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Mucoadhesive buccal formulation for anti-migraine agents: A comprehensive review

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Abstract
The number of migraineurs worldwide has grown dramatically over the past thirty years, with only considerable differences in incidence rates among regions and countries. The two primary varieties of migraines are aura-accompanied and without an aura. Each has peculiar characteristics and causes. The oral route of administration is the most preferred route for drug delivery, even though there are several disadvantages, such as enzymatic breakdown and delayed absorption. Other modes of administration may be employed to provide potential solutions. In this review, attempts are made at differentiated drug delivery strategies that need to overcome the limitations of oral administration by examining mucoadhesive buccal formulations for anti-migraine drugs. The study presents a comprehensive evaluation of the uses of mucoadhesive buccal formulations on anti-migraine medications by gathering data from numerous sources, including research publications. The article analyses mucoadhesive buccal formulations used in tablets, films, patches, hydrogels, and ointments. Research samples have also been studied using the mucoadhesive buccal formulation of several anti-migraine medications, research-evaluated in the article. The article offers details of specific formulations that have been researched for various anti-migraine drugs and provides perspective on the potential of mucoadhesive buccal formulations for effective drug delivery.

Keywords: Migraine, anti-migraine, mucoadhesive buccal formulation, buccal films, patches

Introduction

A severe throbbing and pulsing pain that comes and goes, usually on one side of the head, is the telltale sign of a migraine. This pain results from the activation of nerve fibres within the walls of blood vessels in the brain, specifically within the meninges a protective three-layered membrane enveloping the brain and spinal cord [1]. A thirty-year increase in migraine instances has been seen, with an age-standardized prevalence rate of 1142.54 per 100,000 population in 2019 compared to 62.6 million in 1990. From 1990 to 2019, there was a net drift of 0.089% in the prevalence rate of migraines, according to the widely applicable APC model. In high-middle SDI areas (South Asia, Oceania, and Latin America), the all-age prevalence rate for migraines was 1030.94 per 100,000 people; in low-middle SDI countries, it was 1242.37 per 100,000. At 1191.58 per 100,000 people, the age-standardized prevalence rate, on the other hand, was lowest in low SDI regions and highest in high SDI regions. The APC model's estimation of net drift outcomes shows similar trends. The top four nations in the world in terms of the number of migraine episodes were India (17.9 million), China (12.9 million), the United States (3.8 million), and Indonesia (3.5 million). Together, these countries accounted for 43.6% of all migraine events worldwide. The all-age prevalence rates in 2019 were most significant in Paraguay (1694.58 per 100,000 people) and lowest in Japan (727.36 per 100,000 people) [2].

Categories of migraine

Migraine has two major categories

1. **Migraine with aura:** A migraine with aura is a cluster of related neurological symptoms that often manifest before the headache stage. However, they can sometimes start later in the headache phase or persist. It is a collection of focused neurological, visual, sensory, linguistic, and motor symptoms that are reversible, progressively manifest, spread, and disappear. Between 15% and 1/3 of migraineurs report having an aura with their migraine [3, 4].

2. **Migraine without aura:** Without aura, migraine is more common and does not involve associated focal neurologic symptoms either before or during the headache. The underlying mechanism of migraine without aura is more intricate and is impacted by sociophysiological-environmental variables, sex, and genetics [3, 5].

Diagnosis

The diagnosis of migraine is based on the different criteria as mentioned in the table 1

