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REVIEW ARTICLE

Cannabinoid Oral Mucosal Delivery: Approaches to Formulation, Fabrication, and Permeation Enhancement

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Abstract

Cannabinoids such as cannabidiol (CBD) and tetrahydrocannabinol (THC) have garnered significant interest for their broad-spectrum pharmacological activity in managing chronic pain, neurological disorders, and cancer-associated symptoms. Despite their therapeutic promise, clinical translation remains hindered by poor aqueous solubility, extensive first-pass metabolism, and inconsistent systemic exposure following oral administration. Oral mucosal drug delivery systems offer a viable alternative by enabling transmucosal absorption, bypassing hepatic metabolism, and facilitating both rapid and sustained drug release. This review examines the evolution and design of oral mucosal dosage forms, including fast-dissolving films, mucoadhesive matrices, in situ gels, and particulate systems and highlights the critical role of formulation strategies in enhancing cannabinoid bioavailability. Fabrication techniques such as solvent casting, hot melt extrusion, and emerging 3D printing methods are also discussed, with a focus on their potential to enable personalized dosage forms. Furthermore, the integration of permeation enhancers like terpenes, and novel systems such as inclusion complexes and lipid-based carriers, presents new opportunities for improving the solubility and stability of lipophilic cannabinoids. Together, these innovations provide a framework for the development of stable, effective, and patient-centric oral mucosal cannabinoid delivery platforms with improved pharmacokinetic and therapeutic profiles.

Keywords cannabidiol (CBD) · formulation strategies · oral mucosal delivery · sustained release · tetrahydrocannabinol (THC)

Introduction

Cannabinoids are being increasingly harnessed for their medicinal properties in various dosage forms, with the most common routes of administration being oral and pulmonary. Smoking or inhaling cannabis is the most common and preferred route for both recreational and medical uses because it provides rapid effects and efficient delivery [1, 2]. Despite the advantages, smoking or vaporisation of cannabis is associated with side effects due to mixed tobacco/E-liquids, the possibility of toxic compounds that are formed at high temperatures, unregulated doses in some cases, and it still remains stigmatised by many [3–5]. Also, cannabis administered via the pulmonary route faces fluctuation of absorption and bioavailability due to inter- (between individuals) and intra-individual (within individuals across varying observations) variabilities arising from differences in frequency and depth of inhalation and titration of dose [6, 7]. This variation is also observed with the most frequently used oral route due to factors such as food or drinks consumed. Furthermore, the bioavailability of cannabinoids remains a significant limitation in developing oral formulations [8], which is mainly due to its degradation in the gastrointestinal tract (GIT), inadequate absorption in GIT, and first-pass metabolism in the liver [7, 9]. Moreover, once subjected to first-pass metabolism, the metabolites such as 11-OH-THC (11-OH-Tetrahydrocannabinol) can be four times more psychoactive than THC, posing more side effects [10]. Consequently, considerable research effort has been directed towards alternative administration routes that bypass first-pass metabolism, including oromucosal (buccal and sublingual), transdermal, intranasal, and rectal delivery.

Constraints for the oromucosal delivery of the currently approved product, Sativex, are mainly related to the

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stability of the dosage form in the oral cavity and poor bioavailability since most of the formulation is accidentally swallowed rather than being absorbed into the mucosa, which leads to oral delivery rather than oromucosal [11]. Limitations also include the need for frequent administration [12], slow onset of action [13], and long-term adverse effects of mouth lesions due to the use of excipient ethanol [14]. Limitations of Sativex highlight another essential consideration for developing cannabis formulations, which is the release characteristics of the dosage form. Most of the research done so far with oromucosal delivery of cannabinoids remains constrained to revamping Sativex in terms of its dosage form for targeted delivery into the oral mucosa failing to address the dosage form's drug release properties.

Medications can be formulated in either conventional or sustained-release dosage forms. Traditional fast-release formulations face severe adverse effects as a result of requiring frequent administration of high doses of therapeutics. However, sustained/extended-release systems can provide prolonged release of medication, eliminating the need for repeated administration, and are generally of lower cost. Furthermore, the slow expulsion of the active ingredient from sustained-release formulations avoids severe effects from the sudden release of high doses into the system seen with conventional drugs [15]. Sustained release of therapeutics from dosage forms largely depends on the increased resident time of the formulation in the region of application/administration, which can be achieved by modifying the type of dosage form developed and by using excipients that prolong the release of the drug [16]. The bioavailability and controlled release of active ingredients, particularly cannabinoids, are critical factors affecting their therapeutic efficacy. Thus, the careful selection of excipients and their concentrations is crucial for achieving optimal formulation performance [17].

This review examines the pharmacokinetics of cannabinoids administered via different routes, with a particular emphasis on oromucosal delivery. While buccal and sublingual administration are often collectively described as oromucosal routes, they differ substantially in terms of epithelial thickness, permeability, vascularisation, residence time, and formulation requirements. The buccal mucosa is comparatively thicker and less permeable, making it well suited for mucoadhesive and sustained-release systems, whereas the sublingual mucosa is thinner and highly vascularised, favouring rapid absorption from fast-dissolving formulations [18, 19]. Accordingly, this review focuses on oral mucosal cannabinoid delivery and examines suitable polymers and excipients, fabrication techniques for various dosage forms, strategies to enhance bioavailability and prolong drug release, as well as recent advances in oral mucosal cannabinoid products.

Route-dependent Pharmacokinetic Considerations for Cannabinoid Delivery

Historically, cannabis use has involved smoking or various other methods of inhaling the dried flowers of the plants. However, recent research has expanded to process raw Cannabis or isolated cannabinoids into various dosage forms. The pharmacokinetic effects vary depending on the route that they are administered [20].

Smoking/inhalation

Smoking cannabis is a primary route of drug consumption. Studies show that the effect of smoking on the pharmacokinetics of cannabinoids is similar to the intravenous route in terms of fast onset of action. Smoking leads to rapid absorption of 25% of the cannabinoids present with very short time to peak plasma concentration (Tmax typically within 6–10 min) and high peak plasma levels (Cmax), followed by a rapid distribution phase. Inhaled THC doses typically range from ~2–10 mg per administration and associated with fast onset of pharmacological effects but also marked inter-individual variability due to differences in inhalation technique and pulmonary deposition [21, 22]. However, smoking cannabis with tobacco or vaporising with e-liquids has been associated with poor health outcomes and harmful consequences not yet understood in the case of some e-liquids [23, 24]. Furthermore, the stigma associated with "cannabis smoking" [25], THC's psychoactive actions [1], and the potential of producing toxic compounds at high temperatures [3], in addition to the high THC concentrated strains cultivated today, limits this route in terms of medical administration [21]. Inhalation of cannabinoids results in rapid absorption.

Oral Route

The oral route is recognized for its preference by most patients, excluding unconscious patients and patients with swallowing obstructions. Edibles of cannabinoids have been used widely for recreational purposes due to associated durable effects combined with a lack of difficulty in administration. However, oral administration of cannabinoids is characterised by delayed absorption (Tmax typically 2–3 h), lower and more variable Cmax, and extensive first-pass metabolism, leading to formation of active metabolites when THC is broken down into psychotropic 11-OH-THC, further metabolised to 11-COOH-THC. Typically, oral THC (dronabinol) doses are commonly administered in the range of 2.5–10 mg per dose, while oral CBD in the approved Epidiolex® formulation is typically initiated at low doses

(e.g. 2.5 mg/kg twice daily in approved indications) and titrated upward [9, 10, 26, 27]. When consumed by the oral route, the bioavailability of the cannabinoids is reduced significantly to one third compared to smoking, while there is also an increase in its psychoactive effect. The average bioavailability (considering inter-and intra-individual variability) of CBD and THC is identified as 31% when smoked/inhaled, was significantly higher than the bioavailability of the oral route, with reported absolute oral bioavailability typically ranging from approximately 6–10% for THC and 6–19% for CBD [7, 9, 28, 29]. In addition to the first-pass metabolism effects, variation in absorption from the gut due to inconsistent dosing across different oral formulations and the effects of body composition (presence of higher fat mass) and the degradation in the stomach also contributes to poor bioavailability of the oral route [1, 30]. An exceptionally low proportion of studies considering the impacts of consuming food and drinks could also add to the absorption variation effects [31].

