



Formulation and Evaluation of Pregabalin Buccal Film: A Research

Sanjay Kumar E ¹, Sarathi S ¹, Sasikala E ¹, Shobana S ¹, Malarvizhi K ², Dr. J. Karthi ³, Dr. S. Swarnalatha ⁴

^[1]- Department of Pharmaceutical chemistry, 8th Semester B. Pharm-Pallavan Pharmacy College, Kanchipuram

^[2]- Department of Pharmaceutics, Associate Professor - Pallavan Pharmacy College, Kanchipuram

^[3]-Department of Pharmacognosy, Professor Cum Principal-Pallavan Pharmacy College.

^[4]-Department of Pharmacology, Vice Principal and Head of the Department- Pallavan Pharmacy College.

E mail id: malarkathir.lk@gmail.com

ABSTRACT

Pregabalin is a widely prescribed $\alpha 2 \delta$ -subunit ligand of voltage-gated calcium channels used in the management of neuropathic pain, fibromyalgia, partial-onset seizures and generalized anxiety disorder. Despite its high oral bioavailability ($\geq 90\%$), conventional oral therapy requires frequent daily dosing owing to its short elimination half-life (~ 6.3 h), which can compromise patient compliance, particularly in geriatric and paediatric populations. The buccal mucosa offers an attractive alternative site for systemic drug delivery because it bypasses hepatic first-pass metabolism and gastrointestinal enzymatic degradation, while its rich vascularity supports rapid drug absorption. The present work reports the formulation of a mucoadhesive buccal film of pregabalin by the solvent casting technique using hydroxypropyl methylcellulose (HPMC) and chitosan as film-forming and mucoadhesive polymers, propylene glycol as plasticizer, mannitol as diluent/pore-former, and peppermint oil as a flavouring agent. The prepared films were evaluated for physicochemical, mechanical, mucoadhesive and in vitro release characteristics in accordance with standard pharmacopoeial and literature-reported methods. This article consolidates the drug and excipient profiles, formulation rationale, evaluation methodology and a review of twenty contemporary studies on mucoadhesive buccal and related transmucosal delivery systems, and discusses the findings in the context of the existing literature. The buccal film approach is presented as a promising, patient-friendly alternative dosage form capable of improving the bioavailability, onset of action and compliance associated with pregabalin therapy.

Keywords: Pregabalin; Buccal film; Mucoadhesive drug delivery; Solvent casting; HPMC; Chitosan; Neuropathic pain; Bioavailability.

1.INTRODUCTION

1.1. BUCCAL DRUG DELIVERY

Buccal drug delivery, a significant transmucosal pathway, serves for both localized and systemic administration of medications. The lining of the cheek (buccal mucosa) presents an easily accessible and practical location for drug application. This method offers distinct benefits compared to traditional oral drug delivery.

Unlike oral medications, which can be broken down in the digestive tract and processed by the liver before entering circulation (hepatic first-pass metabolism), drugs delivered via the buccal route bypass these issues.

The abundant blood vessels in the buccal mucosa efficiently transport the medication directly into the bloodstream. Buccal films are thin, pliable dosage forms made from polymers, engineered to attach to the buccal lining and gradually release the drug.

This prolonged contact enhances drug absorption into the body. Typically manufactured using film-forming and mucoadhesive polymers, these films can be especially advantageous for young children, elderly individuals, and those with swallowing difficulties. Furthermore, the specific polymer system employed allows for the controlled or sustained release of the medication.

