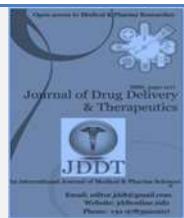
Available online on 15.03.2022 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2022 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited



Open Access Full Text Article



Review Article

Oral Dissolving Films: A Comprehensive Review on Recent Perspectives and Current Approach to Effective Drug Delivery

Arushi Saxena* Taruna Singh

Department of Pharmaceutical Sciences, Rakshpal Bahadur College of Pharmacy, Bareilly, U.P., India, 224001

Article Info:



Article History:

Received 21 January 2022
Reviewed 26 February 2022
Accepted 02 March 2022
Published 15 March 2022

Cite this article as:

Saxena A, Singh T, Oral Dissolving Films: A Comprehensive Review on Recent Perspectives and Current Approach to Effective Drug Delivery, Journal of Drug Delivery and Therapeutics. 2022; 12(2):139-147

DOI: <http://dx.doi.org/10.22270/jddt.v12i2.5244>

*Address for Correspondence:

Arushi Saxena, Department of Pharmaceutical Sciences, Rakshpal Bahadur College of Pharmacy, Bareilly, U.P., India, 224001.

ORCID ID: <https://orcid.org/0000-0002-5604-0613>

Abstract

Oral dissolving films are advanced oral dosage forms implied for the attachment onto the buccal mucosa and have both local and systemic effects. These dosage forms may be favored over other oral drug delivery systems in terms of flexibility and comfort. These films utilize the property of bioadhesion of certain polymers, which on hydration target a particular region of the body for extended period of time thereby bypassing first pass metabolism and promoting increased bioavailability. These films are self-administrable, pharmacoeconomic and have good patient compliance. Various techniques may be used for the formulation of oral dissolving films, among which solvent casting method is the most preferable. Usually hydrophilic polymers along with other excipients are used to formulate buccal films, which disintegrate quickly releasing the incorporated APIs within seconds. Oral dissolving films offer numerous benefits as far as accessibility, administration and withdrawal, retentivity, low enzymatic movement, economy and high patient compliance is concerned, thus having the potential for market and business exploitation. This present review emphasizes on mechanism of action, merits, composition, formulation, evaluation, marketed formulations of oral dissolving films. Additionally, covering the aspects related to novel fast dissolving techniques.

Keywords: Solvent casting method, buccal films, bioadhesion, hydration, bioavailability.

INTRODUCTION

Buccal drug delivery offers distinct advantages over various other routes for systemic effect. Among different transmucosal routes, buccal mucosa is the most appropriate for both local and systemic delivery of drug. The interesting physiological highlights make the buccal mucosa as a perfect route for mucoadhesive medication conveyance framework. These points of interest incorporate detour of hepatic first-pass impact and shirking of pre foundational disposal inside the GI tract¹. For the past decade, the utilization of the oral cavity membranes as drug administration sites has piqued people's curiosity. It is prominent that the absorption of therapeutic compounds from the oral mucosa allows drug into the systemic circulation, thereby avoiding first pass metabolism and GI drug degradation, both of which are associated with peroral administration^{2,3}.

Buccal drug delivery is a favorable route and has several advantages over other routes. Based on biochemical and physiological aspects of absorption and metabolism, many drugs, cannot be delivered effectively through the conventional oral route, because after administration they are subjected to pre-systemic clearance extensively in liver, which often results in a lack of significant correlation between membrane permeability, absorption and bioavailability⁴.

Difficulties associated with parenteral delivery and poor oral availability promoted the need for exploring alternative routes for the delivery of such drugs. Consequently, alternative absorptive mucosae are considered as prospective sites for drug administration. The mucosal linings of the nasal, rectal, vaginal, ocular and oral cavities (transmucosal modes of drug transport) offer different benefits over peroral administration for systemic effect. Buccal mucosa, among the many transmucosal routes, offers great accessibility, an expanse of smooth muscle and relatively immobile mucosa, making it ideal for administration of controlled release dosage forms. In comparison to existing non-oral transmucosal drug delivery systems, this novel drug delivery system offers a high patient adequacy⁵. Direct access to the systemic circulation via the internal jugular vein maintains circumvent from acid hydrolysis in the gastrointestinal (GI) tract and bypasses drug from biotransformation prompting high bioavailability. In addition, fast cell recuperation of the buccal mucosa is other favorable advantage of this route. Buccal drug delivery offers numerable benefits in terms of accessibility, administration, withdrawal as well as retentivity, low enzymatic movement, economy and high patient compliance is concerned. Thus, it is one of the most suited drug delivery system.