Approaches to enhance the bioavailability of oral cannabinoids include using oil-based cannabinoid formulations and developing delivery systems that emulsify under the acidic conditions of the GI tract. Self-emulsifying drug delivery systems (SEDDS), and nanoemulsions are now well-established, scalable, and clinically feasible approaches for improving the solubility and oral bioavailability of lipophilic drugs, including cannabinoids. Self-emulsifying CBD formulations have demonstrated increased plasma concentrations and improved pharmacokinetic parameters compared with non-SEDDS formulations. Nanoformulations such as nanoemulsions and lipid nanocarriers have also been found to enhance cannabinoid solubility, stability, and sustained release [32–35].

Routes to Avoid First-pass Effects

Alternative routes of cannabinoids' administration to avoid first-pass metabolism effects such as transdermal, rectal, intranasal, and oromucosal are currently under investigation. There is, however, a lack of information regarding the pharmacokinetic parameters, such as the bioavailability of cannabinoids via these routes. The transdermal route is an attractive option with the potential to treat demagogical conditions and even skin cancers due to the different cannabinoid receptors present on the skin, which are actively involved in skin cell activities [5]. Research on delivery via the transdermal route is now focused on developing carrier systems for the highly lipophilic cannabinoids and also enhancing diffusion and penetration into deeper layers of the skin to reach the blood circulation. However, the physicochemical instability of cannabinoids presents significant formulation challenges for transdermal systems. Cannabinoids are susceptible to photodegradation and thermal degradation, which can occur during patch manufacturing, storage, or prolonged exposure to body temperature at the skin surface. Such degradation may reduce drug potency and compromise dose consistency, particularly for long-wear transdermal patches. Additionally, transdermal delivery may be impaired in patients with wasting syndrome, a condition characterised by reduced subcutaneous fat, altered skin integrity, and compromised barrier function. These physiological changes can limit the formation of an effective drug reservoir within the skin and reduce reproducibility of drug absorption, thereby affecting systemic exposure. Together, these limitations highlight the challenges associated with transdermal cannabinoid delivery despite favourable lipophilicity Transdermal cannabinoid delivery is associated with slow absorption kinetics, delayed Tmax, and relatively stable plasma concentrations over extended periods, consistent with sustained drug input across the skin barrier. Emerging human studies have evaluated transdermal CBD or THC doses typically in the range of ~ 20–100 mg applied over 24–48 h, although inter-subject variability remains high and comprehensive human pharmacokinetic data are still limited [7, 9, 36].

Mucosal sites offer good alternatives to oral routes for systemic drug delivery. Rectal administration of cannabinoids has been reported to increase systemic exposure (area under the curve, AUC) and partially circumvent first-pass hepatic metabolism compared with oral dosing. Clinical investigations have primarily evaluated rectal THC prodrugs, administered as single-dose equivalents in the low-milligram range (approximately 2.5–5 mg THC equivalents), demonstrating improved pharmacokinetic profiles relative to oral formulations. Nevertheless, limited patient acceptability, variability in rectal retention, and potential impairment of absorption associated with defecation significantly restrict the practical utility of this route for routine cannabinoid delivery [37, 38]. Intranasal delivery of several drugs, including propranolol, progesterone, and anticonvulsants, has successfully circumvented first-pass metabolism and enhanced systemic bioavailability. Intranasal administration of cannabinoids has been investigated only to a limited extent, as their high lipophilicity and poor aqueous solubility hinder effective dissolution within the thin, hydrated mucin layer of the nasal cavity, thereby limiting the fraction of drug available for absorption across the nasal epithelium, in addition to constraints imposed by the relatively small absorptive surface area [39, 40].

The oral mucosa, or oromucosal route, is a popular choice for delivering a wide range of drugs, as it offers a relatively large surface area through which clinically relevant drug doses can be administered. Depending on the formulation and site of administration, the oromucosal route can typically accommodate approximately 0.1–2 mL of liquid formulations, while solid dosage forms such as films, patches,

and tablets are designed to deliver drugs in the milligram dose range with minimal added volume. Formulations exhibiting enhanced mucoadhesive properties enable prolonged retention and controlled dissolution at the site of administration [41]. Oromucosal administration of cannabinoids exhibits intermediate pharmacokinetics between inhalation and oral routes, with reported Tmax values of approximately 45–120 min, depending on formulation and dosing conditions. Clinically used oromucosal spray (Sativex®) deliver low milligram doses per actuation (typically ~2.7 mg THC and 2.5 mg CBD per spray), allowing dose titration [42]. Although cannabinoids are highly lipophilic molecules and inherently capable of permeating biological membranes via transcellular pathways, their bioavailability following oromucosal administration is often limited by factors unrelated to membrane permeability alone. Continuous saliva flow, the presence of a hydrated mucus layer, poor aqueous solubility, and short formulation residence time can restrict the effective concentration of dissolved drug available at the epithelial surface, thereby limiting transmucosal absorption. Consequently, successful buccal/sublingual delivery of cannabinoids requires formulation strategies that improve local solubilisation, stability under physiological conditions, and mucosal residence time to fully exploit their favourable lipophilicity [7, 19].

Approved Formulations of Cannabis Products

Formulations of cannabis approved for use include synthetic preparation of THC and its analogue, or pure CBD, including Dronabinol, Nabilone, Epidiolex, and oromucosal Sativex for a few clinical indications [43, 44]; the clinical indications of these drugs are shown in Table I, along with their bioavailability and onset of action. The use of synthetic THC in oral formulations was a significant cause of concern for adverse CNS effects [6]; although Nabilone, an analogue of synthetic THC, was reported to have higher bioavailability compared with Dronabinol (synthetic THC), it had more severe drowsiness, dizziness, and psychoactive effects [45].

From a regulatory standpoint, cannabinoid-based medicines are subject to heightened scrutiny due to their narrow therapeutic windows, central nervous system effects, and historical classification as controlled substances. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require robust evidence of dose consistency, long-term safety, and manufacturing reproducibility, particularly for novel delivery platforms. For buccal and oromucosal systems, additional regulatory considerations include demonstration of consistent drug release under physiological salivary conditions, absence of mucosal irritation following repeated

Table I Clinical Indications of FDA-Approved Cannabis Products, their Onset of Action and Bioavailability Identified

Drug	Formulation name & dose	Approved clinical indications	Formulation	Average Onset of action	Bioavailability	References
Dronabinol-synthetic THC	Marinol® 5 mg	Chemotherapy-induced nausea, appetite stimulant in AIDS	Soft gelatine oral capsule	1.5 h	10 to 20%	[46–48]
	Syndros® 4.25 mg	Chemotherapy-induced nausea, chronic pain	Oral solution	1 h		
Nabilone-synthetic analogue of THC	Cesamet® 2 mg	Chemotherapy-induced nausea	Oral capsules	1–1.5 h	60%- studies not conclusive	[46, 47, 49, 50]
THC and CBD	Sativex® 5 and 15 mg THC	Spasticity in multiple sclerosis (MS), Clinical trial phase III for cancer pain	Oromucosal Spray	Up to 40 min	5 and 15 mg oral THC- Relative Bioavailability: oral THC 92.6% (coefficient of variation (CV) 13.1%) and 98.8% (CV 11.0%); oromucosal (buccal-predominant) 93.9% vs sublingual 87.2%	[11, 13, 47]
CBD	Epidiolex®	Lennox-Gastaud and Dravet syndromes—epileptic disorders	Oral solution	Not determined	13–19%	[4, 7]

administration, and clear differentiation between transmucosal and gastrointestinal absorption. Emerging technologies such as mucoadhesive films, *in situ* gels, and 3D-printed dosage forms offer regulatory advantages by enabling precise dose control and reproducible manufacturing, although clinical validation remains a prerequisite for approval [9, 42, 47, 51, 52].

Drug Delivery Through the Oral Mucosa

Oromucosal drug delivery systems mitigate the challenges associated with the limited bioavailability of conventional oral routes [51]. There are different routes available for administering drugs within the oral mucosa, including buccal, gingival, sublingual, and soft-palatal mucosa (Fig. 1) [53]. The selection of the delivery route within the oral mucosa is determined by whether the drug is intended for local or systemic effects. Delivery into the gingival regions, encompassing sites near the teeth and negligible areas of the alveolar bone, is limited for local drug requirements and not feasible for systemic delivery. While the soft-palatal sites, consisting of the soft tissues on the roof of the mouth, provide an optimal pH of 7.34 ± 0.38 for stable drug delivery and produce minimal saliva, they are also susceptible to risks associated with the inadvertent swallowing of the medication [54, 55]. Furthermore, the keratinized epithelial layers of the gums and soft palate display permeation rates comparable to those of the skin, which are significantly lower than the higher absorption rates observed in the non-keratinized buccal and sublingual mucosal tissues [56]. Therefore, buccal and sublingual mucosa are commonly chosen for systemic drug delivery because they offer enhanced absorption rates and improved bioavailability compared to other oral mucosal sites.