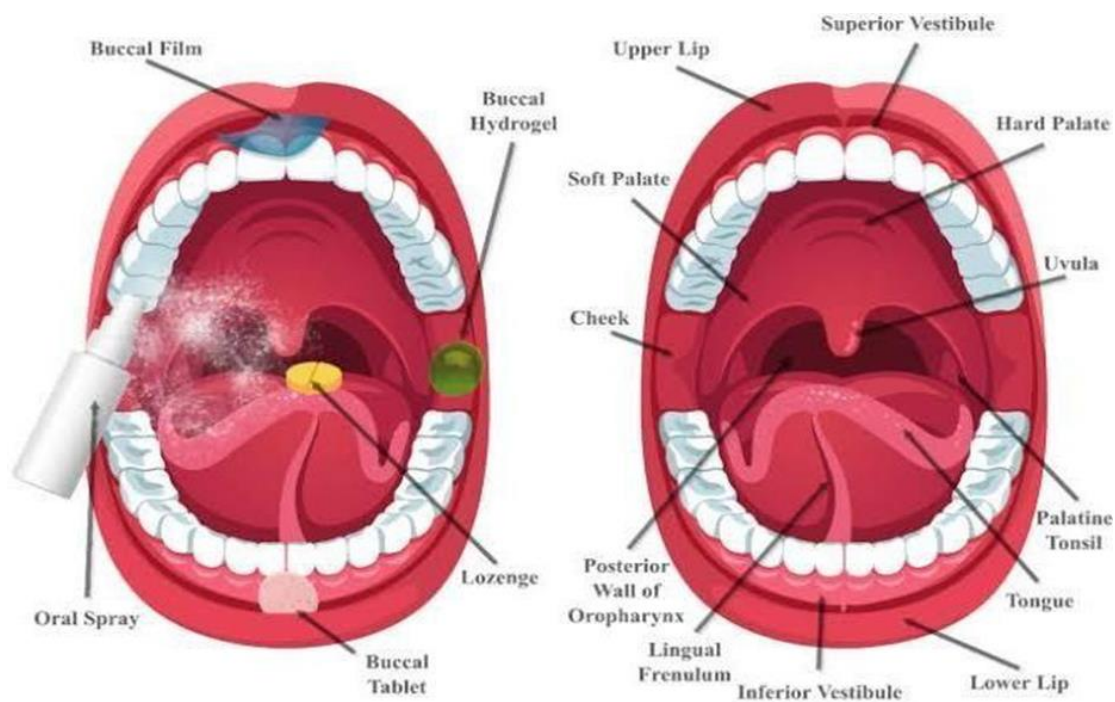


Figure:1

1.2. ANATOMY AND STRUCTURE OF THE ORAL CAVITY

The mouth, anatomically structured into the outer oral vestibule and the oral cavity proper, encompasses the lips, cheeks, hard and soft palates, and the floor of the mouth.

The vestibule is bordered by the cheeks, lips, teeth, and gums, while the oral cavity proper extends from the teeth and gums to the fauces.

Unlike the lining of the gastrointestinal tract, which consists of a single epithelial layer, the oral mucosa is characterized by multiple, variably differentiated cell layers.

Three main categories of oral mucosa are identified

- MASTICATORY MUCOSA:** It is keratinized and found on the gums and hard palate
- LINING MUCOSA:** It is non-keratinized and covers the cheeks, lips, floor of the mouth, and soft palate
- SPECIALIZED MUCOSA :** on the top of the tongue, featuring both keratinized and non-keratinized areas.

Mouth (Oral Cavity)

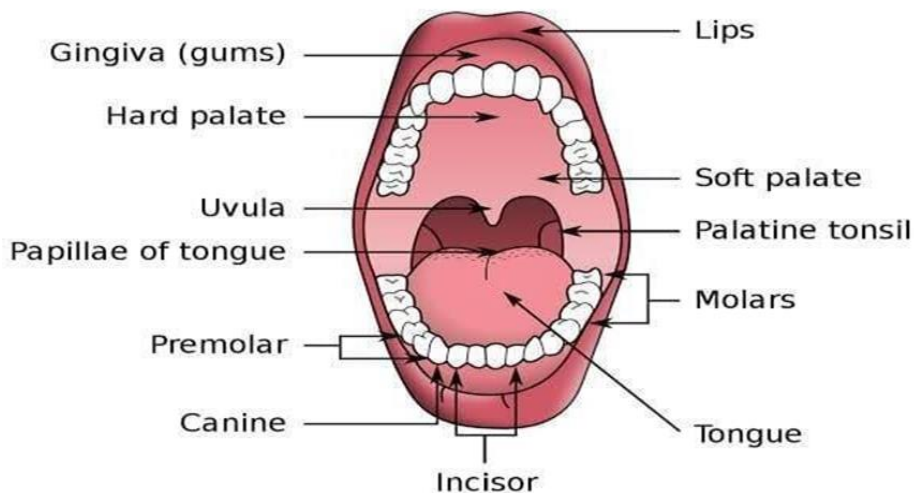


Figure:2

1.3. ROLE OF MUCIN

- a. Mucus is a substance that has a charge and is both sticky and elastic. It contains molecules called mucins, which are made up of proteins.
- b. These proteins have a lot of serine and threonine parts that get covered with sugar molecules.
- c. The mucins also have proline parts that stop them from forming straight shapes. This makes the mucin chains flexible, Stretched out.
- d. These special features help mucins hold water create a layer and connect with cells, surfaces and medicines.
- e. The pH of saliva is usually between 5.8 and 7.4.

