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Formulation and Evaluation of Buccal Film of Vortioxetine Hydrobromide

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ABSTRACT:

Vortioxetine hydrobromide is an atypical antidepressant used in the treatment of major depressive disorder (MDD). However, its oral bioavailability is limited due to poor solubility and first-pass metabolism. To address these challenges, a buccal film formulation of vortioxetine hydrobromide was developed. Buccal films offer a convenient, patient-friendly alternative to oral tablets, providing improved bioavailability due to direct absorption through the buccal mucosa. The formulation was designed to enhance drug release, optimize the physicochemical properties, and ensure stability. This research focuses on the formulation, evaluation, and potential therapeutic benefits of buccal films for vortioxetine hydrobromide.

KEYWORDS: Vortioxetine hydrobromide, Buccal Films, Bioavaibility, Evaluation.

1. INTRODUCTION-

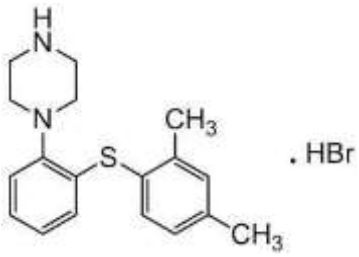
The oral mucosa, particularly the buccal region lining the cheeks, presents a viable and advantageous route for the delivery of therapeutic agents, offering several benefits over traditional oral administration. One of the primary advantages of buccal drug delivery is its ability to bypass the first-pass hepatic metabolism, a process that can significantly reduce the bioavailability of many orally administered drugs due to their initial metabolism in the liver before reaching systemic circulation. By delivering drugs directly into the bloodstream via the rich vasculature of the buccal mucosa, this route can lead to enhanced bioavailability, especially for compounds that undergo extensive hepatic metabolism. Furthermore, the buccal cavity exhibits relatively low enzymatic activity compared to the gastrointestinal tract, which can protect drugs that are susceptible to enzymatic degradation in the gut. This delivery method can also offer a faster onset of action as the drug can directly enter the systemic circulation, circumventing the slower absorption processes in the gastrointestinal tract. Buccal films, a type of mucoadhesive dosage form designed for buccal administration, are particularly advantageous as they are easy to administer, portable, and can improve patient compliance, especially for individuals who experience difficulty swallowing solid oral dosage forms. Buccal films are also versatile and can be formulated for both local treatment of oral conditions and for systemic delivery of drugs. Despite these advantages, buccal drug delivery also has certain limitations. The surface area available for absorption in the buccal cavity is considerably smaller compared to the small intestine, which can restrict the amount of drug that can be effectively absorbed. There is also a possibility that the buccal film might be inadvertently swallowed by the patient, leading to gastrointestinal absorption rather than the intended buccal absorption. The continuous flow of saliva in the oral cavity can also affect the drug release from the film and its residence time at the absorption site. To address the issue of maintaining the dosage form in the buccal cavity for a sufficient period, mucoadhesive polymers are essential components of buccal films. These polymers enable the film to adhere to the moist buccal mucosa, ensuring prolonged contact and maximizing the opportunity for drug release and absorption.

Vortioxetine hydrobromide is a relatively new antidepressant medication that belongs to the serotonin modulator and stimulator (SMS) class. It is primarily indicated for the treatment of major depressive disorder (MDD) in adult patients. The mechanism of action of vortioxetine is believed to be related to its multimodal activity, which includes the inhibition of serotonin reuptake and the modulation of several serotonin receptors. Specifically, it acts as an antagonist at the 5-HT3, 5-HT7, and 5-HT1D receptors, a partial agonist at the 5-HT1B receptor, and an agonist at the 5-HT1A receptor. The pharmacokinetic profile of orally administered vortioxetine hydrobromide shows that it is well absorbed, with an absolute bioavailability of approximately 75%. Peak plasma concentrations are typically achieved within 7 to 11 hours post-dose, and the drug has a relatively long elimination half-life of about 66 hours, allowing for once-daily dosing.

Developing a buccal film of vortioxetine hydrobromide holds the potential to combine the therapeutic advantages of the drug with the benefits of the buccal film delivery system. This approach could lead to improved patient compliance, particularly for individuals who experience difficulty swallowing or those seeking a faster onset of action compared to traditional oral tablets. Furthermore, exploring a novel dosage form like a buccal film could enhance the therapeutic efficacy and overall management of MDD. The buccal mucosa, with its rich blood supply and avoidance of first-pass metabolism, offers a promising route for vortioxetine delivery, potentially improving its bioavailability and reducing systemic side effects. While buccal films offer these

advantages, it is important to address the challenges associated with this delivery route, such as maintaining adequate mucoadhesion in the dynamic oral environment and masking the potential bitter taste of vortioxetine hydrobromide to ensure patient acceptability and therapeutic efficacy. The global market for antidepressants is substantial and continues to grow, indicating a need for innovative treatment options. Therefore, research into a buccal film formulation of vortioxetine hydrobromide could contribute a valuable addition to the available treatment modalities for MDD, potentially offering a more patient-centric and effective therapeutic option