Buccal and Sublingual Mucosa

The buccal and sublingual mucosa, comprising the inner cheek lining and the floor of the mouth (under the tongue), respectively, are popular routes for delivering systemic drugs; comparisons of these regions are represented in Fig. 2 [19]. The buccal region has a relatively larger surface area (around 53 cm^2) and thicker stratified squamous (SS) epithelial layer of cells (500–800 µm) compared to the sublingual region having a surface area of 27 cm^2 and SS epithelial layer of cells comprising 100–200 µm thickness. Under this SS epithelial layer lies a mesh of blood vessels, capillaries, and smooth muscles forming the connective tissue, through which the drugs administered enter systemic circulation [18, 19]. The transport of drugs within the layers of the buccal and sublingual regions involves concentration gradient dependent, transcellular and paracellular pathways. Essential characteristics of the drug governing transport across these regions include lipophilicity, molecular size and degree of ionisation (pKa). Lipophilicity of the drug plays a crucial role in transport, as lipophilic drugs can easily travel through the transcellular route to cross the phospholipid layers of the cells. However, despite paracellular paths being available for hydrophilic drugs, their movement is limited by the tight junctions present. Small-sized drug molecules (< 500 Da) can efficiently permeate, even via tight junctions. High logP values (> 2) and non-ionizable drugs are found to be preferable [57]. Drug bioavailability and stability in formulations, in addition to absorption and transport features of the medicine, are also dependent on factors such as saliva flow, pH of the oral cavity, and the residence time of the formulation [19].

Both the sublingual and buccal routes offer advantages in terms of ease of drug delivery and patient compliance. The sublingual route provides the added benefit of faster drug

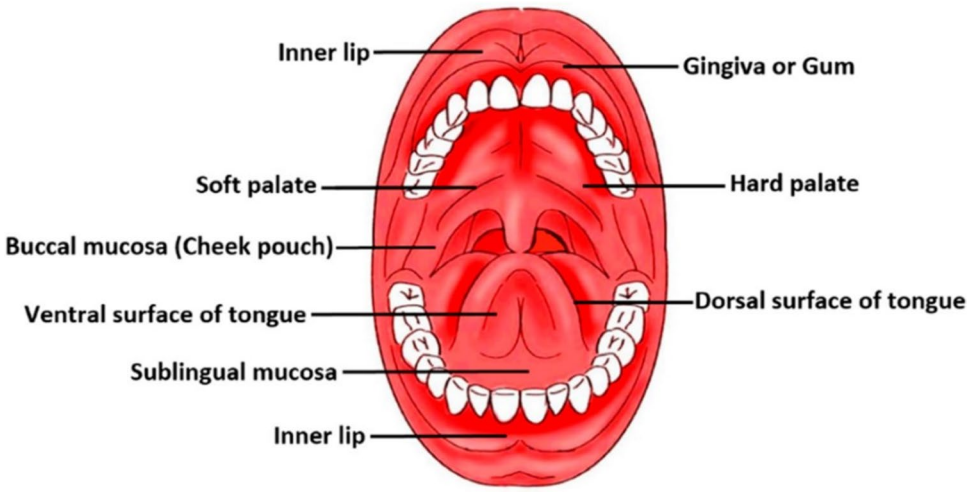

Fig. 1 Regions of the oral cavity; Adopted from [53]

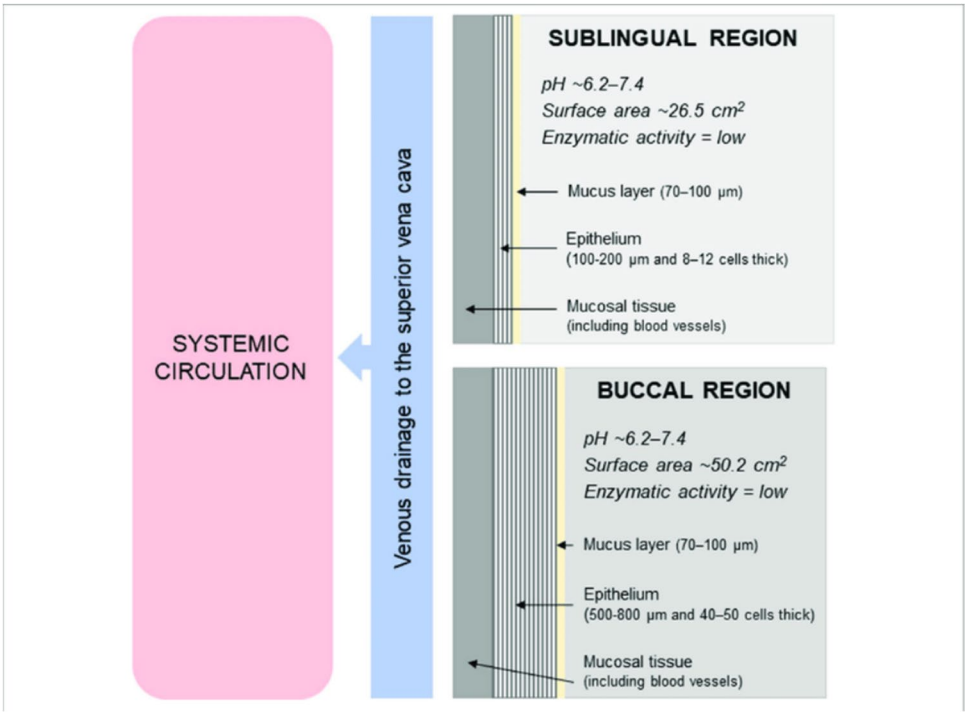

Fig. 2 Comparison of the buccal and sublingual regions for systemic drug delivery; Adopted from [19]

absorption due to its ability to quickly penetrate the mucosal membranes, whereas the buccal region experiences slower penetration due to the presence of a larger number of smooth muscles. However, the sublingual region is generally not suitable for sustained drug release systems as it is constantly affected by saliva secretion and movement of the tongue. Furthermore, buccal mucosa has the lowest enzyme activity in the oral mucosa and an intermediate turnover time of the cells (4–14 days) compared with rapid intestinal and prolonged skin cells. Thus, formulations that possess mucoadhesive properties can reside and act as controlled release systems dispensing the drug slowly [58–60]. Additional benefits of the buccal route include a lower risk of drug degradation due to enzymatic activity. Moreover, patient comfort is preserved through easy administration and the safe removal of dosage forms in cases of mucosal irritation [61].

Release Characteristics of Oral Mucosal Formulations

Various types of dosage forms have been developed to deliver active ingredients/drugs across the oral mucosa, depending on the clinical indication for which they are used. These include hydrogels, mucoadhesive carrier systems, bioadhesive wafers and lozenges, thin films, *in situ* gels, tablets/capsules, carrier oils, extracts, sprays, and particulate systems. Each type of dosage form offers distinct advantages depending on the drug's characteristics and the required pharmacokinetic profile [61]. Drugs can either be required to provide rapid and immediate complete effects within a few minutes of administration or prolonged effects, where the drug is released gradually over an extended period.

Conventional Fast Dissolving Immediate Release Dosage Forms

Conventional oral mucosal drugs are formulated using excipients that wholly and quickly dissolve and release the medicine in a burst effect, making it immediately available for pharmacological action. However, it should be noted that this burst effect is only ideal for drugs to be used in low concentrations, such that there are no toxic effects seen with high concentrations of the administered drugs [62]. These therapeutics are issued for conditions of pain and nausea after acute migraine, anti-epileptic, and anti-histaminic effects in paediatric and geriatric patients [63]. Fast-dissolving polymer matrices can be developed in various dosage forms, including thin films, orally disintegrating tablets, and lyophilised (freeze-dried) wafers. Soluble hydrophilic polymers, with or without mucoadhesive properties, are used for developing these fast-dissolving compositions [64].

