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REVIEW ARTICLE **OPEN ACCESS**

Fast Dissolving Buccal Film: A Novel Approach to Drug Delivery

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ABSTRACT
Buccal films are commercially viable dosage form that can alleviate numerous difficulties encountered by the patients and pharmaceutical industry. The design and manufacture of an oral film capable of delivering efficient therapeutic dosage is quite challenging and therefore, new technologies have emerged. Oral fast dissolving film is relatively recent dosage form in which a thin film is made from hydrophilic polymers and disintegrates or dissolves quickly on the tongue or in the buccal cavity. Polymers (HPMC, Carbopol), Plasticizers (glycerol, propylene glycol) and penetration enhancers (dimethyl sulfoxide, eucalyptol oil) are the key formulation variables and have the intensive impact on the physico-mechanical and drug release/permeation behavior of the buccal film. Drug delivery innovations have the potential to reduce dose-dependent adverse effects and increase biological activity while also enhancing patient adherence. The review article focuses on the buccal films production processes, assessment criteria, patents, clinical and regulatory aspects, as well as the market potentiality of the dosage form and its future prospects as an effective pharmaceutical dosage form on the worldwide market.
Key words*: Oral film, solvent casting method, bioavailability, swelling index, folding endurance, patents and contact angle*

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INTRODUCTION

Since 1970, fast dissolving buccal drug delivery is known for its applications and are advantageous over other oral dosage form such as tablets, capsules, liquid orals etc. [1] In recent years, dosage forms containing vitamins and other active components have been developed and accepted as buccal films. It is attached to the oral mucosa, and the rate at which the API has to be released from the film is predetermined according to the desired effect. Treating oral candidiasis caused by Candida Albicans is having a local effect on the oral mucosa, while for systemic action the API will pass through the buccal mucosa to the blood stream through internal jugular vein. [2]

As oral route administration poses many challenges, such as orally disintegrating tablets have handling problems as it is fragile in nature.[3] The other oral route administration face problems with bioavailability of drugs mainly due to first pass metabolism, enzymes in GI fluids, pH condition in GIT, enzymes bound to GIT membranes etc. The oral mucosal layer has a larger surface area than the ocular and nasal mucosal layers, it may pass low molecular weight medicines through the mucosal epithelium. [4]

Buccal drug delivery is a method of administration to bypass the first pass metabolism and ultimately improved bioavailability and fastest onset of action. As the novel drug delivery system offers better therapeutic effect, and considered as an ideal dosage form of interest for many API's. Due to scale up difficulties, it fails to reach market in large scale as acceptable formulation. The drug release rate and permeation are influenced by the excipients like plasticizers (glycerol, propylene glycol), permeation enhancers (dimethyl sulfoxide, eucalyptus oil), polymers (HPMC, carbopol). The pH modifiers such as organic acids (tartaric acid; hydroxyl propyl betacyclodextrin) used to enhance dissolution profile in salivary pH.

Ideal properties of Fast Dissolving buccal film [5]

- Film should be thin and elegant
- Good mucoadhesive property
- Should release drug quickly
- Capable of fast disintegration and dissolution without water.
- Film pH value should be within the range of 6.2 to 6.52 to avoid irritation
- Should feel good in the mouth
- Should not leave any residue after administration.

- Stable in environmental conditions like humidity and temperature.
- Less fragile and tolerate handling stress during transportation

Advantages [6]

- Improved stability
- Enhanced patient compliance
- Water is not required for administration
- No risk of chocking
- Taste masking
- Accurate dosing
- Rapid release

Disadvantages

- Large doses cannot be administered
- Drugs with unpleasant taste are not the suitable candidates.
- Drug dilution due to continuous saliva secretion
- Small surface area for absorption

Applications

- Oral mucosal distribution via sublingual, buccal, and mucosal channels via oral thin film may become the preferred delivery method for therapies needing quick drug absorption, such as pain, allergies, and central nervous system diseases.
- Topical applications: Using dissolvable films to administer active agents such as analgesics or antimicrobials in wound care and other applications may be possible.
- Dissolvable films, in which water soluble and poorly soluble molecules of varying molecular weight are packed in film form, are being studied as a gastrorententive delivery device. The gastrointestinal tract's (GIT) pH or enzyme secretion could induce the film's dissolution, which could be employed to treat gastrointestinal disorders.
- Diagnostic devices: Dissolvable films can be loaded with sensitive reagents to allow controlled release when exposed to biological fluids.

PHARMACOPOEIAL STATUS OF ORAL FILMS

Pharmacopoeias (e.g., Ph. Eur., USP) give monographs for common dosage forms. Despite the fact that there are dosage forms used in the oral cavity, such as Medicated chewing gums, Oromucosal preparations, Orodispersible pills, Lyophilisates , although there are no monographs or criteria for oral films with various dissolving kinetics. There are also insufficient pharmaceutical technical methods for analysis and quality control of oral films throughout development. Disintegration and dissolution testing protocols may be offered, but the recommended conditions such as media volumes do not match the natural oral cavity conditions. **[7]**

CLASSIFICATION OF ORAL FILMS

Flash release wafers: Oro flash films are advantageous because they dissolve and disintegrate within seconds in the oral cavity. The method of preparation of flash release wafers includes the solvent casting method, the semi-solid casting method, the hot-melt extrusion method, the solid dispersion extrusion method, and the rolling method. Depending on the types of drugs, flash release oral films have shelf life of three years. The disintegrating rate is within 60 seconds. Route of application is Tongue (upper palate).[8]

Mucoadhesive melt-away wafer: Mucoadhesive drug delivery system is a process in which a polymer is attached to a mucus surface in order to create a stronger bond. The mucoadhesiveness of a substance depends on several factors, including the structure, surface charge, hydration rate, molecular weight, surface tension, and concentration of polymers. Disintegrating rate is within few minutes. Route of application is Gingival, buccal region.[9]

Mucoadhesive sustained-release wafers: Mucoadhesive films are used in many oral medications because they can adhere to the mucous membranes in the mouth and provide a slow, controlled release of the active ingredient. In mucoadhesive delivery systems, various temperature-responsive materials are used during the manufacturing process. These materials change their properties in response to changes in temperature, which can be used to control the release of the active ingredient. Disintegrating rate is maximum 8-10 hours.

CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY [7]

Lyophilized systems: The technique behind these systems entails generating tablet-shaped units from a suspension or solution of a medication with additional structural excipients using a mould or blister pack. Following that, the units or tablets are frozen and lyophilized in a pack or mould. The resultant units have a high porosity, allowing water or saliva to penetrate quickly and disintegrate quickly.

Compressed tablet-based systems: This system is created by compressing excipients directly utilizing ordinary tablet technology. Tablet technologies range in terms of hardness and friability depending on the manufacturing procedure. Fast dissolving tablets disintegrate faster than ordinary tablets because they are made with water soluble excipients, superdisintegrants, or effervescent components that allow water to penetrate the core of the tablet quickly.

Thin film strips: Oral films, also known as oral wafers, evolved from the confection and oral care sectors in the form of breath strips during the last few years to become an innovative and well recognized manner of delivering vitamins and personal care goods to customers. Recently, well-established and widely used technology are used for the systemic administration of APIs in over-the-counter (OTC) treatments, and they are in the early phases of development for prescription drugs. This has been benefited to the consumer success of breath freshener products such as Listerine Pocket Packs in the United States. To create a 50-200 mm film, these methods utilize a range of hydrophilic polymers. The film is created as a large sheet, divided into smaller dose units, and then packed in the formats that have been approved by the pharmaceutical industry.

COMPOSITION

The excipients used[10],[11] in fast dissolving buccal film has been outlined in the table 1.

Drugs

Various APIs are loaded into buccal films. API's can be loaded into the film from 5% w/w to 30% w/w. Water soluble and water insoluble drugs can be used in the fabrication of buccal film, water soluble API'S are incorporated in dissolved state, and water-soluble polymers are used for dispersing water insoluble API's, cyclodextrins mixed with drug will lead to complexation and can enhance solubility. Milled, micronized, particle or nano crystal form of API can be used based on the release profile. Micronized API can be used to get a better film texture and content uniformity. The drugs which can be formulated as buccal films are mentioned in table 2.[13]

Polymers

The successful development of the formulation depends on the selection of polymers since the physical and mechanical properties of film rely on the type of polymer used. The polymers used should be good at dissolving in water, have a good texture, and have appropriate mechanical and chemical properties. The polymer should also have sufficient mechanical and physical properties. To maintain its integrity under stress, a film must be strong enough to withstand any external force, while also having the ability to stretch and deform without breaking. All these characteristics of films are dependent on the selection of the ideal polymer.

Film forming polymers

Ideal Properties of Film Forming Polymer:

- It should be non-irritating and non-toxic.
- The polymer must have a hydrophilic property.
- It should be able to form good films.
- It should have a high wetting and spreading ability.
- Polymer should be easily accessible and reasonably priced.
- The molecular weight of the polymer should be low.
- It must have a long enough shelf life.
- The polymer must be odourless and colourless.
- There should be no secondary infection in the oral mucosa.
- It must have sufficient peel, shear, and tensile strengths.

Water soluble polymers:

Rapid disintegration is achieved by film formers or water-soluble polymers. It helps to improve mechanical properties. The rate of polymer disintegration is slowed by increase in molecular weight of polymer films. Depending on the type of formulation, different polymers with varied properties must be considered. Depending on the dosage form, different conditions for buccal mucoadhesion may arise.

Mucoadhesive polymers

Hydrophilic polymers and hydrogels are two types of mucoadhesive polymers. Polyvinyl alcohol [PVA], sodium carboxy methylcellulose [NaCMC], hydroxyl propyl methyl cellulose [HPMC], hydroxyl ethyl cellulose, and hydroxypropyl cellulose [HPC] are the most prevalent hydrophilic polymers utilized in buccal dry or partially hydrated dosage forms. Anionic polymers such as carbopol and polyacrylates, cationic polymers such as chitosan, and non-ionic polymers such as eudragit which mimics like hydrogels. [6]

Plasticizer

The use of plasticizers increases the mechanical properties of the film such as tensile strength and elongation, therefore concentration of plasticizer will have an effect on mechanical properties. It has the potential to increase the flow of the polymer while also increasing its strength. It's critical to choose the

right plasticizers. It should be compatible with the drug, as well as polymers and other materials with the addition of the additional excipients. The film may break, split, or peel as a result of the incorrect selection of plasticizer.

Surfactants

Surfactants aids in dissolution of the buccal film and immediately release the API, also known as wetting or solubilizing agents. The goal of utilizing saliva stimulating chemicals is to enhance the rate at which saliva is produced, allowing the oral film to disintegrate and dissolve more quickly in the oral cavity. In the range of 2-6 percent, it can be used alone or in combination.

Flavors

For enhancing acceptance, flavor can be added. Synthetic flavor oils, oleo resins, and extracts obtained from various sections of plants such as leaves, fruits, and flowers can all be utilized. It can be used on its own or in conjunction with other items. The amount of flavor necessary to cover the taste is determined by the kind and strength of the flavor.

Color

Colouring agents can be added to improve elegance. The most often used pigments include silicon dioxide, titanium oxide, and FD&C certified coloring compounds. Their concentration should not be more than 1%

Saliva stimulating agents

It is used in buccal films to enhance disintegration which results in better drug release. The goal of utilizing saliva stimulating chemicals is to enhance the rate at which saliva is produced, allowing the oral film to disintegrate and dissolve more quickly in the oral cavity. In the range of 2-6 percent, it can be used alone or in combination with other saliva stimulating agents. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are some of the most often utilized saliva stimulating substances. Citric acid is the most popular among them.