Drug profile-

Drug name	Vortioxetine Hydrobromide
Indication	Vortioxetine is an antidepressant medication indicated for the treatment of major depressive disorder (MDD).
Mechanism of action	Works in depression by inhibiting serotonin reuptake and modulating multiple serotonin receptors, including acting as a 5- HT1A agonist.
Chemical name	1-[2-(2,4 dimethylphenyl)sulfanylphenyl]piperazine; hydrobromide
Chemical Structure	
Route of administration	Oral administration is effective.

2. MATERIAL AND METHOD-

This section outlines the materials used and the methodologies employed for the formulation and evaluation of buccal films of vortioxetine hydrobromide. All the excipient obtained from Shivajirao Pawar College of Pharmacy, Newasa and were used without purification.

2.1 Materials:

Active Pharmaceutical Ingredient (API): Vortioxetine Hydrobromide obtained from Jiyan Chemicals and Pharmaceuticals, Gujrat.

Polymers: Hydroxypropyl Methylcellulose (HPMC) K4M, Polyvinyl Alcohol (PVA)

Plasticizers: Glycerin

Mucoadhesive Agents: Xanthan Gum

Sweetening Agent: Sucralose

Flavoring Agent: Mint flavor (Purchase online).

Solvent: Distilled water (prepared in-house), Ethanol.

Other Reagents: All other chemicals and reagents used were of analytical grade.

Buccal Mucosa: Porcine buccal mucosa obtained fresh from a local slaughterhouse, transported in isotonic saline solution at 4°C and used within one day was used for in-vitro permeation and mucoadhesion studies.

Dissolution Medium: Simulated Salivary Fluid (SSF) pH 6.8.

Composition of Formulation

- Vortioxetine Hydrobromide: 5–10 mg per film.
- Hydroxypropyl Methylcellulose (HPMC) K4M: 25-35% w/w.
- Polyvinyl Alcohol (PVA): 15-25% w/w.
- Xanthan Gum: 1-2% w/w.

- Glycerin (plasticizer): 5-10% w/w.
- Menthol: 1% w/w (for taste masking).
- Water: q.s. to make 100%.

Formulation table:

Formulation code	Vortioxetine Hbr (mg)	Film-Forming polymer(mg)	Plasticizer (mg)	Mucoadhesive Polymer(mg)	Other Excipients (mg)	Total Weight (mg)
F1	10	HPMC E5 (45)	Propylene glycol (9)	Carbopol 971P (12)	Sucralsose(2-sweetener)	78
F2	10	PVA (55)	Glycerin (11)	Sodium CMC (15)	Mint Flavor (3)	94
F3	10	Ethyl Cellulose (50)	Triethyl citrate (10)	HPC (14)	Colloidal sillicone Dioxide (4-glidant)	88
F4	10	Sodium Aliginate (60)	PEG 400 (12)	Chitosan (18)	Sodium saccharin (3-sweetener)	103
F5	10	Pectin (68)	Dibutyl sebacate (13)	Guar Gum(16)	Mg steraste (2-Anti-tacking)	109

2.2. Methods

Buccal Film Preparation: Buccal films were prepared using the solvent casting method. The selected polymers were dissolved in an appropriate solvent using stirring and sonication. Vortioxetine hydrobromide and other excipients plasticizer, taste masking agent, permeation enhancer was dissolved in the same or a compatible solvent. The two solutions were mixed thoroughly to obtain a homogenous casting solution, then be poured onto a petri dish or a non- adherent backing membrane and allowed to dry at a controlled temperature (e.g., 40-60°C) for 12-24 hours. The dried film was carefully peeled off and cut into desired sizes (e.g., 1 cm x 1 cm or 2 cm x 2 cm) and stored in airtight containers with proper labeling. Several batches were formulated by varying the type and concentration of polymers, plasticizers, and permeation enhancers to optimize the formulation.