Fast-dissolving formulations can be categorised based on their primary absorption pathway, distinguishing those designed for true buccal or sublingual transmucosal uptake from systems that dissolve rapidly in the oral cavity but are predominantly swallowed, with drug absorption occurring in the gastrointestinal tract. Buccal and sublingual routes involve drug uptake across the oral mucosa into the systemic circulation, bypassing first-pass metabolism, whereas

swallowed formulations behave like traditional oral dosing and are subject to hepatic first-pass effects [65, 66]. For cannabinoids, which are prone to first-pass metabolism, fast-dissolving systems without sufficient mucoadhesion may offer limited advantages over conventional oral formulations. Therefore, effective oral mucosal delivery requires formulation strategies that balance rapid hydration with adequate residence time to enable meaningful transmucosal absorption.

Sustained-release Formulations

Sustained-release formulations can be developed as either slow or fast-dissolving dosage forms. Approaches to developing such formulations include using excipients such as mucoadhesive polymers that release the active pharmacological ingredient (API) in a sustained fashion, developing *in situ* gels, fabricating micro/nanoparticulate dosage forms with or without a pharmacological base, and controlling the type of dosage form produced– bi/multi-layered [16].

Mucoadhesive Polymeric Formulations

Mucoadhesive polymers are the most commonly used excipients for developing various dosage forms, including gels, lozenges, solutions, wafers, microparticles, films, and tablets, and are often used along with or as a base of dosage forms such as *in situ* gels or nanoparticles, respectively [67]. Different theories govern the adhesion of these polymers to the buccal mucosa, creating the contact and consolidation stages. The contact stage is when the formulation encounters the soluble mucins, swells, and is wetted. After this, various noncovalent bonds interconnect the formulation with bound mucins, which diffuse and further form both non-covalent and covalent bonds [59]. Ideally, a mucoadhesive polymer is required to have a molecular weight > 100 kDa, increased and flexible polymer chains with lower crosslinking density, presence of charges and groups involved with strong hydrogen bonding, and favourable surface properties for good adhesion onto the mucosa. They are usually classified into first-generation and new second-generation polymers. However, the classification can also be based on factors such as their charge (anionic or cationic), origin (natural, synthetic, or semisynthetic), water solubility, and mucoadhesive interactions (including electrostatic, covalent, or hydrogen bonding) [68]. Different properties of polymers such as degree and rate of swelling influence their muco-adhesiveness. Insoluble mucoadhesive polymers have been employed to help the drugs slowly diffuse into the target environment, even for longer than 20 h. However, to avoid mucosal irritation and provide better patient compliance, formulations are required to have a maximum residence time of 4–6 h in the buccal mucosa [69].

Mucoadhesive polymeric dosage forms with sustained-release properties can be slow or fast dissolving. Formulations that dissolve slowly usually employ a slowly dissolving polymer layer to provide uni-directional sustained release of the API [53]. Fast dissolving sustained-release formulations are developed with drug-particulate systems in a fast-dissolving polymer base. Rapid dissolution of the pharmacological base helps to eliminate formulation discomfort at the buccal cavity. It ensures that the drug-particulate system is released completely in a short period of time into the mucosal layers, where the particulate system can slowly release the drug [70].

Particulate Systems

Research by Jelvehgari *et al*. [71] showed that particulate dosage forms exhibit slower release characteristics when compared with mucoadhesive films. However, these micro/nanoparticles succumb to easy washout in the mouth or accidental swallowing. Hence, stable formulations are developed with these particulate systems incorporated into hydrophobic mucoadhesive polymers for slow/fast dissolving and release properties [61]. Despite this, the success of such drug-particulate systems is limited by their ability to remain in the mucosal layers without being displaced by saliva. While multi-layered formulations, featuring layers designed for uni-directional flow, mucoadhesive particulate systems, and penetration enhancers, help mitigate this issue to some extent [72, 73], concerns persist regarding the potential toxicity and side effects of these particulate systems accumulating in various organs, particularly in cases of unintended swallowing.

In situ Gels

In situ gels are smart formulations that can transition from liquid to gel or powder to gel once in contact with the physiological environment of the human body. These gels can be fabricated to provide both local and systemic drug effects. *In situ* formulations provide the benefits of intimate adherence to the mucosa layer with increased residence time and ease of applying evenly distributed formulations [53, 74]. Physiological/physical mechanisms that form the gel inside the body include temperature-induced, pH-induced, and ion-induced [75]. Polymers that gel upon stimulation by temperature changes are further classified into negatively activated, positively stimulated, and reversible polymers. Negatively induced polymers possess lower critical solution temperatures (LCST), above which they gel and exist as a flowable liquid below these temperatures. Positively induced polymers holding upper critical solution temperature (UCST) present as a liquid and gel above and below this temperature, respectively [76]. Thermoreversible polymers show reversible gelation by harnessing the ability to convert into a liquid again upon cooling [77]. Table II presents

Table II Benefits and Limitations of Physiological Mechanisms of Gelation

Physiological mechanism of gelation	Commonly used polymers	Benefits	Limitations	References
Temperature-induced	- Negatively induced- poly-N-isopropyl Acrylamide, Chitosan, cellulose, PEG, PLGA - Positively induced- Gelatine, amylose, polyacrylamide, Polyacrylic acid (PAA), agarose, amylopectin - Reversible—poloxamers	- Easy adjusting of LCST and UCST by combinations/varying concentrations of polymers - Absence of any significant irritation with poloxamers at mucosal sites - Transition at body temperature is safe - Does not require any harmful crosslinkers	- Storage issues - Low mechanical strength - Rapid erosion - Poor mucoadhesion -Slow gelling time	[74, 76, 78, 81]
Ion-induced	Gellan gum, Sodium alginate, Carrageenan, pectin	- Non-irritant in nature - Use of natural polymers - Non-cytotoxic	- Weak mechanical properties - Formation of heterogeneous gels in some cases	[74, 81]
pH-induced	PAA derivatives such as carbopols and polycarbophils, and chitosan	- Good stability with drugs not sensitive to pH changes - Some polymers such as carbopol are found to be sufficiently mucoadhesive	-Requires acidic/basic conditions to maintain low viscosity in solution state - Limited in their ability to deliver pH-sensitive actives - Can cause discomfort at the site of application	[74, 79, 81]

the advantages and disadvantages of various physiological mechanisms of gelation, along with the commonly used polymers associated with each mechanism.

Chemical methods include enzymatic crosslinking, irradiation, click-reaction, genipin, and thiol oxidation stimulated gelling reactions [74]. Chemical methods of gelation involve chemical reactions crosslinking the polymer chains. Although crosslinking is known to develop hydrogels with improved mechanical strength, chemical reactions producing side products or even the crosslinkers used, have the potential to be toxic to cells. Chemical reactions such as click-reactions, enzymatic reactions, and other crosslinking strategies have been developed to provide with non-toxic side products. However, instability of gelation or of the enzymes/crosslinkers used and weak mechanical properties of the product gels remain significant constraints [80].

Physiologically responsive *in situ* gels are known to have weak mechanical attributes, require extended time to gel, and in case of thermoresponsive poloxamers even lack mucoadhesion [74, 76]. Incorporating mucoadhesive polymers such as carbopol, HPMC, and hyaluronic acid have been shown to reverse the limitations of these gels and develop sustained-release formulations [82–85].

Mucoadhesive Polymers used in Oral Mucosal Formulations

Polymers that are widely utilized in oral mucosal drug delivery systems and possess mucoadhesive properties due to strong hydrogen bonding include a range of natural, synthetic, and semisynthetic materials. These polymers are particularly effective in enhancing the adhesion of drug formulations to the buccal/sublingual mucosa, improving the retention time and thus the therapeutic efficacy of the drug [86, 87]. Commonly used mucoadhesive polymers for oromucosal drug delivery applications include polyacrylates, cellulose derivatives, alginate, chitosan, pectin, and hyaluronic acid.

Polyacrylates

Synthetic polymers like polycarbophils and carbomers (e.g., carbopol) are polymers of acrylic acid (polyacrylates). These polymers are able to form hydrogen bonds with the mucosal surface, allowing them to adhere strongly to the oromucosal tissue. Their ability to swell in water and form gels further enhances their adhesive strength, making them ideal for controlled or sustained drug release applications in oral mucosal systems [87]. A systematic review conducted by Mohammad Hamdi *et al.* [88] highlighted carbopol's effectiveness as a mucoadhesive polymer, demonstrating its ability to provide strong mucoadhesion, extend residence time in the oromucosal cavity, and enhance the permeation of active ingredients.