1.4. FUNCTIONS OF MUCUS

- a) **Protection:** Mucus creates a layer that protects the surfaces of cells from being hurt by things like rough movement, chemicals, germs and harmful stuff. Its ability to repel water can also stop things that don't mix with water from getting through and keep stuff away from the tissue underneath.
- b) **Cell-cell adhesion:** Mucins can help cells stick to each other and keep the structure and strength of cell layers working
- c) **Lubrication:** Because mucins hold water mucus makes surfaces move smoothly. This helps with actions like swallowing, talking, blinking and moving things through body passages.
- d) **Bioadhesion in drug delivery:** Mucus can connect with special materials used in medicines and help them stay on the inside of the body. This Sticking can help medicines stay in one place longer make more of the medicine available where it is needed and help control how the medicine is released.

1.5. PERMEABILITY OF THE BUCCAL MUCOSA

Studies indicate that the lining of the cheek (buccal mucosa) can be 4 to 4000 times more permeable than the skin. However, this permeability is not uniform throughout the mouth, as it is influenced by variations in the

thickness of the epithelial layer and its degree of keratinization. Specifically, the buccal mucosa is characterized by being thicker and lacking keratin, while the sublingual mucosa is thin and also non-keratinized. The palatal mucosa, on the other hand, has an intermediate thickness but is keratinized.

As a result, the sublingual and buccal areas typically exhibit greater permeability compared to the palate. The primary barrier to permeability is understood to be the intercellular substance originating from membrane-coating granules found in the uppermost superficial epithelial layers.

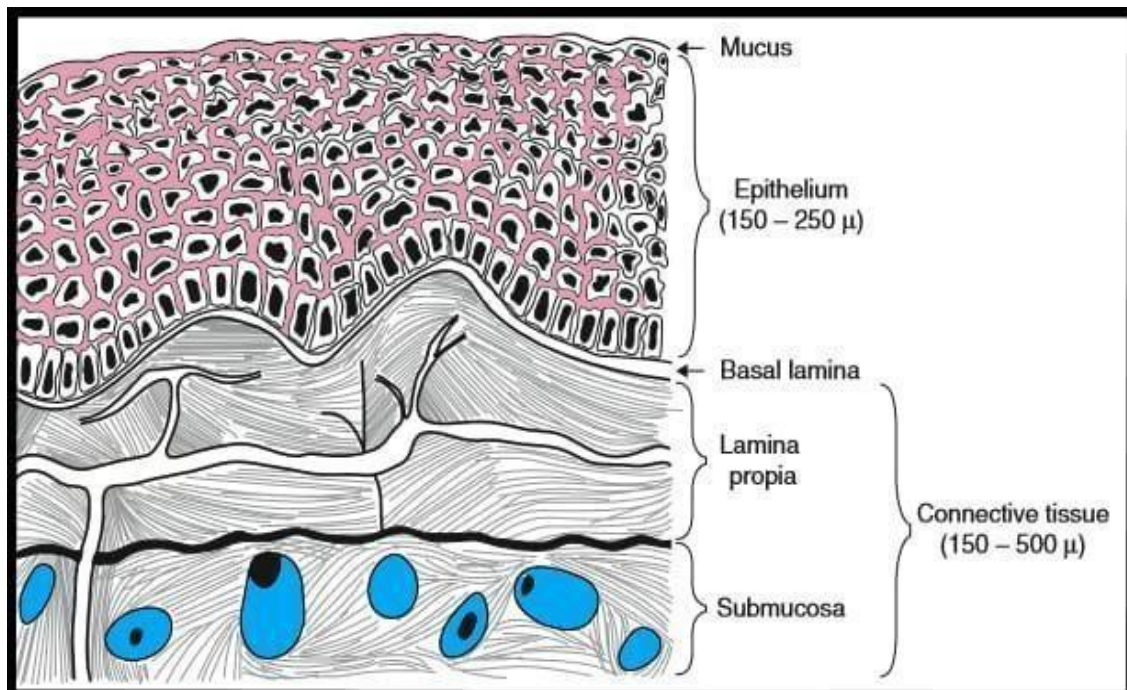


Figure:3

1.6. NOVEL BUCCAL DOSAGE FORMS

The new buccal dosage forms are adhesive tablets, patches, films semisolids such as ointments and gels and powders

a) Patches and Films:

