared with free drug after both, 24 h (CBD-NPs: 29.64 ± 2.94 μM and CBD 33.19 ± 2.57 μM) and 48 h of treatment (CBD-NPs: 20.88 ± 1.25 μM and CBD 23.47 ± 4.10 μM). Similar results were obtained in tumours derived from SKOV-3 in the chick embryo model where CBD-NPs treatment led to greater tumour inhibition compared with CBD alone.

2.2 | Lipid-based nanoparticles

Lipids are amphiphilic molecules that contains hydrophilic and hydrophobic regions which up on self-assembly in an aqueous environment forms aggregates or colloidal nano NPs. Lipid-based colloidal particles such as liposomes, solid lipid nano particles (SLN), lipid nanocapsules (LNC), nanostructured lipid carriers (NLC), self-emulsifying drug delivery systems (SEDDS) and nano emulsions have been extensively studied in recent decades as delivery carriers for lipophilic bioactive molecules (Buse & El-Aneed, 2010; Kumar, 2019; Puri et al., 2009; Shirodkar, Kumar, Mutalik, & Lewis, 2019; Teixeira, Carbone, & Souto, 2017). These lipid-based nano drug delivery systems offer several advantages over polymeric NPs such as high drug entrapment capacity, low toxicity, cost effective production and scalability. In addition, they exhibit biodegradability and high stability. However, there are some limitations associated with lipid NPs such as leakage or expulsion of drug from the formulation due to crystallisation of lipids over time during the storage and high water content of the formulation could decrease loading efficiency.

The following lipid-based nanocarriers have been engineered for the delivery of phytocannabinoids which have shown increased stability and bioavailability of encapsulated drugs.

2.2.1 | Lipid nanocapsules (LNCs)

Lipid nanocapsules consist of oily core of medium-chain triglycerides (MCT) as a drug reservoir which is surrounded by monolayer of rigid surfactant shell as a drug leaking barrier (Huynh, Passirani, Saulnier, & Benoît, 2009; Moura, Pacheco, Pêgo, des Rieux, & Sarmento, 2020). The oily core enables encapsulation of higher amounts of lipophilic drugs and the shell provides the high stability. LNCs can be obtained with generally recognised as safe (GRAS) excipients without the use of toxic organic solvents. Aparicio-Blanco et al. encapsulated CBD into the lipid nanocapsules (LNCs) to investigate their anticancer activity against glioblastoma cells (U373MG) (Aparicio-Blanco

et al., 2019). LNCs were engineered by phase inversion temperature (PIT) method. The encapsulation of CBD within the lipid nanocapsules resulted in increased IC_{50} values (202.6 μM for 20 nm-sized LNCs; 615.4 μM for 50 nm-sized LNCs) compared with free CBD drug (29.1 μM) against the U373MG cells. This could be due to the fact that free CBD is available readily to exhibit its anticancer activity whereas CBD from encapsulated formulation needs to be released from oily core of LNCs to show its cytotoxicity which can take extended periods. Further, to explore the targeting potential of phytocannabinoids towards cannabinoid receptors that are overexpressed in glioma cells, the authors functionalised the lipid nanocapsules with CBD on their surface. CBD-decorated CBD-loaded lipid nanocapsules showed higher glioma cell growth inhibition over CBD-loaded lipid nanocapsules.