Table 1: Criteria for diagnosis of Migraine

ICHD-3 criteria for diagnosis of migraine (3, 6)		
Migraine without aura	**Migraine with aura**	**Chronic migraine**
A. Have at least five experiences that fit the B–D criteria. B. Put up with four-seventy two hour headache bouts (if left untreated or managed ineffectively). C. Display headaches that have at least two of the four traits listed below: 1. pulsating quality 2. unilateral location 3. The intensity of pain is moderate to severe 4. Anxiety brought on by or contributing to an avoidance of regular exercise. D. When experiencing a headache, exhibit one or more of the following symptoms: 1. sonophobia and photosensitivity 2. Nausea and Emesis E. Exclude any further possible diagnosis.	A. Two or more assaults meeting requirements 2 and 3 B. One or more of the completely reversible aura symptoms that follow: 1. Ocular 2. Somatosensory 3. Aphasic or Linguistic 4. Neuromuscular 5. Brainstem 6. Retinotic C. Three or more of the six qualities listed below:- 1. Over ≥five minutes, at least one aura symptom spreads gradually. 2. Each aura symptom lasts between five to sixty minutes. 3. The occurrence of two or more successive aura symptoms 4. At least one positive aura symptom 5. at least one unilateral aura symptom 6. Within 60 minutes of the aura, a headache appears or follows D. Not clearly clarified by another diagnosis on the ICHD-3	A. Have headaches that fit criterion B and C and are migraine or headaches similar to tension headaches for at least fifteen days a month for a minimum of three months. B. A patient must have at least five episodes of these headaches that meet the B and C criteria for migraine with aura or the B–D criteria for migraine without aura. C. Come across any of the following on ≥8 days/month for >3 months: 1. migraines with aura that meet criterion B and Ccriteria 2. C & D criteria for migraine without aura 3. Headaches that the patient initially believed were migraines and that were relived by triptans or ergot derivatives. D. Exclude any other possible diagnosis.

Treatment for migraine

Effective management of migraine includes both acute treatment to alleviate symptoms during an attack and preventive therapy to reduce the frequency and severity of future episodes by using different drugs and dosage form as given in the table 2 and table 3.

Table 2: Acute migraine treatments with proof of effectiveness [7]

Established efficacy	Probably effective
Migraine-specific	
Geptans	
Lasmiditan	
Ergotamine derivatives	Other forms of dihydro ergotamine
Triptans	
Combination analgesic: Acetaminophen + aspirin +caffeine	IV magnesium
	Antiemetics: chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine
	Isometheptene-containing compounds
Nonspecific: NSAIDs : celecoxib, diclofenac, naproxen Aspirin, Oral solution, ibuprofen	NSAIDs : IM ketorolac, IV ketoprofen, and flurbiprofen

Table 3: Treatments for the prevention of migraine with established efficacy

Established efficacy	
Oral	Parental
Divalproex sodium	Galcanezumab
Propranolol	Erenumab
Timolol	Fremanezumab
Metoprolol	OnabotulinumtoxinA
Frovatriptan	Eptinezumab
Valproate sodium	
Topiramate	
Candesartan	

Emphasis on buccal formulations

In drug administration, the oral route is the preferred and widely adopted method due to its patient-friendly nature, painless application, and the convenience of self-medication. The flexibility of a controlled dosing schedule further distinguishes it from other delivery systems. However, this strategy has several significant disadvantages, such as the first-pass impact gastrointestinal tract enzymatic breakdown and a delay in absorption, posing challenges for drugs requiring rapid onset. To address these issues,

researchers have explored alternative delivery routes such as ocular, transdermal, buccal, nasal, vaginal, sublingual and pulmonary, rectal pathways. Among these, the buccal region of the oral cavity emerges as a favourable site for the administration of drugs. Leveraging the buccal mucosal membrane offers systemic and local drug effects opportunities, with advantages such as ease of administration, reduced toxicity, and enhanced bioavailability. The buccal route's accessibility, smooth muscle expanse, and relative immobility make it conducive to administering retentive dosage forms, providing a promising avenue for improving drug efficacy and patient experiences in medication administration within the evolving drug delivery landscape [8, 9, 10].

Mucoadhesive buccal formulation

Adhesion is defined by the American Society of Testing and Materials as the contact between a pressure-sensitive adhesive and a surface. It is the state in which interfacial forces which might include interlocking action, valence forces, or both—keep two surfaces together. Mucoadhesion is the term used to describe an adhesion involving mucus or mucous membranes [11].