Cellulose Derivatives

Cellulose derivatives like hydroxypropyl cellulose (HPC) and hydroxypropyl methyl cellulose (HPMC) adhere to mucosa by the strong hydrogen bonds coupled between the carboxylic group and glycoproteins found in mucin, contributing to a stable and prolonged adhesion to the oral mucosa. These

polymers are commonly used in the formulation of oromucosal tablets, films, and gels, offering advantages like easy fabrication and the ability to control drug release [87]. The concentration of HPMC plays a significant role in modulating the drug release profile in mucoadhesive formulations. In a study by Jaipal *et al*. [89] involving buccal discs, it was found that increasing the concentration of HPMC led to a slower release of mannitol. This was attributed to the more substantial gel formation at higher concentrations, which created a more rigid structure, reducing the rate at which the drug was released. However, the higher concentration of HPMC also improved mucoadhesion, leading to an extended residence time of the formulation in the oromucosal cavity.

Alginate

Alginate, a natural polysaccharide extracted from seaweed, contains both hydroxyl and carboxyl functional groups capable of forming hydrogen bonds with the mucosal surfaces. These interactions contribute to its mucoadhesive properties, making alginate an effective material for buccal drug delivery systems. The mucoadhesive strength of alginate is pH-dependent, with lower pH levels leading to reduced chain entanglement of the alginate polymer. This decrease in chain entanglement results in a smaller surface area of contact between the alginate and mucin, thereby reducing its mucoadhesive properties [87]. In addition to its mucoadhesive properties, the use of alginate as a single polymer in drug delivery systems presents some limitations. One significant drawback is its relatively low gel strength, which leads to the formation of soft gels that may not provide adequate mechanical support for sustained mucoadhesion [90]. Additionally, alginate's *in vivo* degradation is typically slow and can be unpredictable, which may compromise its effectiveness in drug release applications. These challenges can be mitigated by combining alginate with other mucoadhesive polymers, such as chitosan, carbopol, or HPMC, which can enhance its mucoadhesive strength, improve gel integrity, and optimize the degradation rate [91]. Alternatively, the formation of alginate microparticles can address these issues by increasing the surface area available for interaction with mucosal tissues, thereby enhancing mucoadhesion [87, 90].

Chitosan

Chitosan, a cationic polymer derived from chitin (typically sourced from crustaceans), is extensively studied and commonly used in mucoadhesive formulations, particularly in drug delivery. Its solubility in weak acids, such as acetic acid, results from the protonation of its amino groups (-NH2) at low pH, which enhances its mucoadhesive properties in acidic environments. Chitosan's mucoadhesion is driven by hydrogen bonding, electrostatic interactions, and conformational flexibility, which enable strong adhesion to mucin. The extent of adhesion varies with mucin composition, particularly sialic acid content. In buccal drug delivery applications, chitosan faces limitations such as inadequate mechanical strength and excessive swelling, which can impair the controlled release of drugs. However, studies have demonstrated that these issues can be moderated through chemical modification or derivatization of chitosan, enhancing its stability and extending its release profile [87, 92].

Pectin

Pectin, a biodegradable polysaccharide extracted from cell walls of plants, exhibits mucoadhesion through hydrogen bonding and electrostatic interactions with mucin. The carboxyl groups in pectin facilitate H bonding, while increased pectin concentration in aqueous solutions can cause electrostatic repulsion, leading to polymer chain uncoiling and enhanced adhesion. Although hydrogen bonding and electrostatic repulsion mechanisms appear contradictory, both contribute to mucoadhesion. As a hydrophilic polymer, pectin is highly susceptible to water, which can limit its effectiveness in sustained-release buccal formulations by promoting rapid swelling and degradation. However, research has demonstrated that crosslinking pectin can mitigate these water-sensitive limitations by enhancing its structural integrity and reducing its solubility in aqueous environments. While crosslinking improves the stability of pectin in sustained-release applications, it has been observed to reduce its mucoadhesive properties [93].

Hyaluronic Acid

As a biodegradable and biocompatible polymer, hyaluronic acid is another common polymer extensively researched for its mucoadhesive properties. Its bioadhesive properties are primarily attributed to its random coil structure, which allows entanglement with the mucosal layer by formation of hydrogen bonds, enhancing mucoadhesion. Previous research has demonstrated that by structurally modifying the compound by introducing thiolation or by lowering its molecular weight, its mucoadhesive properties can be enhanced. Such modifications allow for sustained release and improved drug absorption, making hyaluronic acid a versatile material for buccal drug delivery systems [87].

A comparative summary of commonly used mucoadhesive polymers, including their adhesion strength, swelling behaviour, and suitability for sustained cannabinoid delivery, is presented in Table III.

Table III Comparative Properties and Limitations of Mucoadhesive Polymers used in Oral Mucosal Drug Delivery

Polymer	Adhesion strength	Swelling	Release control	Key limitations	References
Carbopol/polycarbophil	Very high	High	Excellent	Irritation risk due to high acidity (low pH) and excessive stickiness	[94, 95]
HPMC/HPC	Moderate	Moderate	Good	Weaker adhesion compared to polyacrylates; often requires higher concentrations	[87]
Chitosan	High (pH-dependent)	High	Moderate	Mechanical weakness; Poor solubility at pH > 6.5	[95]
Alginate	Moderate	High	Limited alone	Drug leaching (porous structure) and weak gel strength without ions	[87, 94]
Pectin	Moderate	High	Poor unless crosslinked	Rapid hydration and erosion in aqueous media	[93]
Hyaluronic acid	Moderate	Moderate	Good (modified forms)	High cost, rapid erosion	[68]

Techniques for Fabricating Oral Mucosal Formulations

Fabrication techniques for oromucosal cannabinoid delivery systems must accommodate the unique physicochemical properties of cannabinoids, including high lipophilicity, thermal sensitivity, and susceptibility to degradation. Unlike conventional oral dosage forms, oromucosal formulations require precise control over mucoadhesion, mechanical flexibility, drug loading, and release kinetics, while ensuring patient comfort. Recent studies have demonstrated the feasibility of applying established and emerging fabrication techniques such as hot-melt extrusion, solvent casting, and additive manufacturing to cannabinoid-loaded oromucosal systems, although challenges related to stability, scalability, and reproducibility remain.

Developing oromucosal formulations requires a focus on creating dosage forms that can be administered through the mucosal lining of the mouth. Fabrication techniques involved depend on the choice of dosage form being developed. The choice of formulation directly influences the manufacturing method, which must ensure the proper release profile, drug stability, and patient acceptability.

Solid Dosage Forms

Typical solid dosage forms include tablets and films/patches, with each involving different fabrication techniques [67].

Buccal/sublingual Tablets

Buccal/sublingual tablets are one of the most common solid dosage formulations, which dissolve or disintegrate in the oral mucosa allowing the drug to be absorbed. These are typically formulated using direct compression, a process that begins by ensuring the drug and excipient particles have a consistent size, either by mixing them directly or using a mortar and pestle. Next, binders and lubricants are added to the blend. The final mixture is then compressed into the desired shape and size, usually using a tablet compression machine [96]. Tablets are formulated with the ability to release the drug to be absorbed directly into the oral mucosa or in the saliva, wherein they may face the constraint of being accidentally swallowed. Furthermore, tablets are usually found to cause patient discomfort, especially when fabricated for sustained release of active ingredients [67].

Buccal/sublingual Films and Patches

Buccal/sublingual films and patches are among the most widely preferred dosage forms by patients due to the comfort provided by their flexibility and are ideal for delivering active ingredients in a sustained fashion. They are generally fabricated using either solvent casting or hot melt extrusion. Hot melt extrusion technique involves heating a mixture of drug and other excipients and extruding the molten substance through an orifice or moulded to form homogeneous films. This technique is suitable for drugs that are poorly soluble, as they can be easily dispersed in the dosage forms. However, it is limited for active ingredients, polymer, and other excipients that are temperature sensitive [67, 97]. Solvent casting is a process where the drug and excipients are dissolved in a solvent, which is then poured onto a flat surface to form a thin layer. Afterward, the solvent is allowed to evaporate, leaving behind a thin film. While solvent casting is an effective method for producing buccal/sublingual films, several factors can impact the quality and safety of the final product, such as drug stability, solvent residues, and film uniformity. Some drugs may degrade during the process, and residual solvents, particularly organic ones, can pose toxicity risks or cause irritation. Achieving consistent film thickness and drug distribution is also challenging, which can affect drug release and efficacy [97]. Other methods for fabricating films include electrospinning and spray drying. The former includes the application of high voltage to create polymer

fibres that are then collected, while the latter involves atomizing a drug-polymer solution into a fine mist, which is subsequently dried to form films. Both electrospinning and spray drying have limitations in developing buccal films, including challenges with achieving uniform drug distribution and controlling the mechanical properties of the films [98, 99].