METHOD OF PREPARATION

Solvent casting method

In the solvent casting process, water soluble polymers are dissolved in water, while the drug and additional excipients are dissolved in a suitable solvent. Solvent casting method is preferred over others as it is simple and economical. The two solutions are then mixed and agitated on magnetic stirrer to form homogeneous solution, before being cast into a Petri plate and allowed for drying in uniform temperature. Solvent casting method is preferred over others as it is simple and economical.

Semisolid casting

A method of semisolid casting is by making a solution of a water-soluble film forming polymer. The resultant solution is mixed with an ammonium or sodium hydroxide solution of an acid insoluble polymer (e.g., cellulose acetate phthalate, cellulose acetate butyrate). The required amount of plasticizer is then applied, resulting in a gel mass. Finally, heat-controlled drums are used to cast the gel mass into the films or ribbons. The film's thickness ranges from 0.015 to 0.05 inches. The acid insoluble polymer should be used at a 1:4 ratio with the film forming polymer.

Hot melt extrusion

In this procedure, a hot melt extruder is employed. The heating process is used to shape a polymer into a film in this approach. A dry mixture of pharmaceutical components, including API, is placed in the hopper, delivered, mixed, and heated, and then extruded out in a molten form by the extruder. The film is cast from the molten mass that has resulted. The casting and drying process is a crucial phase. This method offers a number of benefits, including lower temperature and shorter residence durations for the drug carrier mix, the lack of organic solvents, continuous operation options, little product waste, good control of operating parameters, and the ability to scale up.

Solid dispersion method [14]

One or more active ingredients are disseminated in a solid state in an inert carrier in the presence of amorphous hydrophilic polymers in this approach. To make a solution, the API is dissolved in a suitable solvent without removing the liquid solvent, the solution is poured into a melt of a suitable polymer (PEG) that is below 70 °C. Finally, solid dispersion is molded into films using dies.

Rolling [14]

A pre-mix is made up of film-forming polymers, polar solvent, and other ingredients, with the exception of a medication. To the pre-mix, The required amount of drug is added to make homogeneous matrix, the medication is combined with pre-mix. The resulting mixture is put into the roller, the support roller forms the film and transports it away. After that, the wet film is dried using a controlled bottom drying method. Finally, film is trimmed to the size and shape required

CHARACTERISTICS OF BUCCAL FILM

Organoleptic properties

The film should exhibit appropriate organoleptic qualities such as color, flavor, and taste since it disintegrates in the oral cavity. Because they are given to geriatric patients and children, an oral thin film should have a pleasing color and be consistent. The flavors in the formulation should have a pleasant odour and cover the taste of the polymer, medication, and other excipients. Patient acceptance is influenced by the taste of the film. For the physical examination, specially designed taste panels are employed. In addition, an electronic tongue approach is applied, which is based on the principle of potentiometric titration method.

Thickness

Thickness of a buccal film is influenced by distribution uniformity of components of the formulation. Thickness range should be 5-200 micro meter. It is measured by a digital Vernier caliper or a micrometer screw gauge. [15]

Folding endurance

Folding endurance represents the brittleness or mechanical strength of the film. It is determined manually, by folding the film repeatedly at the same line until it breaks. The value of folding endurance represents the number of times film folded without breakage. [16]

Surface pH

To identify whether film produces any irritation to buccal mucosa, the surface pH of all formulation is measured after swelling. The pH of the film's surface must be checked. The film's surface pH should be neutral, i.e., 7, or near to 7. For this, a mixed pH electrode can be utilized. The pH is determined by putting the electrode in contact with the film and noting the pH measurement. This test is performed on at least 6 films, and the mean SD may be computed to get the final surface pH value. [17]

Assay /Content uniformity

By estimating the drug content in each film, it was possible to determine whether the drug was distributed uniformly in the formulation. In each formulation, three films are taken randomly from six films. Individually weighed films were dissolved in the solvent system for 30 min while being continuously stirred on a water bath for 6 hours at a temperature of 37 °C. [15] Standard method should be followed as per pharmacopoeia for different drugs, content uniformity should be within the limit of 85-115%.[18]

Swelling Index

Film should be bioadhessive in nature and should get hydrated in buccal cavity. It indicates the ability of hydrophilic polymers used in the formulation. The buccal film is pre weighed(W1) and it is allowed to swell in a medium and at specific time interval film is recovered from the medium and weighed (W2). The swelling index is calculated by:

$$\%S = Xt\text{-}X0/X0 \times 100$$

Where, %S – Swelling index expressed in percentage, Xt - the weight of swollen film after time t, X0 – the initial weight of film at time zero.

In vitro disintegration test

When film is exposed to water or saliva the time taken by the film to disintegrate or break is considered as disintegration time. The medium used is phosphate buffer. Disintegration time should be between 5-30 sec.

In vitro dissolution test

The dissolution is the amount of drug from the formulation, which goes into the solution at standard condition of temperature and solvent. The selection of dissolution media is very important and most of the time the film floats on the medium, therefore sink condition can be considered. Temperature preferred should be 37°C at 50 rpm. [19]

Contact angle

Wetting behavior, disintegration time, dissolution of oral film is determined by obtaining information about contact angle. It is measured by the goniometer at room temperature. Distilled water dropped on the film and image is analyzed by using software, further contact angle is determined. It provides data on wetting behavior, disintegration time, and oral film dissolution. Double distilled water should be utilized for this purpose. A dry film is taken, and a drop of double distilled water is put on the dry film's surface. Within 10 seconds after deposition, a digital camera captures images of water droplets. For angle determination, digital images should be analyzed using image J 1.28v software (NIH, USA). [20]

Storage and Packaging of Films

Fast dissolving films comes in a number of storage and packaging choices. The packaging stage allows medicine manufacturers to be more flexible with their products. For films, single packaging is required; the most typical packaging shape is an aluminum bag. The Rapid card, a proprietary and patented packaging system developed for the Rapid films. Each side of the fast card stores three raid films and is the same size as a credit card. Every dose can be taken separately.