Since the 1980s, there has been interest in the buccal administration of the desired medication utilizing mucoadhesive polymers [12]. The term "mucoadhesion" was first used by Wisconsin University professor Joseph R. Robinson to describe a novel strategy for prolonging the duration of medication on the ocular surface [13]. In addition to the drug, a mucoadhesive formulation includes one or more hydrophilic polymers. It wets, expands, and releases the medication whenever the dosage form comes into contact with saliva [14].

Mechanism of mucoadhesion

An artificial material that interacts with mucous membranes to sustain or keep them together for an extended duration is called a "mucoadhesive." During the adhesion process, the mucoadhesion mechanism is often defined in two steps, as shown in Figure 1 [15].

1. **Contact stage:** When the mucoadhesive material and mucosal membrane come into contact, this is the moment when intimate wetting occurs. The mucus in the mucosal membrane wets the mucoadhesive polymer.

2. **Consolidation stage:** A robust mucoadhesion is created when the mucoadhesive material sticks to the mucous membrane through several physicochemical forces of attraction. Researchers termed this stage "consolidation" [16].

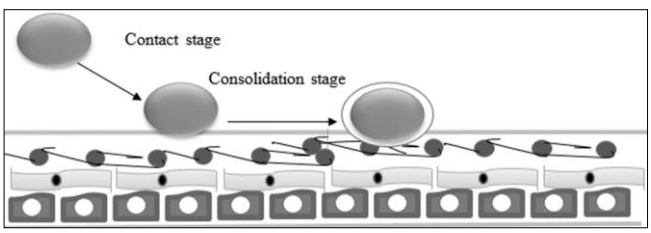

Fig 1: Mechanism of mucoadhesion

Theories of mucoadhesion

The process of mucoadhesion is complex, and multiple theories have been proposed to explain its complicated mechanism. These theories are mechanical interlocking, adsorption, electrostatic interactions, diffusion and interpenetration [17, 18].

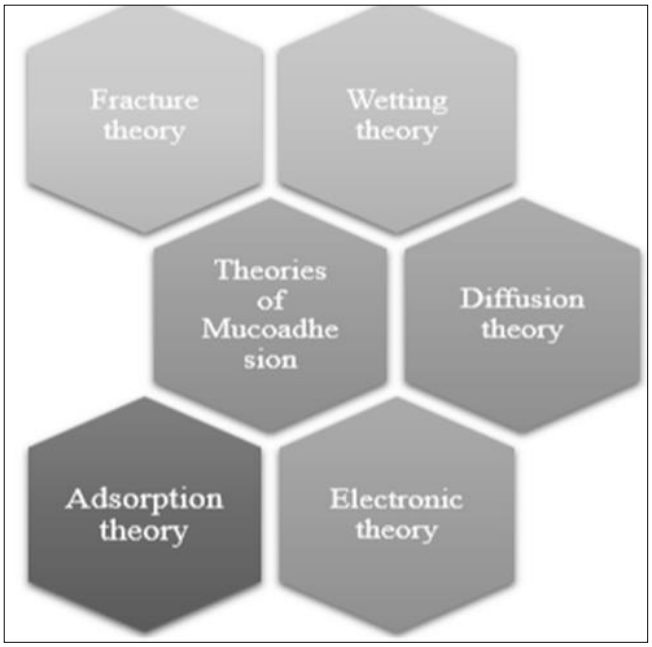

Fig 2: Theories of mucoadhesion

Wetting theory

This concept of adhesion is among the oldest and most well-researched. This theory explains best how the biological surface and low-viscosity bioadhesives or liquids bind together. Surface and interfacial tensions can be used to describe adhesion [19]. The energy released per square centimetre during the formation of an interface is known as the adhesion work. The wetting theory explains the thermodynamic work of adhesion and the contact angle between two substances. Dupre's equation provides the adhesion work [19, 20].

$$S_{a/b} = \gamma_b - \gamma_a - \gamma_{ab}$$

Where,

γ_b = surface energy of solid B

γ_b = surface energy of liquid A

γ_{ab} = surface energy between the solid and liquid.