2.2.2 | Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs) are considered as second generation of lipid-based nano delivery systems developed from modification of SLN (Arora, Katiyar, Kushwah, & Jain, 2017; Iqbal et al., 2012). These systems contain combination of solid lipids and liquid lipids (oils) where as solid lipid nanoparticles (SLNs) comprise of only solid lipids. NLCs were developed to overcome the burst drug release effect of SLN. Further, a higher drug encapsulation can be achieved with NLC as the solubility of drugs is higher in liquid lipids compared to the solid lipids. Hommoss et al. engineered THC encapsulated NLCs formulation as an aqueous nasal spray (Hommoss et al., 2017). The NPs were synthesised using cetyl palmitate, which has good miscibility with the THC. The average diameter of the obtained NPs was close to 200 nm. To make the particles mucoadhesive, their surface is decorated with positively charged cationic stabiliser. NLCs interaction with mucin (negatively charged) was confirmed by the reduction of positive zeta potential. The formulations remained stable physically for 1 year and the chemical stability study showed that 91% and 79% of THC remained at 4 and 40°C, respectively after 6 months storage. Moreover, the developed NLC formulations were able to spray and nebulise without any significant changes in the mean particle size. Similarly, Ananda Pulini Matarazzo et al developed mucoadhesive CBD loaded NLC formulations using oleic acid and stearic acid. Cetylpyridinium chloride and Span 20® were also used as cationic surfactant and co-stabiliser respectively. Addition of in-situ gelling polymer Pluronics® to the CBD-NLCs obtained CBD-NLC gel. Both the formulations (CBD-NLC and gel) exhibited enhanced mucoadhesive properties in vitro compared to CBD in solution. Intranasal administration of CBD-NLCs to the mice with chemotherapy-induced neuropathic pain resulted in improved and long-lasting anti nociceptive effects compared to CBD solution (Matarazzo et al., 2021).

2.2.3 | Nanoemulsions (NE)

Nano emulsion formulations that consists of oil, water and surfactant are formulated through high-energy processes such as ultrasonication or homogenization which breakdown the large droplets to submicron size (Nishitani, Tomiko, Lobenberg, & Araci Bou-Chacra, 2017; Singh et al., 2017). These are thermodynamically stable due to the small size and has been used to deliver the wide range of hydrophobic drugs (Ali, Ansari, Ahmad, Akhtar, & Jahan, 2017; de Campos, Ricci-Júnior, & Mansur, 2012). The oils such as sesame seed oil, soybean oil, cottonseed oil are commonly used to solubilise the lipophilic drugs. Bello et al designed CBD embedded nanovesicular system based on cardanol to increase the stability (Di Bello et al., 2017). Cardanol is an agricultural by-product of the cashew industry which is known for its antioxidant properties. It stabilizes and protect the labile compounds from degradation in an aqueous environment. Nanovesicles were prepared by mixing CBD with cardanol and cholesterol which were used as amphiphilic building blocks. The encapsulation efficiency and the stability of CBD nanoformulations at various temperatures (4 and 20°C) were determined by HPLC-DAD analysis. The results showed 45.89% and 33.92% of CBD was encapsulated into the nanovesicles before and after dialysis. The encapsulation efficiency EE (%) was found to be 73.93%. Further, nanodispersions remained physically stable until at least 30 days at 20°C while their aggregates were observed at 4°C after 21 days.

Nakanoa et al. developed a CBD loaded nanoemulsion (CBD-NE) formulation to improve the aqueous solubility and oral absorption (Nakano et al., 2019). CBD-NE composed of mixture of vitamin E, ethanol and Tween-20 (1.7/3.8/70 w/w% respectively) as oil phase, surfactant and co-surfactant. The average size of the particles in CBD nanoemulsion was 35.3 ± 11.8 nm and their diameter did not change for 6 months at 4°C. The pharmacokinetic profile after oral administrations of CBD-NE and CBD oil in rats showed a three-fold faster absorption (reduction of mean Tmax of CBD-NE [2.40 h]) and 65% increase in total drug concentration in the blood AUC (0.448 ± 0.087 h L/kg) compared to CBD oil (Tmax; 8.00 h, AUC; 0.272 ± 0.045). Moreover, regardless of bile secretion, the nano-emulsion formulation improved the absorption of CBD.

