A Brief Chronological Overview of Buccal Film Formulations

Dudekula Chand Basha¹, Bono Naga Sudha²

¹Research Scholar, Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University, Anantapur, Andhra Pradesh, India.
²Department of Pharmaceutics, Creative Educational Society’s College of Pharmacy, Kurnool, Affiliated to Jawaharlal Nehru Technological University, Anantapur, Andhra Pradesh, India.

DOI: https://doi.org/10.24321/2278.2044.202241

INFO

Corresponding Author:
Dudekula Chand Basha, Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University, Anantapur, Andhra Pradesh, India.

E-mail Id: dchandknl@gmail.com
Orcid Id: https://orcid.org/0000-0001-8300-7002

How to cite this article:

ABSTRACT

The bioadhesive buccal film drug delivery technology that increases the safety, effectiveness, and stability of active pharmaceutical ingredients is the main focus of the current article. The buccal film is cutting-edge technology since it offers a better way to maximise treatment effectiveness. The medications that are used to increase bioavailability and have a high first-pass metabolism are ideal for this drug delivery strategy. Rolling, hot-melt extrusion, solid dispersion, solvent casting, or semi-solid casting can all be used to make Bioadhesive Buccal Films (BBF). The solvent casting method is the most popular of them. Organoleptic valuation, thickness, transparency, surface pH, moisture content, tensile strength, per cent elongation, folding endurance, swelling assets, drug content, and in vitro dissolution tests are a few of the mechanical assets that are assessed for the BBF. A small amount of material on earlier work on BBF has been provided in the article. This article will be useful for quick references to prior BBF attempts and guidance on how to assess them.

Keywords: Buccal, Bioadhesive, Bioavailability, Evaluation, Film, Literature

Introduction

Bioadhesive Buccal Films (BBF) are a type of dosage form that, when applied to the tongue or oral cavity, uses a water-dispersible polymer to quickly hydrate, attach, and dissolve, resulting in systemic drug delivery.¹

The most recent development in buccal administration is BBF. They are now more important than ever as patient-friendly, cost-effective, and cutting-edge Active Pharmaceutical Ingredient (API) delivery techniques.² Since BBF is designed to hold to the BBF, it can be made to have both local and systemic activity.³ The BBF may be more flexible and pleasant than buccal pills. Instead of going through the liver’s first-pass processing, BBF injects API directly into the bloodstream via the internal jugular vein. The BBF’s large surface area also makes it easier to quickly moisten, which speeds up the API’s absorption. The buccal mucosa is an important region for medicine absorption because of its rich blood supply. Its bioavailability is increased by prolonging its residence time at the site of absorption since the dosage form is simple to provide to paediatric and geriatric patients, as well as those who are intellectually challenged, uncooperative, or have physical or mental disabilities.⁴ The difficulty of combining large doses of API with BBF is its main disadvantage. Depending on how they are made, BBF’s API dissolving speeds might
range from minutes to hours. Orally administered dosage forms have the following drawbacks:6,7

- Due to slow absorption or delayed onset of action, it is not suitable for emergencies or patients who are unconscious
- It is challenging for a patient to undergo oral dosage form if they suffer from gastrointestinal issues such as diarrhoea, constipation, ulcers, or hyperacidity in the stomach
- In many cases, the API itself causes these issues, such as aspirin and several NSAIDs, which may eventually lead to stomach ulcers with prolonged use
- Patients with malabsorption syndrome, in which it is impossible to absorb nutrients through the small intestine, shouldn’t have an oral dosage form
- It is insufficient for API that might be inactivated or damaged in the gut. An example of a protein is insulin. Orally ingested protein from foods like meat and fish is broken down in the stomach
- Children or infants that are uncooperative should not receive it
- Patients with chronic vomiting should not have it

The BBF have the following advantages:8,9

- In addition to the area’s high blood supply, it is also possible to accomplish a rapid commencement of the therapeutic action because there are no Gastrointestinal (GI) components that could impede absorption (gastric emptying, presence of food, gastric disease, etc.)
- Some APIs (like peptides) that would usually be damaged by the gastric pH or enzymes can be delivered buccally due to the absence of exposure to the hostile gastric milieu
- Regarding the oral route, by avoiding intestinal and first-pass hepatic processing, avoiding portal circulation can boost bioavailability