Patches are made of two layers. An aqueous solution of the polymer is poured onto an impermeable backing sheet and then the sheet is cut into the oval shape that is needed.

b) Buccal mucoadhesive tablets :

Buccal mucoadhesive tablets are dosage forms that become moist when they touch buccal mucosa. For example a double-layer tablet has a matrix layer of hydroxypropylcellulose(HPC)and polyacrylic acid and inside it contains a core of cocoa butter that holds insulin and a penetration enhancer called sodium glycocholate.

c) Semisolid Preparations (Ointments and Gels):

Gels or ointments are not as acceptable to patients as other solid bioadhesive dosage forms. Most of these dosage forms are used for local drug therapy inside the oral cavity.

d) Powders:

When HPC and beclomethasone are sprayed onto the mucosa of rats in powder form the residence time is significantly longer than with an oral solution. Also 2.5% of beclomethasone stays on the mucosa for more, than four hours.

1.7. PREGABALIN:

- a. Pregabalin is a medicine that's similar to gamma-amino butyric acid, which is known as a GABA analogue.
- b. Pregabalin works as a medicine to stop seizures and to manage pain. The people who created pregabalin wanted it to be better than medicines for epilepsy.
- c. They wanted pregabalin to help with pain and to have features that make it work well in the body.
- d. Pregabalin looks like GABA. It does not work by attaching GABA receptors or affecting how GABA is broken down in the body.
- e. Instead pregabalin helps by changing the way calcium channels function in nerve cells.pregabalin used for pain seizures that begin in one part of the brain, fibromyalgia and generalized anxiety disorder in the places where it is allowed to be used.
- f. Pregabalin is good because it is easy to take by mouth it always works the way in the body and it does not get broken down much in the liver.
- g. This means that pregabalin can be used for a time to treat people with these conditions.
- h. Pregabalin is used a lot because of these properties.

1.8.THERAPEUTIC ADVANTAGES

- a) Pregabalin is really good at helping people who have pain in their nerves. This kind of pain can happen to people who have diabetes or who have had a case of shingles or who have hurt their spinal cord.
- b) Pregabalin also helps people who have seizures. It can calm people down who are very anxious.
- c) It even helps people who have fibromyalgia which's a condition that causes a lot of pain and trouble sleeping.
- d) The way Pregabalin works in the body is very straightforward. It does not get broken down much in the liver, which means it does not interfere with medicines that people might be taking.
- e) This is a plus for people who have to take a lot of different medicines. Pregabalin is a choice, for these people because it is unlikely to cause problems when it is taken with other drug.

1.9. ADVANTAGE OF PREGABALIN

- a) The oral bioavailability is very high at 90% or more.
- b) The pharmacokinetics are linear and easy to predict.
- c) There is no plasma protein binding.

- d) There is a potential for drug–drug interactions.
- e) The medicine is effective in neuropathic pain conditions.
- f) The medicine improves sleep disturbances associated with pain.
- g) The medicine is suitable for long-term therapy.

1.10. LIMITATIONS

- a) This medicine may lead to swelling in your legs or feet.
- b) Taking this medicine for a time is associated with weight gain.
- c) Patients with kidney problems will need a dose adjustment.
- d) Stopping this medicine suddenly may cause withdrawal symptoms.
- e) There is a potential for tolerance or misuse, in some people.
- f) Standard pills may not deliver the medicine to the spot it is needed.

2. METHODS AND MATERIALS

2.1. Chemical requirements

- a) Pregabalin
- b) Hydroxy propyl methyl cellulose (HPMC)
- c) Chitosan
- d) Mannitol
- e) Propylene Glycol
- f) Peppermint Oil

2.2. Apparatus requirements

- a) Weighing balance
- b) Magnetic stirrer
- c) Sonicator
- d) Dissolution apparatus
- e) Laminar air flow
- f) pH meter
- g) UV–Visible Spectrophotometer

3.FORMULATION

3.1. SOLVENT CASTING METHOD:

Step 1: Preparation of the Hydroxy Propyl Methyl Cellulose (HPMC) solution

HPMC is added to distilled water and stirred until a clear, homogeneous solution forms.

