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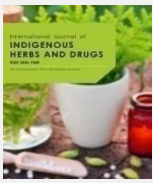

BUPRENORPHINE BUCCAL FILM: A NOVEL MUCOADHEVISE APPROACH FOR CHRONIC PAIN MANAGEMENT

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ABSTRACT

Chronic pain remains a significant clinical challenge requiring long-term, effective, and safe therapeutic strategies. Buprenorphine buccal film has emerged as a novel mucoadhesive drug delivery system that offers an alternative approach to conventional opioid therapy. Buprenorphine is a partial μ-opioid receptor agonist and κ-opioid receptor antagonist with high receptor affinity, providing potent analgesia while exhibiting a ceiling effect on respiratory depression. The buccal film formulation adheres to the oral mucosa, enabling direct systemic absorption and avoidance of first-pass hepatic metabolism, thereby enhancing bioavailability and ensuring consistent plasma drug levels. This review discusses the pharmacological profile of buprenorphine, the principles of mucoadhesive buccal drug delivery, formulation strategies, and clinical efficacy of buprenorphine buccal films in chronic pain management. Additionally, safety, tolerability, patient compliance, and therapeutic advantages over traditional oral and transdermal opioid formulations are critically evaluated. Overall, buprenorphine buccal film represents a promising advancement in chronic pain therapy, combining effective analgesia with improved safety and patient-friendly drug delivery.

Keywords: *Buprenorphine, opioid,buccal patch, mucoadhesion, swelling, pain management.*

INTRODUCTION

Buprenorphine is a semi-synthetic opioid derivative used primarily for the treatment of opioid use disorder (OUD) and chronic pain management. As a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor, buprenorphine offers a unique pharmacological profile with a ceiling effect for respiratory depression, making it a safer alternative to full opioid agonists [1].

Buprenorphine buccal film represents an advanced transmucosal drug delivery system developed to improve the therapeutic efficacy and safety of buprenorphine in the management of chronic pain and opioid use disorder. Buprenorphine is a semi-synthetic opioid derived from thebaine, characterized pharmacologically as a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor. This dual activity contributes to potent analgesic effects while exhibiting a ceiling effect on respiratory depression, thereby offering an improved safety profile compared to conventional full opioid agonists [2].

The buccal film dosage form is designed for application to the buccal mucosa, allowing direct absorption of the drug into systemic circulation and bypassing hepatic first-pass metabolism. This route enhances bioavailability, ensures rapid onset of action, and provides more predictable plasma concentration profiles. Buccal films are thin, flexible, and mucoadhesive, ensuring prolonged residence time at the site of administration and improved patient adherence, particularly in patients who experience difficulty swallowing solid oral dosage forms [3].

Clinically, buprenorphine buccal films are approved for the management of chronic pain requiring long-term opioid therapy when alternative treatment options are inadequate. Commercial formulations such as Belbuca employ advanced film-forming and bioadhesive technologies to enable precise dose titration and sustained drug release. Compared with oral opioids, buprenorphine buccal films demonstrate reduced gastrointestinal side effects, lower abuse potential, and minimized risk of overdose [4].

Overall, buprenorphine buccal film combines the pharmacological advantages of buprenorphine with the

benefits of buccal drug delivery systems, making it a promising therapeutic option. Ongoing research continues to focus on formulation optimization, bioavailability enhancement, and expansion of clinical applications, highlighting its significance in modern pain management and opioid therapy [5].

PHARMACOLOGY

Buprenorphine is extracted from natural sources (Thebaine) or synthesized. it is converted to its Hcl salt for better solubility. Buprenorphine Hcl is hydrophilic(water-soluble) due to the Hcl salt form, making it more soluble in aqueous environments compared to the base form.

The base form of buprenorphine is lipophilic (fat-soluble).The Hcl salt is often used in formulations for better solubility a-nd absorption in aqueous environments like the buccal mucosa [6].

Mechanism of action

Buprenorphine Hcl is a partial agonist at the mu-opioid receptors and an antagonist at the kappa-opioid receptors,and an agonist at the ORL-1(nociceptin) receptor [7].

Table1: mechanism of action of a buprenorphine buccal film

Receptor type	Action	Clinical Outcome
Mu receptor	Partial Agonist	Potent analgesia with a "ceiling" on respiratory depression.
Kappa(k) receptor	Antagonist	Reduced risk of dysphoria and hallucinations.
ORL-1 receptor	Agonist	Potential synergistic analgesia and reduced tolerance.
Dissociation	Slow	Long duration of action and difficult to reverse with Naloxone.