2.2.4 | Self-nanoemulsifying drug delivery systems (SNEDDS)

SNEDDS are anhydrous isotropic liquid mixtures (also known as preconcentrates) of lipophilic drugs in a combination with lipids, surfactants and co-solvents. These systems undergo spontaneous in situ emulsification upon exposure to gastrointestinal tract (GIT) fluids and form transparent O/W nanoemulsions with particle size of less than 200 nm (Cherniakov, Domb, & Hoffman, 2015). Recently, SNEDDS have received significant attention as a drug delivery vehicle for improving the solubility and pharmacokinetic properties of highly lipophilic compounds (Makadia, Bhatt, Parmar, Paun, & Tank, 2013; Uppulurj, 2015). Cherniakov et al. developed SNEDDS termed Advanced ProNanoLiposphere (PNL) to enhance the absorption and oral bioavailability of the phytocannabinoids (THC and CBD) (Cherniakov, Izgelov, Barasch, et al., 2017; Cherniakov, Izgelov, Domb, & Hoffman, 2017). The formulations were engineered by preconcentrate method where soy phospholipid (lecithin) triglyceride,

castor oil, Tween 20 and Span 80 were mixed to form a homogeneous solution. The active ingredients CBD and THC were added to this homogeneous mixture to form CBD-PNL or THC-PNL preconcentrates. Advanced PNLs were prepared by incorporating 2% (w/w) natural absorption enhancers such as piperine, curcumin and resveratrol in the PNLs which have been reported to inhibit some phase I and phase II metabolic reactions of lipophilic compounds. Oral administration of single dose of CBD-curcumin-PNL and CBD-resveratrol-PNL to rats led to lower AUC and Cmax values compared to CBD-PNL. However, increased AUC and Cmax were observed when compared to free CBD. Administration of CBD piperine-PNL led to 2 and six-fold increased AUC compared to CBD-PNL and free CBD solution, respectively. Similar results were obtained for THC-piperine-PNL with 1.7 and 9.3-fold increased AUC compared with THC-PNL and THC solution, respectively.

The synthesised THC-CBD-piperine-PNL formulation was further evaluated for its pharmacokinetic properties in humans.(Cherniakov, Izgelov, Barasch, et al., 2017). Single dose administration of PNL formulation to nine healthy volunteers through oral route resulted in 1.5 and 3-fold increase in AUC and Cmax, respectively for THC compared to the commercial oromucosal spray (Sativex®) whereas in the case of CBD it was 2.2 and four-fold increase in AUC and Cmax, respectively.

Atsmon et al. developed THC and CBD loaded PNL-based formulation (PTL401) as soft gelatin capsules to bypass the first pass metabolism (Atsmon et al., 2018). The formulation contains mixture of THC and CBD (1:1) with combinations of lipids (medium chain triglycerides), surfactants and co-solvent. The pharmacokinetic profile of PTL401 was evaluated in 14 healthy young, male volunteers. Single oral administration of PNL containing 10.8 mg THC and 10 mg CBD resulted in 1.6-fold increase in the Cmax of THC and CBD compared to the equivalent dose of Sativex®. Further, Shorter Tmax (faster absorption) values (1.3 h for PTL401 vs. 3.5 h for Sativex®) were observed for both the drugs.

Knaub et al. engineered self-emulsifying drug delivery system (SEDDS) loaded with CBD rich Hemp-Extract (SEDDS-CBD) (Knaub et al., 2019). The pharmacokinetic parameters of CBD in SEDDS were evaluated in 16 healthy volunteers under fasted conditions. Hemp-extract mixed with MCT was used as a reference formulation. Oral administration of single dose (25 mg) of SEDDS-CBD resulted in 1.70 and 4.4-fold increase of AUC and Cmax, respectively in comparison to the reference formulation. Moreover, faster absorption of CBD (Tmax 1 h) was achieved from SEDDS-CBD over the native hemp extract in MCT (Tmax 3 h). Recently L. Y. Kok et al also prepared MCT-based SNEDDS for delivery of Cannabidiol (10% W/W) (Kok et al., 2022). Oral administration of single dose of SNEDDS-CBD (20 mg/kg) to healthy female Sprague–Dawley rats resulted in faster (lower Tmax) and higher absorption compared to MCT and sesame oil CBD formulations.