Step 2: Preparation of the Chitosan solution

Chitosan is dissolved in a dilute acid solution and stirred until fully hydrated.

Step 3: Preparation of the drug solution

The specified amount of drug is dissolved or uniformly dispersed in an appropriate solvent.

Step 4: Blending of the solutions

The HPMC, chitosan, and drug solutions are combined and stirred until evenly mixed.

Step 5: Incorporation of the plasticizer

Propylene glycol or glycerol is added to enhance the film's flexibility.

Step 6: Incorporation of excipients

The sweetener and flavoring agent are added and mixed thoroughly.

Step 7: Deaeration

The mixture is sonicated to eliminate entrapped air bubbles.

Step 8: Casting and drying

The prepared solution is transferred into a Petri dish and dried at an appropriate temperature

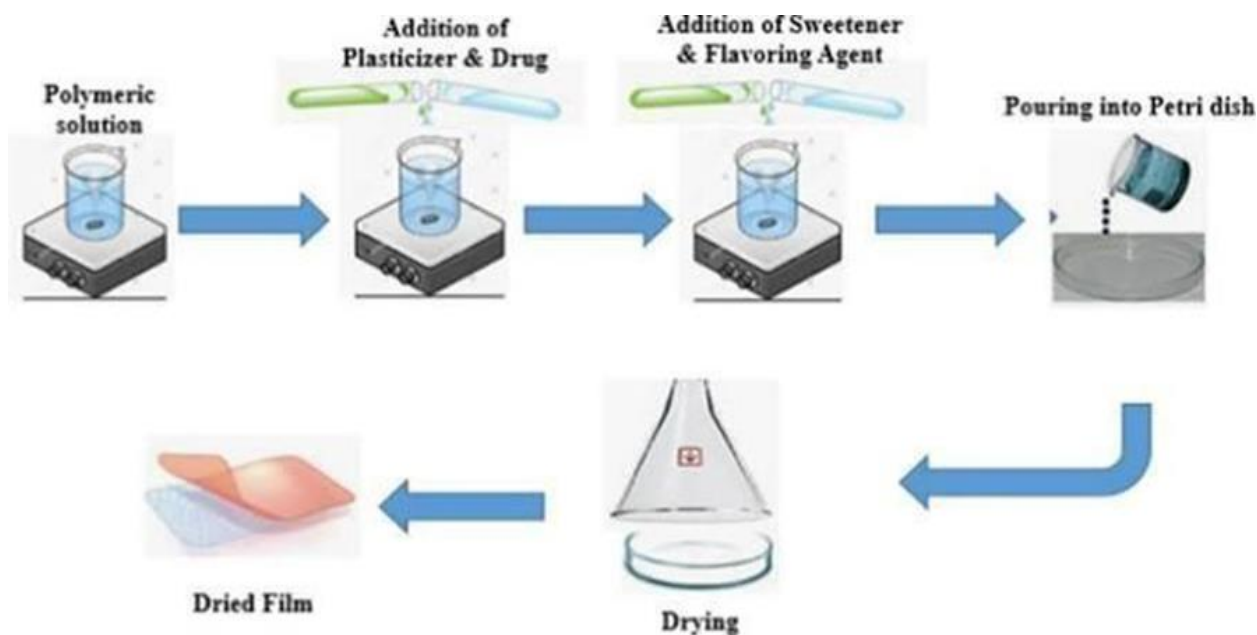


Figure:4

4.EVALUATION OF BUCCAL FILM

a. **Visual Examination:**

Visual Examination of the Prepared Mucoadhesive Buccal Films moved from petri dish, checked and examined visually and formulated films with any imperfection, air bubble, cracks or heterogeneous surface were excluded from further studies. The physical appearance is an important factor specially for patient acceptance and product stability. The formulated dried buccal films were carefully removed from petri dish, checked and examined visually and formulated films with any imperfection, air bubble, cracks or heterogeneous surface were excluded from further studies.