Cellular Signaling (Intracellular Level)

- G-Protein Coupling: Activation of inhibitory Gi/Go proteins.
- Adenylate Cyclase Inhibition: Decrease Cyclic AMP(cAMP) production.
- **Ion Channel Modulation**
  - K+ Channels: Hyperpolarization of the postsynaptic neuron (k+ efflux)
  - Ca2+ Channels: Inhibition of presynaptic Ca2+ influx [8].

Physiological Result

- Reduced Neurotransmitter Release: Decreased release of substance P, Glutamate, and GABA.
- Inhibition of Pain Signaling: Blocks the transmission of nociceptive (pain) signals up the spinal cord to the brain.

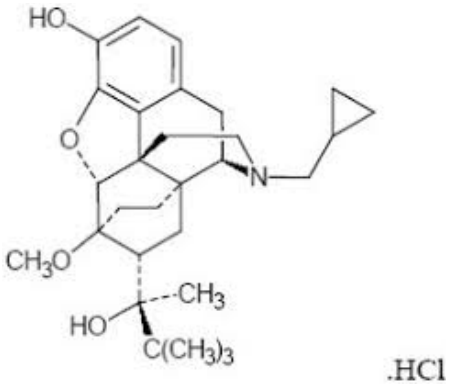


Figure 1: structure of buprenorphine

Chemical formula: $C_{29}H_{41}NO_4$

Pharmacokinetics

Absorption

The BEMA technology uses a backing layer that ensure unidirectional flow of the medication toward the buccal surface. This minimizes the amount of drug washed away by saliva or swallowed, which would otherwise lead to poor absorption in the GI tract. Saliva instantly wets the hydrophilic polymers in the film, causing them to swell and release the medication for absorption.

Plasma drug concentration increased with increasing dose, as expected, with most separation between doses occurring at 2 h postdose for buprenorphine Tmax occurred earlier, and Cmax and the abuse quotient were higher with other from the IR product than with buprenorphine from BBF . Tmax was similar across doses, while Cmax and the abuse quotient increased with higher doses.

Plasma levels of buprenorphine increased with the buccal dose. There was wide interpatient variability in the buccal absorption of buprenorphine , but within subjects the variability was low. Both Cmax and AUC of buprenorphine increased with the increase in dose (in the range of 0.875 to 6.3 mg), although the increase was not directly doseproportional [9].

Dosage Forms and Strengths

buccal film is supplied as a yellow rectangular buccal film in three dosage Strengths:

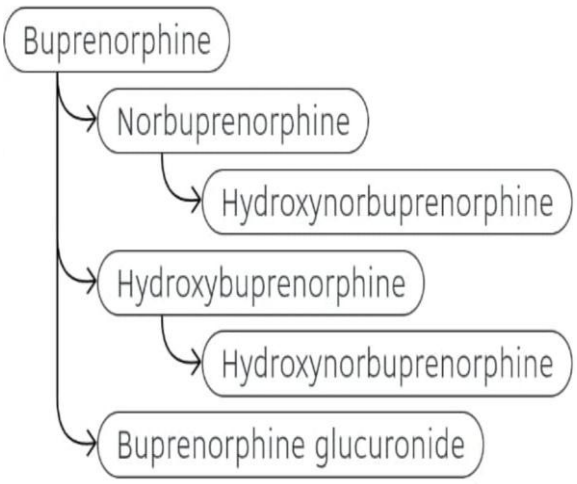
- buprenorphine 2.1 mg.
- buprenorphine 4.2 mg
- buprenorphine 6.3 mg

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha- and beta-globulins.. Buprenorphine has a large estimated volume of distribution, ranging from 188 to 430 L.The buccal route allows the drug to enter the systemic circulation directly through the oral mucosa, bypassing the GIT and initial liver metabolism(first-pass effect). Steady- state plasma concentrations are typically reached within 3days of starting twice-daily dosing. Themean plasma elimination half life for the buccal formulation is approximately 22.6 to 26 hours [10].

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity [11].



Extretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated). In feces, almost all of the buprenorphine was free (buprenorphine, 33% free and 5% conjugated) [12].

Pharmacokinetic parameters:

Table 2: Median T_{max}, Mean, Mean (SD), (min,max),h,C_{max}(SD), Abuse quotient of burprenorphine.