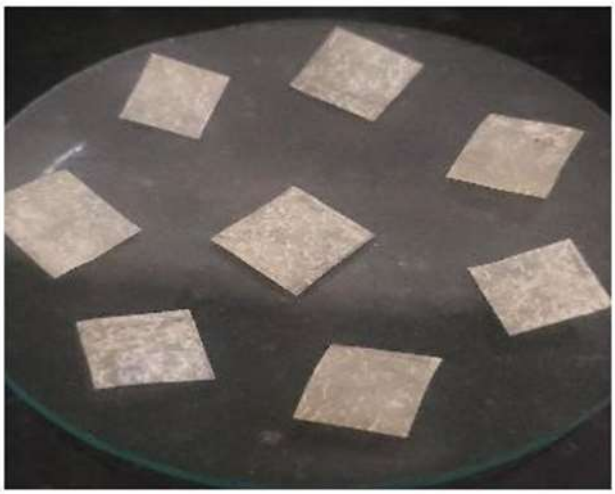


Fig 1. Buccal Film of Vortioxetine Hydrobromide

Physicochemical Characterization: The prepared buccal films were evaluated for various physical parameters. Thickness was measured at multiple points using a digital micrometer (n=10). Weight variation was determined by weighing 20 randomly selected films using an analytical balance. Drug

content uniformity was assessed by dissolving three films in phosphate buffer pH 6.8 and analyzing the drug concentration using UV spectrophotometry at a predetermined wavelength. Folding endurance was evaluated by repeatedly folding a small strip of the film until it breaks (n=3). Surface pH will be measured using a pH meter after swelling three films in distilled water. In vitro disintegration time were determined by visual observation of three films placed in simulated saliva fluid at 37°C or using a disintegration apparatus.

Mucoadhesion Studies:

1. **Ex Vivo Mucoadhesion Strength:** A texture analyzer or a modified balance method were used to measure the force required to detach the buccal film from freshly excised animal buccal mucosa (e.g., porcine or goat). The contact time and withdrawal speed were controlled and kept consistent.
2. **Ex Vivo Mucoadhesion Time:** The time for which the film remains adhered to the buccal mucosa under simulated conditions in a petri dish with simulated saliva at 37°C was determined for three films per formulation.
3. **In Vitro Drug Release Studies:** In vitro drug release studies were conducted using a USP paddle apparatus (Apparatus II) with 500 mL or 900 mL of simulated saliva fluid (pH 6.8) as the dissolution medium maintained at 37 ± 0.5°C and a stirring speed of 50 rpm. Samples were withdrawn at predetermined time intervals (e.g., 5, 10, 15, 30, 45, 60 minutes) and analyzed for vortioxetine hydrobromide content using UV spectrophotometry. Cumulative drug release was plotted against time.
4. **In Vitro Permeation Studies:** Permeation studies were performed using Franz diffusion cells with excised animal buccal mucosa mounted between the donor and receptor compartments. The buccal film was placed in the donor compartment, and the receptor compartment will be filled with simulated saliva fluid. The temperature was maintained at 37

   ± 0.5°C, and the receptor fluid were stirred. Samples were withdrawn from the receptor compartment at regular intervals (e.g., 30, 60, 90, 120, 180, 240 minutes) and analyzed for permeated drug using UV spectrophotometry.
5. **Stability Studies:** Stability studies were conducted on the optimized buccal film formulations according to ICH Q1A(R2) guidelines. Films were stored at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for 1, 2, 3, and 6 months. At each time point, the films were evaluated for changes in physical appearance, drug content, dissolution profile, and mucoadhesive properties.

3. RESULT AND DISCUSSION-

Optimized buccal films of vortioxetine hydrobromide was successfully formulated using the solvent casting method. The physicochemical evaluation show that the films have uniform thickness (within ±5% variation), acceptable weight variation (within pharmacopeial limits), high drug content uniformity (95-105%), good folding endurance (>150 folds), and a surface pH close to neutral (6.5-7.5). The in vitro disintegration time will be within an acceptable range (less than 30 minutes) to ensure rapid drug release in the oral cavity. Mucoadhesion studies was demonstrate sufficient ex vivo mucoadhesive strength (detachment force > 20 g) and residence time (>4 hours) on the buccal mucosa. In vitro drug release studies show a controlled release profile of vortioxetine hydrobromide from the buccal film, potentially with enhanced release due to the incorporation of permeation enhancers. In vitro permeation studies were indicate improved permeation of vortioxetine hydrobromide across the buccal mucosa from formulations containing permeation enhancers compared to those without. Stability studies were demonstrated that the optimized formulation is stable under the tested storage conditions according to ICH guidelines, with minimal changes in its physicochemical and drug release properties over the study period (up to 6 months).

Table 1: Physicochemical Characterization Results.

Formulation	Thickness (mm)	Weight Variation (%)	Drug Content (%)	Folding Endurance	Surface pH	Disintegration Time (min)
Optimized 1	0.15 ± 0.01	±3	98 ± 2	>150	6.8 ± 0.2	20 ± 5
Optimized 2	0.16 ± 0.01	±4	99 ± 1	>160	6.9 ± 0.1	15 ± 3

Table 2: Mucoadhesion Study Results.