For the bioadhesive substance to spread on the biological substrate, the value of $S_{a/b}$ must be positive. The contact angle when a bioadhesive liquid spreads out on a biological substrate is determined using the equation [21].

$$\text{Cos}\theta = \left(\frac{\gamma_b - \gamma_{ab}}{\gamma_a} \right)$$

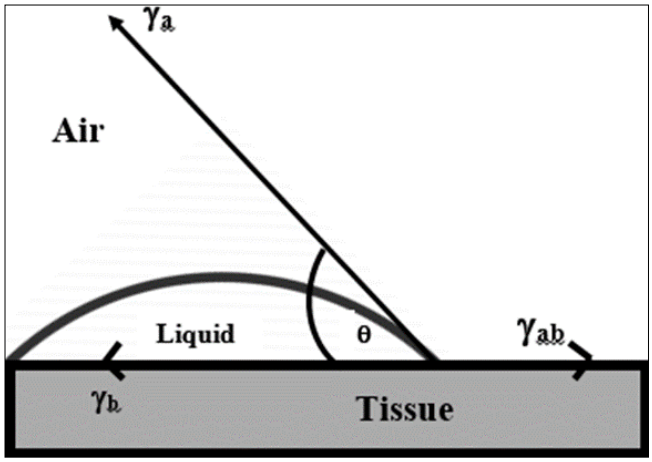

Fig 3: Representation of interfacial forces involved in the wetting theory

Electronic theory

The electronic theory considers the electrical charges of biological and mucoadhesive materials the opposite. As a result, electrons are transferred between two substances and a double electrical layer is formed when they come into contact at the interface. The strength of mucoadhesion is thus determined by the attraction forces present in this electronic double layer [22, 23]. As shown in the figure 4

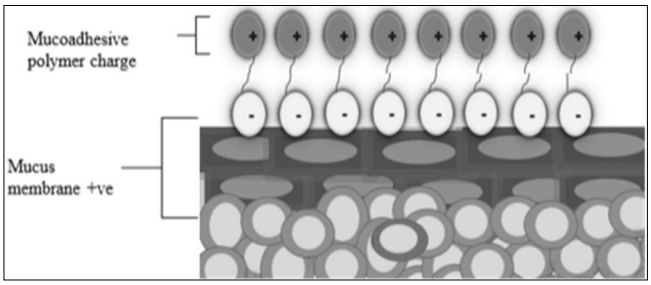

Fig 4: Electronic theory of mucoadhesion

Diffusion theory

The diffusion hypothesis posits that polymeric chains within the bioadhesive interpenetrate and undergo a transformation into glycoprotein mucin chains. This transformation allows them to penetrate deeply into the opposing matrix, facilitating the formation of a semi-permanent bond. The observable initiation of this process occurs at the initial point of contact. Concentration gradients drive the glycoprotein mucin chains and bioadhesive polymer chains into the mucus network and bioadhesive matrix until an equilibrium penetration depth is achieved [24, 25, 26].

$$S = \sqrt[3]{2tD}$$

Where,
t = contact period
D = diffusion coefficient.

Adsorption theory

Following the adsorption principle, after establishing first contact with both surfaces, the material can adhere due to surface forces between the atoms. These forces give rise to two distinct types of chemical bonding: [27, 28, 29].

1. Due to their high strength, primary (1^0) covalent bonds are undesirable in bio adhesion as they may lead to the development of long-lasting bonds.
2. Secondary (2^0) chemical bonds exhibit a variety of forces of attraction, such as hydrophobic and van der Waals forces, hydrogen bonds and electrostatic force.