Evaluation

The BBF is assessed using the following tests:

API Excipient Compatibility

After choosing the Active Pharmaceutical Ingredient (API) and excipients for BBF, analytical measures must be used to determine whether the API and its mix with excipients are compatible. DSC, or differential scanning calorimetry, is used to verify if the API has been impregnated with the excipients. To determine the API presence as its crystalline nature in the excipient blend, they have to confirm by powder XRD. Later, FTIR spectra have to be acquired to verify the API’s characteristic stretches and peaks undisturbed in the blend.

Measurement of Mechanical Properties

Elongation at break and tensile strength are the two mechanical characteristics of the films that are measured (tensile tester-Vantage NX). The film strip is trimmed to the required proportions (60x10 mm), made free of visible flaws, and placed between two clamps spaced 3 cm apart. The top clamp drags the strips apart until they break at a rate of 2 mm/sec, at which point the force and lengthening of the film at that location are recorded. Clamps enable the BBF to maintain film integrity throughout the test without squeezing it.10

Surface pH

On an agar plate, BBFs are permitted to swell for two hours. A pH paper is placed on the surface of the swollen area to measure the surface pH.11

Thickness Measurements

Using an electronic digital micrometre, the thickness of each film is measured in five separate places (the centre and the four corners). For this test, either a vernier calliper or a screw gauge is employed.12

Swelling Study

BBF is weighed individually (W1), placed separately in 2% agar gel plates, maintained at 37±1°C, and examined for any physical changes in weight gain (W2). Every hour for up to three hours, films are removed from the gel dishes, and any excess surface water is carefully cleaned away with filter paper (eq. 1).13

Swelling Index = (W2-W1)/W1 X 100----(1)

Water Absorption Capacity Test

In an incubator that is kept at 37±0.5°C, circular films with a surface area of 2.3 cm² are preserved. These films are indorsed to protrude on the surface of agar plates prepared in simulated saliva (2.38 g Na₂HPO₄, 0.19 g KH₂PO₄, and 8 g NaCl per litre of distilled water adjusted with phosphoric acid to get a pH of 6.7). The final constant weights are recorded after samples are dried for 7 days in a desiccator over anhydrous CaCl₂, at room temperature. Samples are weighed (wet weight) at various time intervals (0.25, 0.5, 1, 2, 3 and 4 hours). (eq. 2).14

Water Uptake (%) = (Wf-Wi)/Wi X 100----(2)

Where Wf = Final weight of BBF, and Wi = initial weight of BBF.

Ex Vivo Bioadhesion Test

Phosphate buffer is used to separate and clean the young sheep’s mouth (pH 6.8). The open entrance of a glass vial holding phosphate buffer has a bit of gingival mucosa twisted inside it (pH 6.8). This glass vial hardly touches the mucosal surface since it is designed to fit tightly inside a glass beaker filled with phosphate buffer (pH 6.8 at 37 ± 0.5°C). A rubber stopper’s bottom side is attached to
the film using cyanoacrylate adhesive. A 5 g weight is balanced using two balance pans. The left side pan, which was loaded with the pan attached with the film over the mucosa, has had its 5 g weight removed. Throughout the five-minute contact period, the balance is held in this position. Water is gradually added to the right-side pan at a rate of 100 drops per minute until the film is detached from the mucosal surface. By weighing the film in grams, until it could be removed from the mucosal surface, the bioadhesive strength is ascertained.\textsuperscript{15}

**In Vitro Drug Release**

The API released from bilayered and multilayered films is investigated using the rotating paddle method. The dissolving agent that is used has a pH of 6.8, which is phosphate buffer. At a speed of 50 rpm and a temperature of \(37 \pm 0.5^\circ\text{C}\), the release is carried out. Using an instant adhesive, the glass disc is fastened to the BBF’s supporting layer. The disintegration vessel’s bottom encloses the disc. At predetermined intervals, 5 ml samples are removed and replaced with new media. After being adequately diluted, the samples are filtered using Whatman filter paper, and their API content is then analysed.\textsuperscript{16}