The effect of different lipid compositions [long chain (LCT) or medium chain triglycerides (MCT)] in oral self-nano emulsifying drug delivery systems (SNEDDS) of THC and CBD were studied by Izgelov, et al. (Izgelov et al., 2020) Nano emulsions (oil-in-water) formulations were synthesised by pre-concentrate method. The nano emulsion with particle diameter of 50 nm or less was obtained to improve the water solubility and absorption of lipophilic drugs. Pharmacokinetic assessment following oral administration of formulations to rats at a dose of 15 mg/kg of drugs was investigated. Results showed that differences in the absorption of LCT and MCT based formulations was not significant for sesame oil, however, the differences are significant for cocoa butter or tricaprin. In addition, De Pr´ et al investigated partially hydrolysed long-chain triglycerides glyceryl monolinoleate (GML) incorporated SEDDS on oral bioavailability of CBD which was administered as cannabis extract in mice and humans (de Prá et al., 2021). The CBD and THC contents of cannabis extract were 73.7% and 1.7%, respectively. SEDDS were prepared by using polyoxyl 40 castor oil (emulsifier) and polyethylene glycol 400 (co-emulsifier). Oral administration of SEDDS with a CBD dose equivalent to 100 mg/kg resulted in improved Cmax and AUC values that are four-fold higher than MCT based formulations. Similar results were observed for SEDDS in clinical studies that were conducted in 11 volunteers with 1.5-fold higher AUC compared to MCT based formulations.

2.3 | Ethosomes

Ethosomal systems contain phospholipid, ethanol and water (Anitha, Ramkanth, Alagusundaram, & Gnanapraksah, 2011). Ethosomal carriers offer advantages such as simple method of preparation, ability to encapsulate wide range of hydrophilic, lipophilic and high molecular weight molecules (Touitou, Dayan, Bergelson, Godin, & Eliaz, 2000). The efficient encapsulation of hydrophilic and lipophilic drugs could be due to the multilamellar nature of the vesicles, and the presence of ethanol enhances the solubility of many drugs. Several reports have demonstrated that ethosomal carriers deliver the drugs more efficiently than other lipid nano formulations and hydro alcoholic solutions (Ainbinder, Paolino, Fresta, & Touitou, 2010; Mbah, Builders, & Attama, 2014; Paiva-Santos et al., 2021).

Lodzki et al. engineered transdermal delivery formulation for CBD consists of 2%–5% Soybean phosphatidylcholine (Phospholipon 90), 40% ethanol, 3% w/w CBD (Lodzki et al., 2003). Ethosomes were synthesised using solvent and fusion/melting methods where CBD and Phospholipon 90 formed a eutectic mixture which was visualised by confocal microscopy. The CBD ethosomal application to the abdominal skin of CDI mice led to a greater accumulation of the drug in the skin. The pharmacokinetic profile revealed that steady-state plasma concentration (SS) levels were achieved within 1 day of application. Moreover, application of ethosomal formulation led to the prevention of inflammation and edema in carrageenan induced animal models.

2.4 | Cyclodextrins (CDs)

Cyclodextrins (CDs) are natural cyclic oligosaccharides that contain hydrophobic central cavity which can solubilise lipophilic drugs. CDs

possess unique ability to entrap guest molecules in their lipophilic central cavity and form inclusion complex without forming covalent bonds. The CD inclusion complexes are widely used to increase the stability, aqueous solubility and bioavailability of several hydrophobic drugs (Jansook, Ogawa, & Loftsson, 2018; Kim, Lee, Pyo, Tran, & Park, 2020; Popielec & Loftsson, 2017). Several authors have prepared the cannabinoid-CD inclusion complexes to improve the stability, water solubility, and pharmacokinetic properties of cannabinoids (Table 2). Shoyama et al. showed that the chemical stability of THC was improved significantly upon complexation with β-CD (Shoyama, Morimoto, & Nishioka, 1983). In another study, the water solubility of THC increased up to 1,000-fold upon complexation with hydroxypropyl- β-cyclodextrin (HP-β-CD). The solubility was further improved (30%) by the addition of 0.1% hydroxypropyl methyl cellulose to the cyclodextrin solution (Jarho, Pate, Brenneisen, & Järvinen, 1998). Mannila et al. used randomly methylated -cyclodextrin (RM-β-CD) to prepare host-guest complexes with THC (Mannila, Järvinen, Järvinen, Tarvainen, & Jarho, 2005). The pharmacokinetic profile of THC after oral and sublingual administrations of THC/RM- β -CD complexes was investigated in rabbit models. The results showed that THC/RM-β-CD inclusion complex bioavailability was higher when it was administered sublingually compared to orally administered complexes and sublingually administered ethanolic THC solutions. Further, the mean Tmax of THC/RM- β -CD following sublingual administration was 120 min which increased to 140 min after oral administration indicating that sublingual administration not only led to improved bioavailability, but also facilitates faster absorption and thus the therapeutic response. Similar results were obtained in rabbit models with native β–CD inclusion complexes (THC/β-CD, and THC/β-CD) (Mannila, Järvinen, Järvinen, & Jarho, 2007; Mannila, Järvinen, Järvinen, Tervonen, & Jarho, 2006).