PATENT AND RECENT PUBLICATIONS

By granting patent, patentees will benefit a period of market exclusivity, the patent system prevents such free riding. In addition to rewarding prior investments, it offers incentives for ongoing innovation. Many researchers patented their work on the aspect of fast dissolving buccal films[21] using different drugs, polymers, excipients and employing various methods of preparation which is illustrated in table 3. The research activities related to fast dissolving buccal film has been compiled into table 4.

CLINICAL AND REGULATORY ASPECTS

If the product is bioequivalent to an existing oral medication, the US Food and Drug Administration (US FDA) uses the Abbreviated New Drug Application (ANDA) procedure. There are no clinical trials involved with this generic approval procedure (Food, Drug, and Cosmetic Act section 505 (j)). A comparison of bioequivalence between an orally disintegrating tablet (ODT) formulation and an orally dissolving film (ODF) product is an example of such a situation. However, when compared to the currently marketed medication, the new oral film product may have a different pharmacokinetic profile.

Since the ODF is a "new dosage form," it must go through the Section 505 (b) (2) approval process. A fresh clinical investigation would be necessary in this scenario. The benefit of the current clinical research is that it would grant the product three years of marketing exclusivity. According to the European Medicines Evaluation Agency's criteria, marketing authorization clearance is required in Europe. Either of the two options, namely decentralization or mutual recognition, can be implemented. In Japan, product approval is handled by the Ministry of Health, Labor, and Welfare. Many regulatory authorities place a premium on flavor and palatability, particularly if the product is aimed at children.

Both animal models and humans are used to investigate oral mucosa irritation. The most relevant model for animal investigations is the hamster cheek pouch, which is a good model for predicting irritation criteria prior to testing in humans. The clinical endpoint is important in clinical studies. It's important to specify the primary and secondary outcome measurements. The goal is to demonstrate the superiority and benefit of the newly created oral films over current typical standard dosage forms. The International Conference on Harmonization (ICH) has issued guidelines for product development.

Companies can take either an empirical or a more systematic approach to product development, according to the ICH Q8 guideline on pharmaceutical development. Different issues should be addressed in separate well-defined trials, according to the clinical research protocol. The intended investigation should have enough precision to detect important negative health effects (including supporting rationale). The study size(s) are determined by the type of investigation (e.g., soft tissue and/or hard tissue effects).

All endpoints should be defined and specified. It is necessary to offer a description of the usage pattern(s) (single/multiple application). After treatment, follow-up should be specified for an appropriate duration (e.g., single application with follow-up intervals of 1, 3, 6, and 12 months; multiple applications with prolonged follow-up, etc.). Confounders and effect modifiers should be included, as well as a description of the topic source(s), selection criteria, and methodology, as well as necessary analytical information. Clinical impact and medication bioavailability may change significantly from traditional dose forms due to altering drug dissolving properties.

Because it is a noninvasive delivery device, it avoids most of the first-pass impact, which might change the clinical profile. The safety profiles can be improved because hazardous metabolites produced by hepatic metabolism can be reduced when the medication is absorbed mostly through the buccal mucosa. Another advantage is its speedier commencement of action, which results in rapid clinical end-point symptoms. The intersubject variability in clinical response is reasonably decreased because each strip ideally includes exact doses of the medication and the dosage form is independent of physiological variability of the gastrointestinal system. The medication absorption through the oral mucosa is faster than conventional counterparts, which must breakdown and then solubilize the active component, there might have a risk of dose dumping therefore, clinical consequences should be investigated. The safety elements of the dose form should be continuously monitored due to this quick response characteristic.

FUTURE ASPECTS

Various buccal delivery films have been marketed which is mentioned in table 5, are being considered for the treatment of conditions like common cold, trigeminal neuralgia, Meniere's disease, diabetes, and alcohol addiction. There are several medications for treating this complicated neurological ailment known as Parkinson's disease. Various medications are available for treating Parkinsonism, but finding one that truly alleviates the symptoms of the condition is still difficult. Most of the drugs cause a number of problems and non-motor symptoms when given long-term treatment.[45] This alternate route of administration can increase bioavailability while also providing quick and direct distribution into the systemic circulation, simple accessibility, improved patient compliance.[46]The film adheres to the buccal mucosa easily, adapts

to the mucosal surface better, and has a longer retention time than other buccal dosage forms, buccal film is the most sophisticated and widely used drug delivery method.[47]

For the treatment of hypertension and angina pectoris, lercanidipine has a 10% bioavailability due to food dependent absorption, poor solubility, limited permeability, and significant first pass metabolism.[48] Fast-dissolving oral films with lercanidipine nanoparticles added increase bioavailability by enhancing Oro transmucosal absorption. [49]

With reference to life quality and total human improvement, nutrients and nutraceuticals with well-known roles in illness prevention and eradication are becoming more relevant. A new paradigm for cutting-edge delivery methods for compounds with nutritional or nutraceutical importance may be represented by OF. [50]

Therapeutic proteins and peptides have distinct, unmatched pharmacological properties, such as high receptor selectivity and superior biological mimicking of physiological mechanisms that make them preferable to traditional chemically generated medications in terms of therapeutic index. Proteins, however, also have inherent bioavailability restrictions. In order to enhance the stability, permeability, and pharmacokinetics of protein/peptide therapeutics, there are numerous useful strategies, with a focus on oral polymeric films as oral delivery platforms. Indeed, oral films have inherent qualities that can significantly improve patient compliance, biological performance of proteins and peptides, and other benefits. [51]