Buccal/sublingual films and patches have been investigated for cannabinoid delivery due to their flexibility, improved patient acceptability, and capacity for sustained release. CBD-loaded buccal films fabricated by solvent casting and hot-melt extrusion have demonstrated effective mucoadhesion and controlled drug release, with polymer selection strongly influencing residence time and release kinetics. More recently, hot melt extruded CBD buccal films have shown rapid hydration, uniform drug distribution, and suitability for poorly water-soluble cannabinoids, although thermal stability of the active ingredient remains a critical consideration [100–102].

3D Printing Techniques for Fabricating Solid Dosage Forms

Three-dimensional printing is a type of additive manufacturing fabrication method that involves depositing material in a layer-by-layer fashion. 3D printing provides the ability to achieve consistent drug distribution within the material, ensuring uniformity throughout the dosage form. This technology also enables the creation of personalized dosages tailored specifically to individual patient needs. By customizing the shape, size, and drug release profile, 3D printing allows for more precise control over the therapeutic dose, accommodating variations in patient-specific factors such as age, weight, and disease conditions [103, 104]. There are several 3D printing techniques, with fused deposition modelling (FDM) and extrusion-based printing being among the most widely used for the development of buccal formulations [97].

Fused Deposition Modelling (FDM)

In FDM, the material, typically a polymer or drug-loaded composite, is heated and extruded to form thermoplastic filaments. These filaments are then used to build up the desired structure layer by layer. When combined with Computer-Aided Design (CAD), specific design models with precise shapes and dimensions can be created. This technique is particularly suited for creating complex geometries and can be used to print mucoadhesive buccal formulations that provide localized drug release. This technique has several limitations when applied to pharmaceutical formulations, including a restricted range of suitable materials, particularly for heat-sensitive drugs, as the high temperatures involved can degrade certain active ingredients. Nozzle clogging and filament quality are critical factors that often compromise the quality and dose consistency of the dosage form developed [97, 105].

Extrusion-based Printing

This technique involves the continuous extrusion of a material through a syringe-based nozzle to build up the desired shape layer by layer. It is commonly used in the pharmaceutical industry for creating oral dosage forms, including buccal patches and films, as it allows for the integration of multiple components (e.g., drugs, excipients, and polymers) into a single printed object with high precision. Extrusion-based 3D printing of polymers, especially natural mucoadhesive polymers, has been found to be beneficial to fabricate controlled drug release systems [106–108]. Bioprinting, a technique used to print scaffolds and cells into functional biomaterials, is being popularly used for 3D printing pharmaceuticals. Allevi 3D extrusion bioprinter has been widely used for printing oromucosal films. The use of extrusion-based bioprinters in pharmaceutical applications offers significant benefits, such as the ability to develop films with higher doses. Additionally, this method allows for the printing of thermolabile active ingredients and polymers without degradation, due to the lower temperatures required for printing compared to the higher temperatures needed in fused deposition modelling and hot melt extrusion techniques [52]. Research by Sjöholm, Sandler [109] used Allevi 3D extrusion bioprinter to print orodispersible films containing hydroxypropyl cellulose polymer combined with warfarin sodium as the active ingredient to provide paediatric and geriatric patients with personalized doses. Another study utilized a bioprinter to fabricate mucoadhesive oromucosal films in various shapes and sizes, considering the potential of these films to be tailored to meet specific patient needs for treating mouth ulcers [97].

A significant example of 3D printing's capability to produce personalized pharmaceutical doses was seen in 2015, when the FDA approved Spritam® (levetiracetam). This orodispersible tablet, created through 3D printing, highlighted the potential of additive manufacturing in developing tailored drug formulations [110]. Patient-specific personalization of drugs such as cannabinoids can be achieved through 3D printing techniques. The technology could transform how cannabis products are made, allowing for not just personalization but also precision and new forms of consumption. However, it's an emerging area that is still under research. Monou *et al*. [111] 3D printed films with polymers such as alginate, along with cannabinoids encapsulated in nanoparticles intended for promoting topical wound healing. Research is ongoing into oral food-grade formulations

of cannabidiol. In a study by Andriotis *et al*. [112], cannabinoid-based inks were developed using pectin and honey. These inks, when 3D printed and dried, resulted in the formation of solid structures suitable for potential oral delivery. Research by Abdella *et al*. [100] demonstrated the potential of 3D printed mucoadhesive films incorporating nanocarriers of cannabinoids to offer sustained release capabilities while also enabling personalized dosing. This highlights the flexibility and precision of 3D printing technology in creating tailored cannabinoid formulations with controlled release profiles. Highly lipophilic drugs like cannabinoids, coupled with their poor solubility, present significant formulation challenges. To overcome these issues and improve the bioavailability of the dosage forms, careful selection of excipients is crucial, especially when designing oromucosal delivery systems.

Semi-solid Dosage Forms

Semi-solid buccal formulations, including gels, ointments, creams, and pastes, offer numerous advantages for localized and systemic drug delivery via the buccal mucosa. Gels are widely favoured, particularly when formulated with mucoadhesive polymers, due to their ability to sustain drug release into mucosal tissues. However, they often struggle to provide precise drug dosages, which limits their applicability [61]. *In situ* gels address this limitation by allowing for accurate dosage delivery through a solution-based formulation [113]. Semi-solid dosage forms are typically prepared by either mixing the drug and excipients at room temperature (cold-method gelation), evaporating the solvent, or creating emulsions by combining oil and aqueous phases, particularly in the formulation of creams [114, 115].

Formulation Strategies for Enhanced Oral Mucosal Delivery of Cannabinoids

Cannabinoids such as cannabidiol (CBD) and tetrahydrocannabinol (THC) are highly lipophilic compounds, with their $\log P < 5$ values reflecting their significant hydrophobicity. This poor water solubility creates formulation challenges, making it difficult to incorporate them into conventional dosage forms [116]. Additionally, their low bioavailability upon administration can further hinder the development of effective cannabinoid-based therapies. The oral mucosal route, however, offers a promising alternative to enhance the bioavailability of cannabinoids. To optimize cannabinoid delivery via this route, formulation strategies must focus on integrating these lipophilic active ingredients effectively into dosage forms. This involves careful selection of excipients as well as the use of compounds that enhance the permeation of cannabinoids into the buccal cavity, ensuring efficient absorption and improved therapeutic outcomes. To address the physicochemical challenges of cannabinoids, researchers are exploring innovative dosage forms and advanced delivery mechanisms.

Development of Lipid-based Formulations

Cannabinoids such as CBD and THC are soluble in lipids and hence have been formulated as oral and oromucosal solutions using a wide range of oil carriers. Studies have consistently shown that lipid-based dosage forms exhibit superior bioavailability compared to lipid-free formulations. This advantage can be attributed to several key factors that work synergistically to enhance drug absorption and improve therapeutic outcomes. First, lipid-based formulations significantly improve the solubility of drugs, especially those that are poorly soluble in water, by incorporating the drug into lipid carriers such as emulsions, micelles, or liposomes. This increases the drug's availability for absorption in the gastrointestinal tract. In addition, lipid-based systems enhance membrane permeability, facilitating the passage of drugs through the intestinal walls and into the bloodstream. The lipid molecules interact with cell membranes, allowing for more efficient passive diffusion of the drug, particularly for lipophilic compounds that have difficulty crossing aqueous environments. Moreover, lipid-based formulations promote drug absorption via the lymphatic system. Researchers have also proven the ability of medium-chain triglyceride oils to significantly improve the delivery of CBD [117]. However, oil-based formulations delivered via the buccal route face the issue of being unintentionally swallowed. Johnson *et al*. [118] found that the bioavailability of oral CBD capsules and sublingual CBD oils was similar, indicating that the CBD was likely swallowed before any absorption could occur through the oromucosal membrane.