300µg	2.15(2.13,3.20)	0.413(0.215)	0.17(0.09)
600µg	3.13(1.12,6.00)	0.796(0.853)	0.30(0.20)
900µg	2.17(2.13,6.00)	1.06(0.414)	0.41(0.11)

Penetration

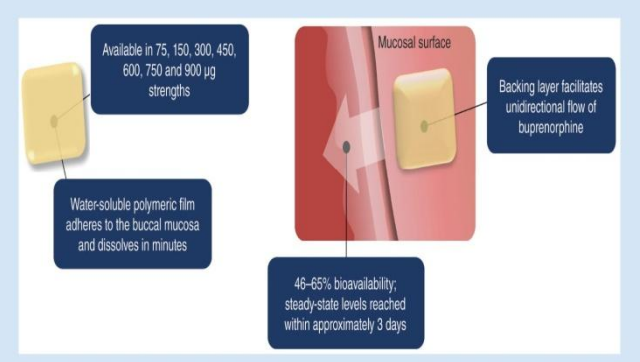
The buccal mucosa is an intensively vascularized tissue with vessels that drain into the jugular vein, although drugs penetrate the epithelium to enter directly into systemic circulation rather than undergoing first-pass hepatic elimination in the gastrointestinal tract [13]. once the film adheres to the mucosal tissue and hydrates with saliva, buprenorphine penetrates the epithelium through two primary pathways:

Transcellular(lipoidal) route.

Paracellular (aqueous) route.

Applications of Buprenorphine Buccal Film

- Management of chronic pain
  Used for severe, persistent pain that requires long-term opioid treatment.
- Pain not controlled by non-opioid analgesics
  Prescribed when pain is not adequately managed with NSAIDs, acetaminophen, or weaker analgesics.
- Alternative to traditional opioids
  Buprenorphine has a lower risk of respiratory depression compared to full opioid agonists.
- Cancer-related chronic pain
  Helpful in patients with moderate to severe cancer pain requiring continuous analgesia [14-15].
- Musculoskeletal pain
  Used in chronic conditions such as arthritis, back pain, and joint disorders.
- Neuropathic pain (adjunct therapy)
  Cin an be used as part of a treatment plan for nerve-related pain.
- Patients with difficulty swallowing tablets
  Buccal film is useful for patients who cannot swallow oral dosage forms.
- Pain management in Elderly patients
  Belbuca is preferred in elderly populations because of celling effects on respiratory depression.
- Stable plasma drug levels
  Buccal absorption avoids first-pass metabolism, providing consistent analgesic effect.
- Long-term pain therapy
  Suitable for round-the-clock pain control, not for acute or short-term pain [16].



Advantages of Buccal Film

- Bypasses first-pass metabolism
  Drug is absorbed directly into systemic circulation, improving bioavailability.
- Rapid onset of action
  Buccal mucosa is highly vascularized, allowing faster drug absorption.
- Improved patient compliance
  Thin, flexible film is easy to apply and comfortable to use.
- Suitable for patients with swallowing difficulties
  Ideal for pediatric, geriatric, and dysphagic patients [17].

Comparision of buprenorphine as buccal patch and transdermal patch [18]:

Feature	Buccal Film (Belbuca)	Transdermal Patch (Butrans)
Bioavailability	Higher (~46–65%)	Lower (~15%)
Onset of Effect	Faster (~2.5–3 hr)	Slower (24–72+ hr)
Dose Range	Wide (75–900 µg)	Limited (5–20 µg/h)
Dosing Frequency	Twice daily	Once weekly
Dose Flexibility	High	Moderate
Convenience	Moderate	High

CONCLUSION

The clinical data presented here support buprenorphine buccal film as a generally welltolerated treatment option for chronic pain that effectively and continuously reduces pain. The Schedule III classification of buprenorphine by the US Drug Enforcement Administration confirms its enhanced safety profile and reduced abuse potential As a result, buprenorphine should be considered a first-line

treatment for chronic pain in appropriate patients identified by risk/benefit analyses . The increased bioavailability (4665%) and extended available dose range(75–900 µg) of buprenorphine buccal film compared with that of the buprenorphine transdermal system support its preferential consideration for chronic pain treatment. These characteristics combined with The US Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force recommendations support buprenorphine buccal film as a first-line treatment option for chronic pain management at a time when better-tolerated options are needed.

AUTHOR CONTRIBUTIONS

All authors contributed equally.

COMPETING INTEREST STATEMENT

No conflict of interests regarding publication of this paper.

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ETHICAL APPROVAL

Not applicable.

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