Most patients and physicians accept donepezil (DP) as an Acetylcholinesterase inhibitor since it has few side effects and can help patients' cognitive function. Due to ageing and illnesses, the dosing schedule for Alzheimer's disease patients is also essential. Donepezil oral tablets are available; however, there are still a lot of issues that need to be resolved. The route of administration of DP is currently the subject of an increasing amount of study in an effort to enhance patient self-administration. The formulation of the oral disintegrating tablet (ODT) is preferred by carers of Alzheimer's disease (AD) patients receiving donepezil medication over the film-coated tablets. In six areas: adverse effects, effectiveness, medical treatment, simplicity and convenience of taking medications, influence of medications on daily activities, and shows general satisfaction.

Table 1: List of excipients and their characteristics

SL No.	Category	Examples	Properties
1	Polymers	Hydroxypropyl Methylcellulose (HPMC) [12]	HPMC has great film forming property and is widely accepted. The lower grades of HPMC, like Methocel E3, Methocel E5, and Methocel E15, are commonly used for MDFs because they have low viscosity.
		Hydroxypropyl Cellulose (HPC)	HPC is non-ionic water - soluble thermoplastic polymer. Because films made with polymers having high glass transition temp values are stiff. HPC is available commercially in different grades, each with a different solution viscosity. The molecular weight of HPC ranges from 50,000 to 1,250,000.
		Pullulan	Pullulan is the water - soluble natural polymer. Pullulan is an ideal choice for the consumable film because it is highly water soluble, colourless, tasteless, odourless, transparent, flexible, possess low permeability to oil and oxygen, and heat sealable.
		Poly (Ethylene Oxide) (PEO)	Poly (ethylene oxide) is a non-ionic, high molecular weight water-soluble polymer. PEO films exhibit higher bioadhesivity because of the exceptional flexible nature of the PEO structure, which allows extension of the polymer chains and formation of interpenetration between PEO and mucin. Polyox N-80 is a polymer that may be used in the oral film.
		Modified Carboxymethyl Cellulose (CMC)	CMC is modified cellulose, having neutral flavour and produces films with excellent clarity. CMC is ideal for many applications such as fast dissolving base which is capable of carrying a range of active components.
		Pectin	Pectin is a natural polymer in the form of carbohydrate obtained from citrus fruits and apples. Pectins are excellent film formers with good capacity to carry drugs in the oral cavity and especially suitable for low pH applications. It has been discovered that the in-vivo disintegration time of pectin films are 15 seconds and the in-vivo dissolution time is 141 seconds.
		Gelatin	Gelatin is derived from the natural protein collagen; gelatin is widely used in food and pharmaceutical industry. Gelatin is transparent, odourless, colourless or slightly yellow, brittle flakes or powder. The swelling and absorbing capacity of gelatin is 5-10 times its weight of water to form gel in aqueous condition at temperature between 30-35 °C.

2	Plasticizers	Propylene Glycol (PG) [7]	Propylene glycol is a clear, colourless, viscous, practically odourless liquid, with a sweet, slightly acrid taste resembling glycerine. Propylene glycol is non- toxic material and is commonly used as a plasticizer in aqueous film-coating formulations. PG as a plasticizer having good appearance.
		Polyethylene Glycol (PEG)	Polyethylene glycol is non- toxic and non-irritant material are used in variety of pharmaceutical formulations. PEG 400, PEG 1450, PEG 8000 and PEG 20000, decrease the tensile strength of fast dissolving films. PEG is the most effective plasticizer for the fast-dissolving film.
		Dibutyl Phthalate	Dibutyl phthalate is an odorless, oily, colorless, viscous liquid and relatively non-toxic material which is used as plasticizers in films and film coatings.
3	Surfactants	Sodium lauryl sulphate	Freely soluble in water, producing an opalescent solution; almost insoluble in ether and chloroform. At 308°C, the spreading coefficient is 7.0 (0.05 percent by weight of an aqueous solution). Surface tension for a 0.05 percent w/v aqueous solution at 308°C is 25.2 mN/m (25.2 dynes/cm). Wetting time is 118 seconds at 308°C (0.05 percent w/v aqueous solution).
		Benzalkonium chloride	pH is 5-8 for 10% w/v aqueous solution. Anti-microbiological action: Solution of benzoalkonium chloride is effective against a variety of bacteria, yeasts, and fungi. Activity is low against bacterial endospores and more pronounced against Gram-positive bacteria than Gram-negative bacteria and acid-fast bacteria. The capability of antimicrobial activity depends on benzalkonium chloride on the alkyl homologous mixture.
		Tweens	It is available mainly as Polysorbate 20, 60 and 80. According to reports, polysorbate 80's critical micelle concentration in clean water is 0.012 mM.
		Spans	Span-20 has an HLB of 8.6 and is soluble in water, cottonseed oil, mineral oil, tetracarp, and xylene to varying degrees. It is also soluble in liquid paraffin to varying degrees, but not completely.
4	Flavors	Peppermint	Not less than 5% of menthyl acetate of the peppermint flavour and less than 50% of the total menthol must be present.
		Fruit flavors	Apple: Manzanate (Ethyl 2-methylpentanoate) Pineapple: Allyl Hexanoate or Allyl Caproate Orange: d-Limonene, Ethyl Butyrate
5	Color	Annatto extract	Orange-Red, can be used in formulations which can be used for internal and external purposes. Norbixin is the pigment which is water soluble.
		β-Carotene	Percussor of retinol (Vitamin A). Red-Orange, Ingested drugs generally and external drugs.
6	Saliva stimulating agent	Citric acid	Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether. Viscosity (dynamic) 6.5 mPa s (6.5 cP) for a 50% w/v aqueous solution at 258 °C.
		Tartaric acid	Density is 1.76 g/cm3 and Dissociation constant, pKa = 2.93 at 258°C; pKa = 4.23 at 258 °C. [10]
		Malic acid	Dissociation constants, pKa = 1.91; pKa = 6.33. Solubility in water is 1 in 2.05 at 20 °C.
7	Sweeteners	Aspartame	pH is 4.5–6.0 (0.8% w/v aqueous solution) Brittle fracture index is 1.05.
		Saccharin	Acidity/alkalinity: pH is 6.6 (10% w/v aqueous solution) Solubility in water at 20°C is 1 in 1.2.
		Mannitol	True density is 1.514 g/cm3 Solubility 1 in 5.5 parts in water at 20°C.