Inclusion Complexes of Cannabinoids

Inclusion complexes are non-covalent molecular associations where a smaller guest molecule is encapsulated within the cavity of a larger host molecule, offering benefits like enhanced solubility, stability, and controlled release. Cannabinoids can be encapsulated within the cavity of a host molecule, typically a cyclodextrin or a polymer. Cyclodextrins, which are cyclic oligosaccharides, are commonly used as host molecules due to their unique ability to form inclusion complexes with a wide variety of substances, including hydrophobic compounds like cannabinoids. The host molecule's cavity allows the guest (the cannabinoid) to be trapped within, often improving its solubility, stability, and bioavailability. By forming inclusion complexes, the water solubility of cannabinoids is enhanced, making them more suitable

for oral, sublingual, or topical administration. Additionally, these complexes can help protect cannabinoids from environmental factors like oxidation and degradation, improving their shelf life and stability [119]. Studies have shown that incorporating cannabinoids as inclusion complexes developed with cyclodextrins or chemically modified cyclodextrins can improve the permeation, release, and bioavailability of cannabinoids in buccal formulations [120–122].

Cannabinoids in Nano-formulations

Nanoformulations, including nanoemulsions, nano-lipid carriers, and nanoparticles, are advanced dosage forms that improve cannabinoid stability, enhance absorption through oromucosal membranes, and increase bioavailability. These nanoformulations improve bioavailability through several mechanisms, such as altering surface characteristics, minimizing particle size, optimizing drug distribution, and safeguarding poorly soluble compounds. By reducing particle size, these formulations increase the surface area for absorption, leading to more efficient uptake by the body. Surface modifications can also enhance interactions with biological membranes, facilitating better penetration and absorption. Additionally, nanoformulations help protect sensitive, poorly water-soluble drugs from degradation, ensuring greater stability and more effective delivery to target sites. These strategies collectively enhance the therapeutic potential of cannabinoids by ensuring they are absorbed more efficiently and effectively in the body [123, 124].

The optimization of cannabinoid nanoformulations relies on precise mechanical and electrochemical engineering to overcome the inherent lipophilicity of CBD and THC. To achieve uniform particle size reduction, techniques such as High-Pressure Homogenization (HPH) and ultrasonication are employed to shear lipid droplets into the 50–200 nm range, significantly increasing the surface-area-to-volume ratio for rapid mucosal uptake [125]. Particle homogeneity and stability are often assessed via zeta potential measurements, with values exceeding approximately ± 30 mV generally associated with improved electrostatic stabilization and reduced aggregation, although steric stabilization via surfactants may also play a dominant role in some systems [126]. Furthermore, the transition from simple emulsions to Solid Lipid Nanoparticles (SLNs) or Nanostructured Lipid Carriers (NLCs) is significant for sustaining drug release. In these systems, the cannabinoid is encapsulated within a solid or semi-solid lipid core, which acts as a reservoir, slowing the diffusion rate and providing a controlled release profile that extends the therapeutic window while protecting the cannabinoids from enzymatic degradation in the oral cavity. This sustained-release mechanism, when coupled with mucoadhesive polymers, ensures that the drug remains at the absorption site long enough to penetrate the epithelial barrier effectively, maximizing bioavailability [100].

Despite promising preclinical outcomes, including improved stability and enhanced *in vitro* or *ex vivo* permeation, the long-term *in vivo* safety of cannabinoid nanoformulations remains insufficiently characterised. Potential concerns include nanoparticle accumulation, mucosal irritation, and formulation-dependent toxicity related to surfactants or lipid excipients [127]. Consequently, comprehensive toxicological evaluation and controlled clinical studies are required before nanoformulated cannabinoid systems can be considered suitable for routine oromucosal or buccal administration.

Incorporating Terpenes into Dosage Forms

The incorporation of terpenes into cannabis-based dosage forms not only enhances the flavour profile but also amplifies the therapeutic effects of cannabinoids through synergistic interactions. Both terpenes alone and in combination with cannabinoids have demonstrated a range of beneficial effects, including anti-inflammatory, analgesic, neuroprotective, and other therapeutic properties, as evidenced by numerous *in-vitro*, animal, and clinical studies. These studies suggest that the presence of terpenes may optimize the medicinal potential of cannabis by potentiating the biological activity of cannabinoids, offering a broader spectrum of health benefits [128]. Furthermore, terpenes are found to improve the permeation capability of cannabinoids. Terpenes are recognized for their safety by the U.S. Food and Drug Administration (FDA), and studies have found that naturally occurring terpenes are less toxic than synthetic permeation enhancers like laurocapram (Azone). This underscores the potential of terpenes as safer alternatives in various formulations, offering both therapeutic benefits and a lower risk of adverse effects [129, 130].

A comparative summary of formulation strategies with potential application in oral mucosal cannabinoid delivery, highlighting their advantages, limitations, and translational relevance, is presented in Table IV.

Cannabinoid Formulations Developed for Oromucosal Routes

Sprays

Formulations comprising cannabinoids as active ingredients for oromucosal delivery are being researched. Sativex, an oromucosal spray, is approved by the FDA for treating spasticity in multiple sclerosis (MS) patients and contains 70% of CBD and THC in similar ratios (1:1), 5% minor cannabinoids, and other phytochemicals of two standardised

Table IV Comparative Formulation Approaches for Oromucosal Cannabinoid Delivery: Advantages, Limitations, and Translational Considerations

Formulation approach	Typical oral mucosal dosage forms	Key advantages for cannabinoids	Major limitations in oromucosal delivery	References
Fast-dissolving matrices	Fast-dissolving buccal/sublingual films, wafers	Rapid disintegration; patient-friendly; suitable for low-dose CBD/THC; simple manufacturing	Very short mucosal residence time leading to involuntary swallowing; limited transmucosal absorption	[131, 132]
Mucoadhesive polymeric systems	Buccal/sublingual films, tablets, patches	Prolonged mucosal residence; higher local drug concentration; reduced first-pass metabolism; improved absorption consistency	Mouthfeel issues; need to balance adhesion and irritation; salivary wash-off	[101]
In situ gelling systems (thermo- or ion-triggered)	Thermosensitive or ion-activated buccal/sublingual gels	Uniform mucosal coverage; sustained cannabinoid release; improved comfort compared with solid patches	Weak mechanical strength without modifiers; limited mucoadhesion when used alone	[133]
Cyclodextrin-based systems	Inclusion complexes incorporated into films, gels, or sprays	Enhanced aqueous solubility of CBD/THC; improved dissolution and physicochemical stability; reduced crystallisation	Limited permeation enhancement alone; dilution effects; cost of modified cyclodextrins	[119–122]
Nano-enabled systems (polymeric or lipid nanoparticles in matrices)	Nanoparticles embedded within oromucosal films or gels	Protection of cannabinoids from degradation; sustained release; improved local concentration and penetration	Need for safety/toxicity evaluation; formulation complexity; risk of nanoparticle wash-off without mucoadhesive carriers	[100]
Lipid-based systems (nanoemulsions)	Pre-formed surfactant-stabilised nanoemulsions incorporated into oromucosal films, gels, or applied as mucosal dispersions	High solubilisation capacity for lipophilic cannabinoids; nanoscale droplets maintain drug in a solubilised state at the mucosal interface; improved dispersion and dose uniformity compared with crude oils	Risk of salivary wash-off and swallowing when used alone; formulation and long-term physical stability; need for *in vivo* validation	[125]
Permeation-enhanced systems (terpenes)	Oromucosal films, gels, or sprays containing terpenes	Synergistic effects, reversible lipid-disordering of mucosal epithelium; significantly enhances buccal permeation of cannabinoids	Irritation at higher concentrations; volatility; compatibility constraints with polymers	[128–130]
3D-printed buccal systems	Three-dimensionally printed films or patches	Dose personalisation; spatial control of cannabinoid and permeation-enhancer distribution; design flexibility	Regulatory uncertainty; scalability challenges; equipment and production costs	[100]

Several approaches (e.g. lipid-based systems) are well established for oral delivery but exhibit reduced effectiveness for buccal/sublingual administration due to involuntary swallowing and limited mucosal residence time

cannabis plant extracts. It is also currently under phase III clinical trial for the treatment of cancer pain and is being investigated for therapeutic effects in polyneuropathy, HIV-associated neuropathy, and palliative care [44, 47, 134]. However, formulation limitations of the spray include the need for repeated administration to achieve desired effects [12], varying onset of action (15–40 min) [13], and excipients such as ethanol causing ulcers and lesions due to frequent use [14]. Furthermore, similar 11-OH-THC/THC ratios were observed with both Sativex and oral formulations, indicating failure to evade first-pass effects, as it was found that a larger amount of the dose administered was accidentally swallowed [11, 134].