b. **Film Thickness:**

The thickness of the formulated buccal films was determined by means of digital micrometre. The thickness of five films was measured and the mean $\pm$ SD values were calculated of all formulation.

c. **Weight Uniformity:**

The variations in weight may be due to change in density of different combination of polymers as a result of difference in molecular weight and proportion of the polymer used in the films. Films (2×2 cm) were cut and the weights of three films were weighed individually using digital electronic balance and the average weights $\pm$ SD were calculated.

d. **Folding Endurance :**

Folding endurance is a good test to examine the physical and mechanical properties of the films. Five films of each formulation of size (2×2 cm) were cut by using sharp blade.

Folding endurance of the buccal films was determined by repeatedly folding one film at the same place till it broke or folded up to 200 times manually, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance for film. This test was done on all the films for three time.

e. **Swelling Studies:**

The swelling rate of mucoadhesive film was evaluated by placing the film in phosphate buffer solution pH 6.8 at $37 \pm 1^\circ\text{C}$. Buccal films (n=5) were weighed individually (W1) and placed separately in petri dishes containing 25 mL of phosphate buffer (pH 6.8) solution. The dishes were stored at room temperature. Then, films were removed and excess surface water was removed carefully using the filter paper after specified time intervals of 5 minutes and 15 minutes. The swollen films were then again weighed (W2) and swelling index (SI) was calculated using the equation,

$$SI = [(W2 - W1) \div W1] \times 100$$

Where,

W1 = Initial weight of the patch

W2 =Final weight of the patch.

f. **Surface pH:**

Measurement the films were allowed to swell by keeping it in contact with 5 ml of distilled water ($\text{pH } 6.5 \pm 0.05$) for 2 hours at room temperature and pH was noted by bringing glass electrode of pH meter in contact with the microenvironment of the swollen films and allowing it to equilibrate for 1 minute. The average $\text{pH} \pm \text{SD}$ of three determinations was reported

5.RESULT ND DISCUSSION

a. **Visual Examination of the Formulated Mucoadhesive Buccal Films**

All the prepared formulations were elegant in appearance, showed no visible cracks and showing good flexibility except that was excluded from further studies due to the cracks and fragmentations appeared.

b. **Film Thickness**

Average and standard deviation of all readings were calculated and recorded. F1–F5 formulations showed thickness from 0.17 ± 0.01 to 0.22 ± 0.02 mm. F2 showed the lowest thickness (0.17 ± 0.01 mm), indicating a thin and comfortable buccal film.

FORMULATION	THICKNESS(mm)
F1	0.19 ± 0.02
F2	0.17 ± 0.01
F3	0.22 ± 0.02
F4	0.21 ± 0.02
F5	0.18 ± 0.01

Table:1Weight uniformity:

The weight uniformity of the prepared buccal films was found to be within acceptable limits, indicating consistency in the film-casting process. The mean weight ranged from 48.7 ± 1.1 mg (F2) to 58.9 ± 1.2 mg (F4). Among the formulations, F2 exhibited the lowest weight, whereas F4 exhibited the highest weight. The low standard deviation values indicated good uniformity and reproducibility of the prepared films.

FORMULATION	WEIGHT (mg)
F1	51.2 ± 1.3
F2	48.7 ± 1.1
F3	55.4 ± 1.4
F4	58.9 ± 1.2
F5	50.1 ± 1.0

Table:2

c. Folding Endurance:

The flexibility of the polymeric thin films which is required for their easy handling can be measured with respect to its folding endurance. The folding endurance is determined by folding the film repeatedly at 180° angle of the plane at the same place until it breaks. All the films resisted breakage upon folding them for more than 300 times at same place and did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point.

Folding endurance ranged from 248 ± 5 to 289 ± 7 folds. F2 showed the highest value (289 ± 7 folds), indicating better flexibility and resistance to breaking.

d. Surface pH:

The surface pH of the prepared buccal films was determined using a pH meter, and the results are presented in Table 2. The surface pH values of the formulations ranged from 6.0 ± 0.1 (F3) to 6.4 ± 0.1 (F2). All the prepared films showed surface pH values close to neutral, indicating their suitability for buccal application and suggesting a low possibility of mucosal irritation.

The acceptable surface pH may contribute to better patient comfort and compliance.