Recently, Lv et al. prepared CBD-cyclodextrins inclusion complexes by suspension method (Lv et al., 2019). The characterisation of CBD inclusion complexes using various spectroscopy and microscopy techniques showed entrapment modes of CBD within α-CD, β-CD and γ-CD cavities forming 1:1, 2:1 and 2:1 host-guest complexes respectively. The aqueous solubility of CBD was significantly improved from 6.3×10^{-5} to 3.7, 2.1 and 5.3 mg/mL upon complexation with α-CD, β-CD and γ-CD, respectively. In vitro studies showed that CBD inclusion complexes has greater cytotoxicity on Hep G2, and A549 cancer cells (9.97–14.6 μM) compared to CBD (25.3–31.24 μM) and CDs (>100 μM) alone. In addition, the toxicity of CBD inclusion complexes against normal human lung cell line (MRC-5) has been significantly decreased over the free drug. The water solubility of cannabidiol was further improved (42.38 and 28.34 mg/mL) by encapsulation in bridged cyclodextrins with varying chain lengths (succinic acid and thiodipropionic acid respectively) in the study led by Chen et al. (Chen et al., 2022). The structural characterisation data of inclusion complexes indicates CBD is incorporated in to two cavities of bridged cyclodextrins with stronger binding forces compared to single cavity control 2,6-Di-Omethyl- β -cyclodextrin. The inclusion complexes are biocompatible with minimal toxicity towards normal cells. However, the anticancer activities were lower compared to free CBD against breast cancer cell lines.

TABLE 2 Summary of various cyclodextrin- phytocannabinoids complexes.

Type of CD	Drug	Dose	Route of administration	Status of investigation	Outcome	Ref
β-CD	THC	–	–	In vitro	• Increased chemical stability	Shoyama et al. (1983)
HP-β-CD	THC	–	–	In vitro	• Increased solubility	Jarho et al. (1998)
Randomly methylated-β-CD	THC	250 μg/kg	Sublingual, oral	In vivo	• Improved bioavailability • Reduction of mean Tmax	Mannila et al. (2005)
β-CD	THC	250 μg/kg	Sublingual, oral	In vivo	• Improved bioavailability • Reduction of mean Tmax	Mannila et al. (2006)
β-CD	CBD	250 μg/kg	Sublingual, oral	In vivo	• Improved bioavailability • Reduction of mean Tmax	Mannila et al. (2007)
α-CD, β-CD and γ-CD	CBD	10–83.5 μM	–	In vitro	• Increased aqueous solubility • Lower toxicity against normal cells	Lv et al. (2019)
Succinimide β-CD dimer and Thiodipriopionic amide β-CD dimer	CBD	5.5–42 μM	–	In vitro	• Increased aqueous solubility • Biocompatible	Chen et al. (2022)

2.5 | Miscellaneous delivery systems

Recently various drug delivery carriers such as extracellular vesicles (EVs), mesoporous silica and electrospun fibres and has been used to deliver the cannabinoids (Andriotis et al., 2021; Patel et al., 2021; Söpper, Hoffmann, & Daniels, 2021).