**Pervasion Study of BBF**

Buccal permeation through the buccal mucosa of sheep and rabbits is examined in vitro at a temperature of \(37 \pm 0.2^\circ\text{C}\) using a glass diffusion cell of the Keshary-Chien/Franz type. The fresh buccal mucosa is connected and held in place between the donor and receptor compartments by magnetic bead churning at 50 rpm. Samples are removed and their API content is checked regularly.\textsuperscript{17}

**Ex Vivo Bioadhesion Time**

Ex vivo bioadhesion tests are carried out on freshly cut buccal mucosa after the BBF is applied (sheep and rabbit). Fresh buccal mucosa must be moistened with 1 drop of phosphate buffer (pH 6.8) before applying the bioadhesive film. This process takes 30 sec. The glass slide is then attached to the bioadhesive film and placed in the beaker with 200 ml of phosphate buffer (pH 6.8 and \(37 \pm 0.5^\circ\text{C}\)). Film adherence is observed for 12 h after the application of a 50 rpm stirring rate for 2 min to mimic the buccal cavity environment. When the film alters in colour, shape, collapse, and contain API is mentioned.\textsuperscript{18}

The earlier attempts made on BBF are illustrated in Table 1.

### Table 1. Previous Work on BBF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rizatriptan benzoate\textsuperscript{19}</td>
<td>Sodium starch glycolate</td>
</tr>
<tr>
<td>Sertraline HCl\textsuperscript{20}</td>
<td>Polyvinyl Pyrrolidone (PVP), and Carbopol P 934 (CP-934)</td>
</tr>
<tr>
<td>Amiloride\textsuperscript{21}</td>
<td>Hydroxypropyl Methyl Cellulose (HPMC K4M), CP-934, and PVP</td>
</tr>
<tr>
<td>Ropinirole HCl\textsuperscript{22}</td>
<td>Pullulan</td>
</tr>
<tr>
<td>Diclofenac sodium\textsuperscript{23}</td>
<td>Sodium Alginate (SA) and pectin</td>
</tr>
<tr>
<td>Norethindrone\textsuperscript{24}</td>
<td>SA, Carboxy Methyl Cellulose (CMC), HPMC, and PVP</td>
</tr>
<tr>
<td>Carvedilol\textsuperscript{25}</td>
<td>HPMC and CP-934</td>
</tr>
<tr>
<td>Ivabradine HCl\textsuperscript{26}</td>
<td>HPMC</td>
</tr>
<tr>
<td>Amlodipine besylate\textsuperscript{27}</td>
<td>CMC and HPMC</td>
</tr>
<tr>
<td>Valsartan\textsuperscript{28}</td>
<td>CP-934, HPMC, SA, and CMC</td>
</tr>
<tr>
<td>Ondansetron HCl\textsuperscript{29}</td>
<td>HPMC</td>
</tr>
<tr>
<td>Rizatriptan benzoate\textsuperscript{30}</td>
<td>Tamarind seed xyloglucan and CP-934</td>
</tr>
<tr>
<td>Lisinopril\textsuperscript{31}</td>
<td>HPMC K4M, sodium CMC, PVP K30, eudragit RL 100, and CP-934</td>
</tr>
<tr>
<td>Selegiline HCl\textsuperscript{32}</td>
<td>Polyvinyl Alcohol (PVA), and poly(d,L-lactide-co-glycolide)</td>
</tr>
<tr>
<td>Lidocaine HCl\textsuperscript{33}</td>
<td>HPMC, CMC, and Chitosan (CS)</td>
</tr>
<tr>
<td>Simvastatin\textsuperscript{34}</td>
<td>CMC and PVP</td>
</tr>
<tr>
<td>Metformin HCl\textsuperscript{35}</td>
<td>CS</td>
</tr>
<tr>
<td>Saxagliptin HCl\textsuperscript{36}</td>
<td>HPMC K100M and Eudragit RL-100</td>
</tr>
<tr>
<td>Omeprazole\textsuperscript{37}</td>
<td>HPMC</td>
</tr>
<tr>
<td>Metoprolol\textsuperscript{38}</td>
<td>PVP K-30</td>
</tr>
<tr>
<td>Ondansetron HCl\textsuperscript{39}</td>
<td>HPMC</td>
</tr>
<tr>
<td>Sumatriptan succinate\textsuperscript{40}</td>
<td>HPMC</td>
</tr>
<tr>
<td>Drug</td>
<td>Excipients</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Hydroxyethyl Cellulose (HEC) and Xanthan gum (XG)</td>
</tr>
<tr>
<td>Rizatriptan benzoate</td>