Fracture theory

Fracture theory is the most extensively recognized theory based on the mechanical assessment of mucoadhesion. It provides a relationship between the pressures needed to separate polymers from mucus and the adhesive binding strength of those polymers. It is discovered that the work fracture increases as the extent of interconnection decreases or the network strands are more extended. It is essential to use the equation: [30, 31].

$$\sigma = (E \times \varepsilon/L)\ 1/2$$

Where the fracture strength is described by
(YM) = fracture energy - critical crack length (L).
YM- Young's modulus of elasticity

Types of Mucoadhesive buccal formulations

Many dosage formulations have been created in recent years for buccal medication administration. Different types of mucoadhesive buccal formulations are shown in the figure 5.

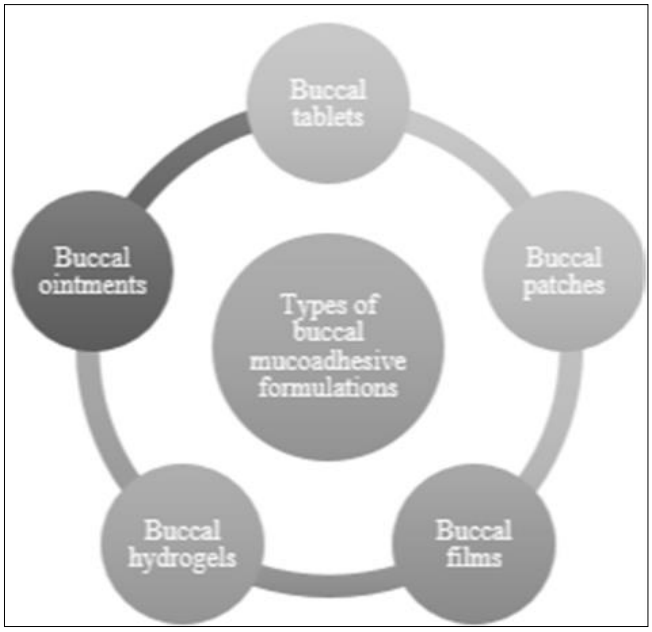

Fig 5: Types of mucoadhesive buccal formulations

Buccal tablets

Mucoadhesive tablets, designed for a buccal delivery system, leverage the dehydration of the buccal mucosa facilitated by saliva. Over recent years, significant advancements have been made in developing tablets with exceptional mucoadhesive properties, aiming to release drugs locally in the buccal cavity while achieving a systemic effect. These tablets can be formulated through the compression of drugs directly mixed with bioadhesive polymers through dispersions or solid solutions of drugs in bioadhesive polymers obtained by solvent spray drying. The

versatility of these formulations allows for targeted delivery of drugs. Buccal tablets, characterized by their small, oval shape and flat, have emerged as the most widely explored dosage form for buccal drug delivery. Notably, these tablets offer the advantage of allowing drinking and speaking without causing significant discomfort. Their ability to absorb saliva, stick to the mucosa, and remain in position until complete dissolution and drug release make them a promising option for efficient drug delivery through the buccal route [32, 33].

Table 4: List of Investigated Mucoadhesive Buccal Tablets of the Anti-Migraine Drug

Active ingredients	Investigators(ref.)
Eletriptan Hydrobromide	Harnath C *et al* (34), Ghadge PS *et al* (35)
Zolmitriptan	Gad S *et al* (36)
Rizatriptan Benzoate	Singh H *et al* (37), Mandal MK *et al* (38)
Sumatriptan	Fatima S *et al* (39)
Naratriptan	Rajesh G *et al*(40)

Buccal patches

Buccal patches are frequently used in oral drug administration systems. They are prepared by pouring a solution over a surface that includes a polymer, medication, and pertinent excipients. These patches can be as small as 1 to 15 cm^2, with a typical size of 1-3 cm^2. They are frequently shaped like ovals to fit nicely within the buccal mucosa. These patches usually comprise two layers: a) a drug-containing layer and b) an impermeable backing layer with mucoadhesive qualities. Because of its composition, the medication may be released under regulated conditions, resulting in efficient and precise distribution via the buccal route [41, 42].