FORMULATION	SURFACE pH(mean±SD)
F1	6.3 ± 0.1
F2	6.4 ± 0.1
F3	6.0 ± 0.1
F4	6.2 ± 0.1
F5	6.3 ± 0.1

Table:3

RANGE: 6.0 ± 0.1 - 6.4 ± 0.1

F2 showed the highest surface pH 6.4 ± 0.1

e. Swelling Index:

The swelling studies of the prepared buccal films were performed using pH 6.8 phosphate buffer for 5 and 15 minutes. The swelling index increased with increasing hydration time. Among the formulations, F5 showed maximum swelling at 15 minutes ($186.72 \pm 2.36\%$), whereas F1 showed minimum swelling ($59.17 \pm 1.42\%$). The observed swelling behaviour may be attributed to water uptake and hydration of HPMC and chitosan. The films remained intact during the study, indicating adequate polymer cohesiveness.

Formulation	5 min(%) Mean ± sd	15 min(%) Mean ± sd
F1	42.18 ± 1.26	59.17 ± 1.42
F2	56.24 ± 1.35	78.46 ± 1.58
F3	71.36 ± 1.47	102.84 ± 1.76
F4	96.52 ± 1.62	145.38 ± 2.14
F5	128.64 ± 1.85	186.72 ± 2.36

Table:4

6. SUMMARY

Pregabalin mucoadhesive buccal films were successfully prepared by the solvent casting method using HPMC and chitosan, along with mannitol, propylene glycol and peppermint oil. The prepared films were dried at 40°C for 6–8 hours and evaluated for physical appearance, thickness, weight uniformity, folding endurance, drug content, surface pH, swelling behaviour and in-vitro drug release. The formulations showed acceptable appearance, good flexibility, suitable surface pH and satisfactory swelling behaviour. Among the five formulations, F2 was identified as the optimized formulation, showing 0.17 ± 0.01 mm thickness, 289 ± 7 folds folding endurance and approximately 98% drug release within 8 hours. F5 showed the highest swelling index of $186.72 \pm 2.36\%$ at 15 minutes. Overall, the results demonstrated that the developed Pregabalin buccal films possess suitable physicochemical and drug-release characteristics and have promising potential as a mucoadhesive buccal drug-delivery system.

7. CONCLUSION

The Pregabalin mucoadhesive buccal films were successfully formulated by the solvent casting method and showed satisfactory physicochemical properties, good flexibility, swelling behaviour, and controlled drug release. F2 was identified as the optimized formulation, showing approximately 98% drug release within 8 hours with a diffusion-controlled mechanism. Overall, the developed buccal film demonstrated promising potential for sustained Pregabalin delivery and improved patient convenience. Further in-vivo studies are recommended to confirm its bioavailability, safety, and therapeutic efficacy.

ACKNOWLEDGMENTS:

I would like to acknowledge the Tamil Nadu chemists and druggist educational trust (TNCDE) and Pallavan pharmacy college for their extended support.

Disclosure of conflict of interest:

There is no conflict of interest.

AUTHOR CONTRIBUTION:

Sanjay Kumar E , Sarathi S , Sasikala E , Shobana S had principal responsibility for the conception, design of the study and drafting of manuscript .Malarvizhi.K was responsible for the revision of the manuscript for important intellectual content, Dr. J. Karthi, Dr. S. Swarnalatha contributed towards reviewing of the literature.