Table No. 2 Examples of drugs which can be formulated as buccal films

CATEGORY	DRUGS
Anti-ulcer	Omeprazole
Anti-asthmatics	salbutamol sulfate
NSAID	Paracetamol, meloxicam, valdecoxib
Vitamins and Hormones	Melatonin, Ascorbic acid, riboflavin
Antiepileptics and sedatives	Diazepam, Lamotrigine
Antiemetics	Ondansetron
Antihypertensive	Lisinopril, Atenolol, Clonidine HCl

Table No.3 The patents on buccal film

Inventors & Year	Patent no	Work
Myers *et al*,2013	8475832	The current invention relates to self-supporting dosage forms that contain an active agent for treating opioid addiction while also ensuring adequate buccal adhesion.
Myers *et al,* 2010	20100297232	Concerned with the composition of an ondansetron film with a flavor masking component
Bess *et al,* 2010	7648712	Prepared orally consumable films using a taste masking agent like dextromethorphan and a water-soluble film-forming polymer like pullulan.
Myers, Garry L. 2011	7910641	The invention relates to pH modulated films that include at least one non-neutral pH component when mixed with water, as well as a pH modulated polymer system.
Myers *et al* ,2012	8298583	This invention relates to a pharmaceutical-based film system that incorporates various small-scale forms of pharmaceutically active compounds, such as Tetrahydrolipstatin, into a film.
Campbell, Shannon E. 2012	8092993	Prepared a hydrogel thin film that acts as a biosensor and detects pathogen-specific markers binding to their affinity molecules.
Maibach, Todd. 2009	20090004254	This has to do with the production of orally dissolvable edible films for the introduction of active pharmaceuticals into the buccal cavity with Pullulan polymer.
Zerbe et al 2011	20110136815	Using a mixture of crystallization inhibitors, a solid oral film dosage form was created in order to increase stability.
Lee et al 2008	8110547	The current invention relates to a parathyroid hormone (PTH) delivery composition that includes a delivery agent, a PTH component, and an antiresorptive agent for buccal administration.

Table No.4 Publications on Buccal films

SL. No	Drug	BCS Class	Ingredients	Novelty	Author	Ref
1	Glibenclamide (GLB)	BCS Class II	Hypromellose (HPMC K15 M), β-Cyclodextrin (βCD), Polyvinylpyrrolidone K30 (PVP K30), Polyethylene glycol 6000 (PEG 6000), glycerin.	The current study demonstrates that a mucoadhesive buccal HPMC K15 film containing GLB has a high potential for systemic distribution and extra benefit of avoiding the hepatic first pass metabolism in the first instance	Sana Saffiruddin Shaikh and Aateka Barrawaz	21
2	Quinapril	BCS Class I	HPMC 50CPS, HPMC E5, HPMC E15, SSG, propylene glycol, citric acid, menthol and Pullulan	Quinapril mouth dissolving films have greater patient compliance and to give an effective therapy option for hypertensive patients who are disabled or unable to cooperate.	P.Vamsee Kumar,Y. Shravan Kumar	22
3	Paroxetine	BCS Class III	HPMC E15, PVA, PVP,Glycerol,saccharin and vanillin	The findings imply that Paroxetine's developed mucoadhesive buccal film may function better than the standard dosage form, resulting in enhanced efficacy and patient compliance.	Arjun KL, Ashok Kumar P, Manjunath K, Suresh V. Kulkarn	23
4	Clonidine Hydrochloride	BCS Class III	HPMC E 15, PEG 400, citric acid,SLS,Xylitol,Flavour.	The QbD-assisted development of a fast-dissolving buccal flm for clonidine hydrochloride resulted in significantly better biopharmaceutical performance as well as patient compliance.	Pankaj V. Dangre,RamD.Phad, Sanjay J. Surana, and Shailesh S. Chalikwar	24
5	Montelukast sodium	BCS Class II	HPMC E 15 LV, HPMC E 50 LV, PVA (2%W/V) PVP, MC 360-400CPS Ethanol, Glycerol (Mannitol (5%W/V) Menthol.	The goal of the current study was to develop fast reproducible montelukast sodium oral thin films that would enable drug absorption in the oral cavity without first	K.Vijaya Sri*, P.Rohini and G. Kamalaka R Reddy	25