<td>HPMC, PVA, and Polyethene Oxide (PEO)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CS and PVP K-90</td>
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<tr>
<td>Baclofen</td>
<td>CP-934 and PVP</td>
</tr>
<tr>
<td>Amlodipine besylate</td>
<td>HPMC and CP-934</td>
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<tr>
<td>Risperidone</td>
<td>CP-934 and SA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>PVP, PVA, and CS</td>
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<tr>
<td>Tizanidine HCl and meloxicam</td>
<td>HPMC</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Hydroxypropyl cellulose (HPC) and Ethyl cellulose (EC)</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Proloc 15 and Eudragit® RL 100</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Fenugreek (Trigonellafoenum-graecum L.) seedMucilage, HPMC K4M and EC</td>
</tr>
<tr>
<td>Ornidazole and dexamethasone</td>
<td>PVA, HPMC K4M, K15M and Eudragit L100</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>HPMC</td>
</tr>
<tr>
<td>Benzydamine HCl</td>
<td>Methylcellulose and PVP</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Pectin and gelan gum</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Acritamer 940, manugel, and hypromellose</td>
</tr>
<tr>
<td>Captopril</td>
<td>PEO and HPMC K4M</td>
</tr>
<tr>
<td>Domperidone</td>
<td>PVP K-90</td>
</tr>
<tr>
<td>Cetlypyrnidium chloride</td>
<td>CS, HPMC, methylcellulose (MC), HEC, and PVA</td>
</tr>
<tr>
<td>Losartan potassium</td>
<td>PVP, HPMC, pectin</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>HPMC3cps,</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>HPMC F4M, HPMC K4M and HPMC K100M</td>
</tr>
<tr>
<td>Etilerfine HCl</td>
<td>Sodium alginate</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>Carboxymethyl Cellulose (CMC)</td>
</tr>
<tr>
<td>Ciclopirox olamine</td>
<td>Poly(Ethylene Oxide) (PEO) and Eudragit</td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>HPMC K4M</td>
</tr>
<tr>
<td>Terbinafine HCl</td>
<td>HPMC</td>
</tr>
<tr>
<td>Ibufrofen</td>
<td>Hydroxypropylcellulose (HPC), CS, and methylcellulose</td>
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<tr>
<td>Clotrimazole</td>
<td>CS and pectin</td>
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<td>Ondansetron HCl</td>
<td>HPMC</td>
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<td>Itraconazole</td>
<td>HPMC and chitosan</td>
</tr>
<tr>
<td>Sumatriptan succinate</td>
<td>HPMC and XG</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>CS</td>
</tr>
</tbody>
</table>

**Conclusion**

According to the results of the current investigation, buccal film is the most precise and palatable dose form since it avoids the hepatic first-pass impact and exhibits good absorption. This is the most innovative and promising technology, beneficial to people of all ages, particularly children, the elderly, and people who have trouble swallowing. Due to their advantages over conventional dosage forms and their ability to be produced at a cheap cost, buccal films can take the place of conventional dosage forms, including rapid disintegrating tablets. This technique offers a useful tool for maintaining the pharmacoeconomic and therapeutic value of drugs.
Acknowledgement

The authors thank the college management for their encouragement and support.

Source of Funding: None

Conflict of Interest: None

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