Table 5: List of Investigated Mucoadhesive Buccal Patches of the Anti-Migraine Drug

Active ingredients	Investigator
Zolmitriptan	Rajendra MM *et al* (43), Sridhar G *et al* (44)
sumatriptan Succinate	Shidhaye SS *et al* (45)

Buccal films

Buccal films offer a promising option for buccal administration due to their easy application, versatility in achieving either local or systemic effects, mucoadhesive properties ensuring sufficient absorption time, and their small size and flexibility, promoting patient compliance. Recently developed, these films have become crucial in drug delivery, being both efficacious and novel while maintaining cost-effectiveness and high patient compliance.

Buccal films are designed to adhere to the buccal mucosa, offering the potential for both local and systemic effects. A notable advantage lies in their rapid entry into the systemic blood flow through the internal jugular vein, bypassing hepatic first-pass metabolism. This mechanism ensures high bioavailability and contributes to their efficacy. When applied to the tongue or oral cavity, this dosage form's water-dissolving polymer facilitates rapid hydration, adhesion, and dissolution, which promotes efficient systemic drug administration. The buccal film's large surface area makes quick wetting possible, speeding up medication absorption [46, 47].

Table 6: List of Investigated Mucoadhesive Buccal Films of the Anti-Migraine Drug

Active ingredient	Investigator (ref)
Almotriptan	Nair AB *et al* (48)
Rizatriptan benzoate	Salehi S *et al* (49)
Metoclopramide	Mady O *et al* (50)
Frovatriptan	Singh H *et al* (51)
Zolmitriptan	Pandey P *et al* (52)
Eletriptan Hydrobromide	Safhi AY *et al* (53)
Ergotamine tartrate and Caffeine anhydrous	Jelvehgari M *et al* (54)
Sumatriptan	Kaur P *et al* (55)

Buccal hydrogels

Hydrogels, polymer networks with hydrophilic groups, can take in and retain a large amount of water while forming a 3D structure due to cross-links within the polymeric network. This hydrophilic structure allows the hydrogel to swell significantly in aqueous media. Cross-links are required to prevent polymer chains from dissolving before use. Since water is an essential component of the human body, hydrogels' ability to engross large amounts of water makes them promising for biomedical applications. The interconnected 3D networks formed by cross-linked hydrophilic polymer chains enhance their suitability for a range of biomedical applications [56, 57].

Buccal gels and ointments

Mucoadhesive ointments, or abases, are more successful in local drug delivery to the mucosa. The hydrogel-forming polymers that comprise these or abases are distributed inside a hydrophobic base. They swell and stick to the application site when they touch saliva. The particular requirements of this application site must be adequately accommodated for ointments intended for treating oral mucous membranes. Saliva flows nonstop, and the buccal cavity's continual motion creates mechanical tension, making it difficult for the ointment to remain in place upon application.

Mucosal adhesive ointments must be sufficiently hydrophilic to form close contact with the skin and adhere to its surface to be effective. Furthermore, they must include a lipophilic ingredient to either stop or slow the washing away of the ointment base. This explains why these ointments frequently have a hydrogel ingredient floating in a lipophilic base, which only expands and becomes sticky when it comes into contact with saliva and mucous membranes. By addressing the problems presented by saliva flow and mechanical stress in addition to the requirement for adhesion, this strategic formulation guarantees excellent performance in the dynamic environment of the oral cavity [58, 59].

Conclusion

In conclusion, the review discusses the increasing prevalence of migraines globally and the top countries with the highest number of migraine incidents. It also provides information on the two major categories of migraines, with and without aura, and the various treatment options available. Additionally, the review explores the concept of mucoadhesive buccal formulations for drug delivery, including the theories and mechanism of mucoadhesion, as well as different types of buccal formulations such as tablets, patches, and films.

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