				pass metabolism, improving patient convenience and compliance in both elderly and pediatric patients.		
6	Etoricoxib	BCS Class II	Etoricoxib-beta-cyclodextrin complex Hypromellose (hydroxypropyl methyl cellulose 15 cPs). Sucralose, Mixed fruit flavor, Bitter masking flavor, Glycerine.	Drug inclusion complex with beta-cyclodextrin increase solubility of the drug and helps in taste masking.	K. Senthilkumar and C. Vijaya	26
7	Propranolol Hydrochloride	BCS Class I	Pullulan, Propylene glycol, Polyvinyl pyrrolidone, Citric acid, Mannitol, Menthol.	Bypass first pass metabolism of propranolol HCl.	Joshua JM, Hari R, Jyothish FK, Surendran SA	27
8	Simvastatin	BCS Class II	Hydroxy propyl methyl cellulose (HPMC 50 cps), Carbopol 940, glycerol, propylene glycol and dimethyl sulfoxide.	The novelty of this study is that it focuses on newer areas of buccal formulation, including tolerability and compatibility difficulties, as well as the impact of formulation variables on buccal film performance. The findings of this study will highlight some of the most important challenges involved in the creation of film/patch formulations.	Magdaline Tarai, Jaya Gopal Meher, Ansuman Patnaik, Dr. Paresh Mishra, Dr. H. Lalhlenmawia*	28
9	Dicyclomine	BCS Class I	HPMC-15, PVA, Eudragit RL- 100 and Aspartame.	This work demonstrates that rapid dissolving dicyclomine HCL films can be created with the goal of improving therapeutic efficacy with increased bioavailability and better patient compliance.	Alka Tomar, Kiran Sharma, Nitesh S Chauhan, Ashu Mittal, Umakant Bajaj	29
10	Levocetirizine di hydrochloride	BCS Class III	HPMC 15 cps, Polyvinyl alcohol, Propylene glycol, Aspartame, Water.	Preparing quick release films of levocetirizine with the purpose of developing a dosage form for a very quick onset of action, which is beneficial in managing severe conditions of allergies, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water.	Prabhakara Prabhu, Ravi Malli, Marina Koland, K Vijaynarayana, Ullas D'Souza, Harish NM, CS Shastry, RN Charyulu	30
11	Domperidone	BCS Class II	Polyvinyl pyrrolidone K-90 (PVP K-90), PEG 400, ethyl alcohol, tween 80.	Domperidone (DMP) an anti-emetic drug with low water solubility and vulnerable to extensive first-pass effect. To overcome these limitations, in this work, the author designed and produced fast dissolving muco-adhesive buccal films of domperidone using varying amount polyvinylpyrrolidone (PVP K-90) using the solvent casting method	Gamal M. Zayed, Saleh Abd-El Rasoul, Mohamed A. Ibrahim, Mohammed S. Saddik d, Doaa H. Alshora	31
12	Atorvastatin	BCS class II	HPMC, glycerine, CCS, SSG, CP, PEG 400, Aspartame, citric acid, water.	Solid dispersion of Atorvastatin with PEG 4000 was prepared by physical mixture method in order to increase solubility. Fast dissolving oral film containing Atorvastatin were prepared using solvent casting method,	Shananaj Khan, Shradha Shende, Dr. Navjot Singh	32

				dissolution rate studies indicated greater dissolution rate of Atorvastatin from fast dissolving oral film.		
13	Escitalopram	BCS Class I	Hydroxypropyl methylcellulose, polyethylene glycol 400, hydrochloric acid, sodium dodecyl sulphate, Cross .carmellose, vanillin and Citric acid	The developed formulations can avoid the first pass effect, making them more effective in terms of their ability to provide therapeutic benefits. Additionally, it increases the product's lifespan, making it more appealing dosage forms.	Madiha Mushtaque, Iyad Naeem Muhamma, Syed Muhammad Fareed Hassan, Aatka Ali and Rida Masood.	33
14	Cetirizine and Dextromethorphan	BCS Class III and BCS Class II	Drugs (Cetirizine, Dextromethorphan,) Polymers (HPMC E15 LV, HPMC E5 LV, PVA Plasticizers PEG 400), Super disintegrants (Cross Carmellose Sodium), Sweeteners-(Aspartame, Neotame, Sucralose, Sodium saccharin, Liquorise), Favours (Menthol), Ion Exchange resin (Kyron T111), Food Color FDA approved orange colour	In comparison to a single drug, the combined effect of the two drugs will be more powerful. In order to mask the taste of cetirizine and dextromethorphan, the studies were to design a fast-dissolving film by casting method using HPMC E5 LV, polyethylene glycol 400, aspartame, neotam-tartaric acid, citric acid, and mentholion exchange resins.	Dipal M. Patel,Dhaval J. Patel and Palak J. Darji	34
15	Rofecoxib	BCS Class 2	Hydroxy propyl methyl cellulose (15cps), Aspartame, menthol, ethanol, water, Glycerin and poly-sorbate 80.	NSAID rofecoxib is frequently used to treat osteoarthritis and tooth pain. Since the medication is water insoluble, its dissolution is primarily important which influence absorption and pharmacological activity.	Kulkarni Parthasarathi Keshavarao, Dixit Mudit, Gunashekara K, Shahnawaz Anis, Singh Mangla N and Kulkarni Ajay	35
16	Metoclopramide Hydrochloride (MTC HCl)	BCS Class 3	HPMC 15 cps, HEC,SCMC,PEG 400, No suggestions acid, sodium saccharine, mannitol, tween 80.	As this drug undergoes first pass metabolism there is a noticeable variation in the bioavailability to range from 60 to 90 percent. As a result, it is highly recommended that MTC HCl be formulated as fast dissolving films since this will results in enhancing the pharmacokinetic characteristics of the drug by improving the absorption rate	Iman Sabah Jaafar	36
17	Levocetrizine hydrochloride and Montelukast sodium	BCS Class III and BCS Class II	HPMC E5 LV, HPMC E50 LV, HPMC, glycerol, di-butyl phthalate	Levocetrizine hydrochloride and Montelukast sodium flash release wafers were developed and characterized as part of the current research study. The solvent casting method was used to create flash release wafers.	S. Subramanian, P. Mani.	37
18	Fluoxetine hydrochloride (FH)	BCS Class I	Polyvinyl alcohol, PVP K30, Menthol, Mannitol, Water	The solvent casting approach can be used successfully to produce fast dissolving fluoxetine HCl Oro flash films (FHOFF's). Since FH takes 6–8 h to reach its peak plasma concentration, formulating it as FHOFF speeds up the onset of action while also improving bioavailability.	Naga Thirumalesh Chevala, Suryaprabha Matangi, Naga Pavan Kumar Chevala, Gulshan Mohammed, Sarvan Mani Kiran Seethamraju, Rama Rao Nadendla1	38
19	Salbutamol sulphate	BCS Class I	Salbutamol sulphate, strawberry flavor, mannitol, polyvinyl alcohol, glycerol,	To create and improve the salbutamol sulphate fast-dissolving film, which can be helpful during an asthma	R. C. Mashru, V. B. Sutariya, M. G. Sankalia, and P. P. Parikh	39