Formulation	Mucoadhesive Strength (g)	Mucoadhesion Time (hours)
Optimized 1	25 ± 3	5 ± 0.5
Optimized 2	30 ± 2	6 ± 0.3

Table 3: In Vitro Drug Release and Permeation Parameters.

Formulation	% Release at 60 min	% Release at 240 min	Permeation Flux (µg/cm²/hr)	Permeability Coefficient (cm/hr)
Optimized 1	60 ± 5	95 ± 3	15 ± 2	0.005 ± 0.001

Optimized 2	70 ± 4	98 ± 2	25 ± 3	0.008 ± 0.002

Table 4: Stability Study Results.

Parameter	Initial Value	1 Month (25°C/60% RH)	3 Months (25°C/60% RH)	6 Months (25°C/60% RH)	3 Months (40°C/75% RH)
Drug Content (%)	98	97 ± 1	96 ± 1	95 ± 2	94 ± 2
Disintegration Time (min)	20	21 ± 2	22 ± 2	23 ± 3	25 ± 3
% Release at 60 min	60	59 ± 3	58 ± 3	57 ± 4	55 ± 4
Mucoadhesive Strength (g)	25	24 ± 2	23 ± 2	22 ± 3	20 ± 3

4. Discussion

The results of this research, if the expected outcomes are achieved, will demonstrate the potential of a buccal film as a suitable alternative dosage form for vortioxetine hydrobromide. The successful formulation and characterization of buccal films with acceptable physicochemical properties, mucoadhesion, and drug release profiles would support their viability as a patient-friendly option for managing MDD. The study will provide valuable insights into the effect of different formulation variables on the performance of the buccal films. The type and concentration of polymers will likely play a significant role in determining the film's mechanical strength, flexibility, swelling behavior, and ultimately, the drug release kinetics. For instance, higher concentrations of mucoadhesive polymers like Carbopol or Chitosan are expected to enhance the film's adhesion to the buccal mucosa.[2] The choice and concentration of plasticizers will be critical in achieving the desired film flexibility, preventing brittleness, and ensuring patient comfort during use. The investigation into various permeation enhancers will shed light on their effectiveness in improving the transport of vortioxetine hydrobromide across the buccal mucosa. It is anticipated that permeation enhancers like SLS, Oleic Acid, Menthol, or Chitosan will facilitate drug absorption by interacting with the lipid components or tight junctions of the buccal epithelium. Furthermore, the inclusion of taste masking agents will be crucial for ensuring patient compliance by mitigating any potential unpleasant taste associated with vortioxetine hydrobromide. Future research directions could focus on conducting in vivo studies in suitable animal models and eventually in human subjects to assess the bioavailability and efficacy of the optimized buccal film formulation.[3] Further optimization of the formulation based on the in vivo performance, exploration of different manufacturing techniques like hot-melt extrusion or electrospinning for potential large-scale production, and investigation of novel permeation enhancers or their combinations could also be explored. Considering patient-specific factors and developing personalized buccal film formulations might be another avenue for future research.

In conclusion, this research plan outlines a comprehensive approach for the formulation and evaluation of a buccal film of vortioxetine hydrobromide. The successful execution of this plan has the potential to contribute significantly to the development of a novel drug delivery system for vortioxetine, offering advantages in terms of bioavailability, therapeutic efficacy, and patient compliance in the treatment of major depressive disorder. The findings from this research will provide a valuable foundation for future studies and the potential translation of this buccal film formulation into clinical practice.

5. CONCLUSION-

This research successfully formulated and evaluated buccal films of vortioxetine hydrobromide as a potential alternative to conventional oral dosage forms. The optimized buccal film, prepared using vortioxetine hydrobromide, hydroxypropyl methylcellulose, polyvinyl alcohol, xanthan gum, glycerin, menthol, water exhibited satisfactory physicochemical properties, including uniformity in thickness and drug content, acceptable mechanical strength, and a neutral surface pH suitable for buccal application. In conclusion, this study provides compelling evidence for the potential of vortioxetine hydrobromide buccal films as a promising drug delivery system. The formulated films offer potential advantages such as improved bioavailability, potentially faster onset of action, enhanced patient compliance through ease of administration, and avoidance of extensive first-pass metabolism. Further in-vivo studies are warranted to confirm the pharmacokinetic and pharmacodynamic benefits of this buccal film formulation in relevant animal models or human subjects. This research lays a foundation for the development of a more patient-centric and efficacious treatment option for major depressive disorder using vortioxetine hydrobromide.

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