8. REFERENCES

1. Zhang X. et al. (2023). Investigated the PKC ϵ /TRPV1 signalling pathway in a rat nerve-injury model and demonstrated that pregabalin's analgesic action involves inhibition of PKC ϵ /TRPV1 signalling and reduced spinal cord inflammation. [Journal name, volume(issue), page range — to be completed and verified by the author].
2. Okorochukwu N. et al. (2017). Developed pregabalin mucoadhesive buccal patches by solvent casting using HPMC K4M, Eudragit RL100 and PVP K30; the optimized formulation (F4) showed satisfactory thickness, uniform drug content, good mucoadhesion and 93.76% cumulative release over 12 h following diffusion-controlled kinetics. [Journal name, volume(issue), page range — to be completed and verified by the author].
3. Alles S.R.A. et al. (2020). Reviewed pregabalin pharmacology as a second-generation gaba pentinoid, highlighting $\alpha 2\delta$ -subunit binding, reduced neurotransmitter release, and efficacy across neuropathic pain, fibromyalgia and epilepsy. [Journal name, volume(issue), page range — to be completed and verified by the author].
4. Alles R.A. et al. (2020). Described pregabalin's binding to $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 subunits of voltage-gated calcium channels and its broad efficacy in partial-onset epilepsy, neuropathic pain, fibromyalgia and GAD. [Journal name, volume(issue), page range — to be completed and verified by the author].
5. Stahl S.M. (2013). Reviewed the pharmacology of the $\alpha 2\delta$ ligand pregabalin, relating CNS regional binding to both clinical efficacy and adverse-effect profile. [Journal name, volume(issue), page range — to be completed and verified by the author].
6. Verma V. et al. (2014). Reviewed pregabalin as a selective $\alpha 2\delta$ subunit antagonist with established first-line efficacy in diabetic neuropathy, post-herpetic neuralgia, fibromyalgia and chemotherapy-induced neuropathic pain. [Journal name, volume(issue), page range — to be completed and verified by the author].
7. Author(s) (2022). Reported buccoadhesive films of duloxetine hydrochloride (HPMC/PVA, solvent casting); the optimized F2 film showed higher C_{max}, lower T_{max} and 296.39% relative bioavailability compared with marketed oral capsules. [Journal name, volume(issue), page range — to be completed and verified by the author].
8. Suryawanshi S. et al. (2022). Developed fast-dissolving tablets of nitrendipine with rapid disintegration, good stability and improved bioavailability. [Journal name, volume(issue), page range — to be completed and verified by the author]. Nair A.B. et al. (2021). Developed rizatriptan mucoadhesive buccal films (HPMC, Eudragit RS100) by solvent casting; the optimized film followed Weibull release kinetics and achieved 245% relative bioavailability in rabbits versus oral solution. [Journal name, volume(issue), page range — to be completed and verified by the author].
9. Jaipal A. et al. (2015). Confirmed controlled release, good mucoadhesion and improved bioavailability for buspirone hydrochloride bioadhesive buccal discs. [Journal name, volume(issue), page range — to be completed and verified by the author].
10. Author(s) (2022). Developed losartan potassium mucoadhesive buccal films (HPMC K15M, Eudragit RL100, Carbopol 934P, 3:1 ratio) showing sustained release (~95% in 6 h) and high permeation (~98% in 6 h). [Journal name, volume(issue), page range — to be completed and verified by the author].

11. Kavoussi R. (2006). Reviewed pregabalin's mechanism of action via the $\alpha 2\delta$ subunit of voltage-gated calcium channels and its clinical efficacy in epilepsy, neuropathic pain and generalized anxiety disorder. [Journal name, volume(issue), page range — to be completed and verified by the author].
12. Kumar et al. (2023). Optimized losartan potassium buccal films (HPMC K15M : Eudragit RL100, 3:1) achieving $95.39 \pm 0.37\%$ release and $98.38 \pm 2.08\%$ permeation in 6 h, following Higuchi kinetics with non-Fickian diffusion. [Journal name, volume(issue), page range — to be completed and verified by the author].
13. Yelave A. et al. (2021). Reviewed buccal mucoadhesive films for antihypertensive drug delivery, highlighting rapid absorption via buccal vasculature and avoidance of first-pass metabolism. [Journal name, volume(issue), page range — to be completed and verified by the author].
14. Venkateshwarlu K. et al. (2016). Developed fast-dissolving oral films using hydrophilic polymers to achieve rapid disintegration and improved absorption. [Journal name, volume(issue), page range — to be completed and verified by the author].
15. Shamim et al. (2022). Reviewed mucoadhesive buccal drug delivery systems using HPMC, chitosan, sodium alginate, and carbopol; solvent casting and hot-melt extrusion identified as the most common preparation techniques, producing films with prolonged mucosal residence. [Journal name, volume(issue), page range — to be completed and verified by the author].
16. Shamim et al. (2022). Reviewed mucoadhesive buccal drug delivery systems using HPMC, chitosan, sodium alginate, and carbopol; solvent casting and hot-melt extrusion identified as the most common preparation techniques, producing films with prolonged mucosal residence. [Journal name, volume(issue), page range — to be completed and verified by the author]