Extracellular vesicles or exosome (vesicles of 30–150 nm) have gained great attention as drug delivery carriers for both lipophilic and hydrophilic drugs for various diseases because of their higher stabilities and safer toxicity profiles (Elsharkasy et al., 2020; Herrmann, Wood, & Fuhrmann, 2021). Recently, Patel et al. used extracellular vesicles isolated from human umbilical cord mesenchymal stem cells (hUCMSCs) to encapsulate cannabidiol (Patel et al., 2021). The EVs showed more than 90% drug entrapment efficiency with mean particle diameter of 114.1 ± 1.02 nm and zeta potential of 30.26 ± 0.12 mV. The drug-loaded EVs are stable at 4°C for several months. In vitro drug release studies showed approximately 50% of the released drug after 48 h. CBD-EVs and pure enhances the sensitivity of doxorubucin towards breast cancer cells (MDA-MB-21). In addition, intraperitoneal administration of CBD-EVs (5 mg/kg) to Female Envigo nude mice resulted in significant inhibition of tumour volume (25%, $^{**}p < .01$) compared to control.

Söpper et al engineered cannabidiol loaded mesoporous silica carriers for buccal drug delivery (Söpper et al., 2021). To enhance mucoadhesion, the silica carriers were coated with hydroxypropyl methylcellulose (HPMC), carbomer and chitosan and the formulations were evaluated for mucoadhesive effects. The results showed that coating of silica carriers with HPMC, carbomer and chitosan improved the mucoadhesion by 16, 20 and eight-fold respectively compared to pure CBD. In addition, mucosal absorption of CBD was also increased 3- fold with CS. In a separate study, electrospun fibres prepared from polyvinyl(pyrrolidone) (PVP) and Eudragit L-100 were used to increase the solubility of CBD and CBG (Andriotis et al., 2021). The synthesised fibres have smooth texture with size ranges of 700–900 nm and 1–5 μm for PVP and Eudragit L-100 respectively. Both the fibres encapsulated the drugs with higher than 90% efficiency. In vitro release studies in simulated fluids showed burst release of CBD and CBG followed by slow release from PVP fibres whereas pH-dependent drug release was observed with Eudragit L-100 fibres.

3 | CONCLUSIONS AND FUTURE PERSPECTIVE

Despite the incredible medicinal properties of phytocannabinoids such as CBD and THC, the development of an effective formulation remains elusive due to some of their major limitations such as low aqueous solubility, extensive first-pass metabolism, resulting in poor systemic availability. To surmount these major limitations, different types of nano drug delivery systems have been engineered as discussed in this review, such as polymeric NPs, lipid NPs, ethosomes and cyclodextrin complexes. Each of these technologies have their own advantages and limitations as described above. Most of the engineered formulations exhibit biocompatibility and efficient encapsulation of cannabinoids. Although, burst release of encapsulated drug from the formulation is common with lipid nano particles. SEDDS are among the most widely used techniques for encapsulation of cannabinoids which has demonstrated excellent physico-chemical stability and improved oral bioavailability. This approach offers advantages such as simple method of preparation and scale up for large scale manufacturing without any sophisticated technology.

The experimental evidence suggests that a well-formulated nano formulation approach leads to an enhanced aqueous solubility, improved physicochemical stability and improved bioavailability of the cannabinoids. Further, encapsulation in nano formulations can protect cannabinoids from metabolism allowing prolonged residence time in the blood, thus reducing frequency of drug administrations. Safe toxicological profiles of the various cannabinoid nano formulations and their efficacy in in vitro and in vivo highlight their potential as therapeutics. Some nanoformulations such as SNEDDS were also evaluated in clinical trials after single dose administration. However, these studies were carried out in small number of volunteers. Therefore, extensive high-quality human clinical trials have to be conducted to establish the safety and efficacy of cannabinoid nano formulations particularly after repeated and chronic use. So far, majority of the engineered nano formulations were targeted particularly against cancer, but some of the reports have shown that the formulations can also be potentially used for the treatment of bone defects, seizures and inflammatory diseases.

AUTHOR CONTRIBUTIONS

T. Srinivasa Reddy collected the literature and wrote the original draft. Roby Zomer and Nitin Mantri wrote, reviewed and revised the manuscript. All the authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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