Pilot studies of NanaBis™, a buccal spray containing aqueous soluble nanoparticle solutions of CBD and THC, demonstrated that it was two times higher in bioavailability when compared with Sativex. The formulation comprises of strategic delivery of cannabinoids using nanoparticles, which enhance their absorption from mucous membranes. More than 40% of the patients with progressive cancer experiencing severe pain (total number of participants, n = 25) reported amelioration from pain, measured by their mean pain scores upon administering up to 3 sprays every 4 h. This spray is currently under clinical trial phase III for opioid management in metastatic cancer patients. It was noted that 72% of the patients reported mild or moderate drowsiness, nausea, and vomiting [135]. Similarly, Provenzano *et al*. [124] formulated a solution of cannabinoid nano-emulsion with the ability to self-assemble. The *in-vivo* bioavailability of the formulation was found to be higher when compared with oral formulations of cannabinoids. Such formulations of nanoparticles and nanoemulsions require frequent administration and lack evidence demonstrating effective drug penetration.

Solid Dosage Forms

Alternative to sprays, research has also explored formulation of solid dosage forms to deliver cannabinoids through the oromucosal routes. Solid formulations containing complexes of THC/CBD with cyclodextrins, which are cyclic oligosaccharides known to improve the lipophilicity of the API, were developed as either compressed tablets or as gelatine capsules to enhance the bioavailability of the cannabinoids [121, 122]. Mannila *et al*. [122] identified in their later research that naturally available β cyclodextrin could be added at lower bulk masses compared with randomly methylated cyclodextrins. These complexes were found to have quicker dissolution than when using plain cannabinoids in capsules and superior bioavailability compared with oral administration of ethanolic cannabinoids [120]. However, the formulation faces disadvantages of low residence time in the sublingual region, which might lead to the cannabinoids being swallowed rather than penetrating the mucosal area. Cannabinoid lozenges (Trokie® Lozenges) as alternative formulations to Sativex for treating chronic pain and palliative care are being researched. These Lozenges are susceptible to accidental swallowing, have reported late-onset of action, and lack validated pharmacokinetic data in humans [136]. Monton *et al*. [137] developed tablet wafers containing cannabis extracts that disintegrate in saliva, enabling the immediate release of cannabinoids into the oromucosal cavity for fast absorption. However, the wafers can be unintentionally swallowed and require *in-vivo* studies to validate their effectiveness and safety.

Mucoadhesive Formulations

As understood previously, the use of excipients that can adhere to the mucosa might be suitable for carrying the active ingredient stably. Itin *et al*. [138] fabricated a mucoadhesive shell by compressing mucoadhesive polymers carbopol and hydroxypropyl cellulose of high molecular weight (Klucel) and other excipients. Upon completion of adhesion of the shell to the porcine buccal mucosa in both *ex-vivo* and *in-vivo* studies, CBD in 1:1 ethanol: propylene glycol was administered orifice of the mucoadhesive shell facing away from the mucosa, and the shell was able to hold the solution without any leakages from inside. The entire formulation was removed within 8 h. The researchers were able to show in their *in-vivo* study, slow and controlled permeation of CBD in the oral mucosa, upon measuring the plasma levels. However, there was a lack of correlation between their *in-vivo* and *ex-vivo* permeation studies, as no permeation occurred when using a diffusion chamber. The researchers attribute this to the ineffectiveness of the organic solvents used to facilitate CBD release into the receiver chamber. Furthermore, the formulation composition used was similar to Sativex, thus not eliminating the long-term adverse effects associated [138].

Taha *et al*. [101] employed hot melt extrusion to develop buccal films containing CBD, utilizing various mucoadhesive polymers. Among these, carbopol was found to exhibit superior mucoadhesive strength compared to hydroxypropyl cellulose and other polymers tested. Their work successfully demonstrated the effectiveness of these films for the immediate release of cannabinoids within the buccal cavity. Buccal bi-layered thin films of CBD were fabricated by Laoasoke *et al*. [102] using solvent casting technique. Such films demonstrated excellent mucoadhesive strength attributed to HPMC incorporated, and was able to sustain CBD release over 4 h. Abdella *et al*. [100] 3D printed buccal films containing nanolipid carriers of CBD to enhance the delivery and bioavailability of cannabinoids. These films were made mucoadhesive by incorporating polymers like hydroxyethyl cellulose and polyethylene glycol, which help the films adhere to the buccal

mucosa for prolonged release. The research demonstrated the feasibility of creating personalized dosage forms for CBD, as well as the potential for developing sustained-release cannabinoid formulations. However, the safety, efficacy, and *in-vivo* performance of these nanoparticle-based systems still need to be validated through clinical studies to ensure their effectiveness and suitability for therapeutic use.

Söpper *et al*. [139] created buccal dosage forms with mucoadhesive polymers, namely carbopol, chitosan, and HPMC, and incorporated CBD in mesoporous silica (carrier) into it. Mucoadhesion with carbopol surpassed other polymers used. However, the use of carbopol also led to lower mucopenetration, which was found to be enhanced by using 5% propylene glycol as the penetration enhancer. While carbopol-based systems were not superior in terms of overall mucosal penetration, the study demonstrated the critical role of polymer–excipient combinations in balancing adhesion, residence time, and permeation, highlighting the need for rational formulation optimisation in buccal cannabinoid delivery.

Recent buccal formulation research has also explored nanoemulsion-based platforms to aid the delivery of highly lipophilic cannabinoids across the oral mucosa. For example, a stable, surfactant-stabilized nanoemulsion of a high-CBD cannabis extract was developed using a Tween/Span mixture to produce nanoscale droplets with favourable cohesion, wettability, and physical stability for oral mucosal application. *In vitro* characterisation demonstrated uniform nanoscale droplet size and strong association with model membranes, suggesting enhanced mucosal retention compared with crude cannabis oil and improved suitability for localized mucosal interaction. Such nanoemulsion systems show promise in addressing solubility and dispersion limitations of lipophilic cannabinoids at buccal sites, although further work is required to optimise residence time and confirm *in vivo* transmucosal absorption [125].

Conclusions

Oromucosal drug delivery represents a compelling and clinically relevant strategy for cannabinoid administration, offering the potential to partially bypass first-pass hepatic metabolism, improve systemic bioavailability, and provide more consistent pharmacokinetic profiles compared with conventional oral formulations. The buccal route further enables flexible dosing strategies, supports sustained or controlled drug release, and enhances patient compliance through non-invasive and easily removable dosage forms.

This review highlights the significant progress made in the design and fabrication of oromucosal cannabinoid delivery systems. Ongoing research into mucoadhesive polymers, *in-situ* gel systems, and nanocarrier-based formulations is focused on enhancing cannabinoid retention, mucosal permeability, and bioavailability, with particular emphasis on optimizing formulation parameters and understanding their mechanistic interactions with the buccal mucosa. Advances in formulation techniques, such as solvent casting, hot melt extrusion, and 3D printing have further expanded the possibilities for creating patient-friendly and personalized cannabinoid therapies.

Despite these advances, several critical challenges remain. Variability in mucosal residence time, salivary wash-off, and inconsistent transmucosal absorption continue to limit the clinical translation of many buccal/sublingual formulations. In addition, while nano-based systems and permeation-enhanced formulations show promising improvements in solubilisation and local drug concentration, their long-term safety, mucosal tolerability, and *in vivo* pharmacokinetic performance remain insufficiently characterised. Future research should therefore focus on systematic comparative evaluations of buccal dosage forms, optimisation of formulation parameters governing mucoadhesion and release kinetics, and mechanistic studies elucidating cannabinoid–mucosa interactions. Importantly, comprehensive toxicological assessment and well-designed clinical trials are essential to establish safety, efficacy, and reproducibility. With continued formulation optimisation and clinical validation, cannabinoid-based buccal delivery systems are well positioned to become reliable and patient-centred therapeutic platforms.

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Declarations

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