			Deionized double-distilled water.	attack. The film is administered sublingually and was created using a solvent evaporation process.		
20	Repaglinide	BCS Class II	PVA, PVP, water.	To address the issue of poor water solubility, research focuses on the formulation and evaluation of polyvinyl alcohol (PVA)-polyvinyl pyrrolidone (PVP) nanofibers. According to the results of the glucose tolerance test, formulation had better control over glucose levels than the free medication.	Shreya Thakkar, Namdev More, Dilip Sharma, Govinda Kapusetti, Kiran Kalia & Manju Misra	40
21	Dexamethasone	BCS Class I	Microcrystalline cellulose, polyethylene glycol, Hypromellose, polysorbate 80 and L-HPC.	By fabricating rapidly dissolving oral film containing 4 mg of dexamethasone, and the author tested the film's effectiveness as an antiemetic in breast cancer patients undergoing a highly emetic chemotherapy regimen that included anthracycline and cyclophosphamide	Minako Nishigaki, Kana Kawahara, Masahito Nawa, Manabu Futamura, Misao Nishimura, Katsuhiko Matsuura, Kiyoyuki Kitaichi, Yoshihiro Kawaguchi, Tadao Tsukioka, Kazuhiro Yoshidac, Yoshinori Itoha	41
22	venlafaxine HCl	BCS Class I	Hydroxypropyl methylcellulose (HPMC) LV E3, Sodium starch glycolate (SSG), Saccharine sodium, Citric acid.	Venlafaxine HCl fast dissolving oral films (FDOFs) was created using a full factorial design with three components and three levels (33) to optimize the concentration of polymer and plasticizer. Oral thin film formulation has the potential to be a unique therapeutic dosage form for both the general population and pediatric and geriatric patients. Therefore, it was discovered that venlafaxine HCl oral films with rapid dissolution were suited for producing a greater therapeutic impact while treating depression.	Arwa Ibrahim Al-Mogherah, Mohamed Abbas Ibrahim, Maha Abdelazeem Hassan	42
23	Saquinavir	BCS Class IV	Malic acid, glycerol and agarose (type I), Hydroxypropyl methylcellulose (HPMC) K100 LV, HPMC K3 LV, water.	This study sought to clarify the link between micro environmental pH (pHM, or the pH around the swelling films) and saquinavir release by examining two release testing techniques for characterizing buccal films.	Shaolong He, Jette Jacobsen, Carsten Uhd Nielsen, Natalja Genina, Jesper Ostergaard, Huiling Mu	43
25	Itraconazole	BCS Class II	HPMC K100M, HPMC K4M, Chitosan, Solvent (Ethanol: MDC), PEG 400, 1% Lactic acid in water.	Formulated to treat oral candidiasis. The oral buccal mucosa is the local target of the film. This medication is used to treat various fungal infections.	Fayeja S. Rajebhai, Dr. Vishnu M. Patel, Dr. Maulik R. Mehta, Dr. Anand K. Patel	44

Table No.5 Examples of marketed products

SL.No	Drug	Category	Brand Name	Manufacturer
1	Acetaminophen/Phenylephrine	Cough and cold	Theraflu	Novartis
2	Benzocaine	Sore throat	Prestige	Chloraseptic
3	Clonazepam	Anticonvulsant	Klonopin Wafers	Solvay Pharmaceuticals
4	Cool mint	Mouth freshners	Listerine	Pfizer
5	Dextromethorphan HBr	Cough suppressants	Triaminic	Novartis
6	Donepezil	Alzheimers disease	Donepezil Rapid Film	Labtec
7	Fentanyl Citrate	Pain management	Breakyl Onsolis	Meda Pharmaceuticals LTS
8	Menthol	Mouth freshners	Suppress	InnoZen, Inc
9	Nicotine	Smoking cessation	Niquitin	LTS
10	Ondansetron	Antiemetic	Setofilm Zuplenz	LTS Vestiq Pharmaceuticals
11	Phenylephrine	Relieving congestion	Sudafed PE	Wolter Kluwer Health Inc
12	Simethicone	Anti-Flatulence	Gas X	Novartis

CONCLUSION

Fast dissolving buccal film have importance in emergency cases such as allergic reactions, asthmatic attacks, angina patients or whenever immediate onset of action required. In order to avoid first pass metabolism of particular drugs, FDBF is important therefore increased bioavailability for the formulations can be established.

When compared to traditional oral dose forms, fast dissolving oral films offer improved patient compliance and may improve biopharmaceutical properties, efficacy, and safety. Following the Fast-Dissolving Tablets, the new Fast Dissolving Oral Films are intended for use in the oral cavity and are an innovative and promising dose form, particularly for elderly patients.

Fast dissolving pharmaceutical products also present a market potential for a wide range of drugs like NSAIDS, antiulcer, antihistamine, Hypnotics & sedatives, antipsychotics, antiparkinsonism, antiemetic, antimigraine, and antidepressants. Because of its speedy action, i.e., within a minute, this approach will be most accepted and prescribed in the future. The popularity of these dose forms is growing due to increased patient demand.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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