ANATOMY AND PHYSIOLOGY OF BUCCAL CAVITY:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium, below this lies a basement membrane and a lamina propria followed by the submucosa as the innermost layer as shown in **Figure 1.**⁵

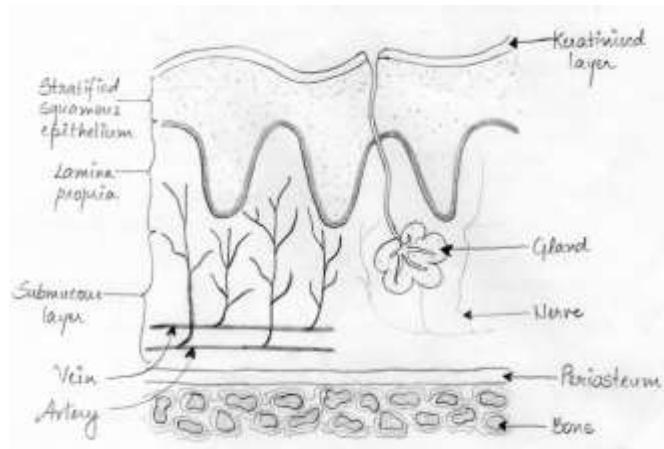


Figure 1: Cross Section of Oral Mucosa

The epithelium is similar to the rest of the body's stratified squamous epithelia in that it has a mitotically active basal cell layer that progresses through a series of developing intermediate layers to the superficial layers, where cells are shed from the epithelium's surface. The buccal mucosa epithelium is 40-50 cell layers thick, whereas the sublingual epithelium contains fewer cells. As they travel from the basal to the superficial layers, epithelial cells grow in size and become flatter. The buccal mucosa has a thickness of 500-800 μ m, while the mucosa of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae has a thickness of 100-200 μ m.

The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas that are subjected to mechanical stress (such as the gingivae and hard palate) are keratinized similar to epidermis. The soft palate, sublingual and buccal mucosae on the other hand, are not keratinized.⁴ Neutral lipids such as ceramides and acylceramides have been associated to the barrier function of keratinized epithelia. Non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, contain modest amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosylceramides and are relatively impermeable to water. These epithelia have been found to be far more water permeable than keratinized epithelia. In both keratinized and non-keratinized epithelia, the oral mucosa comprises of large amount of protein in the form of monofilaments in the cell layers.⁶

MECHANISM OF BUCCAL ABSORPTION

Buccal drug absorption occurs through passive diffusion of nonionized species through the epithelium's intercellular spaces, a process driven mostly by concentration gradient. The primary transport mechanism is the passive transfer of non-ionic species via the lipid membrane of the buccal cavity. The buccal mucosa, like many other mucosal membranes, has been regarded as a lipoidal barrier to drug passage, with the more lipophilic the drug molecule, the more quickly it is absorbed. The kinetics of drug absorption through the buccal mucosa could be adequately characterized by a first order rate process. Several potential barriers to drug absorption through the buccal mucosa have been identified. Salivary secretion

alters the buccal absorption kinetics of drug solution by modifying the concentration of drug in the mouth, according to Dearden and Tomlison (1971). The equation for the linear relationship between salivary secretion and time is given by:⁷

$$\frac{dm}{dt} = \frac{KC}{V_i V_t}$$

Where,

M - Mass of drug in mouth at time t.

K - Proportionality constant

V_i - Volume of solution put into oral cavity.

V_t - Rate of Saliva secretion.

C - Concentration of drug in mouth at time.

PHYSIOLOGICAL FACTORS AFFECTING BUCCAL BIOAVAILABILITY

- Epithelial permeability:** The permeability of the oral mucosal epithelium falls somewhere between that of the skin epithelium, which is highly specialized for barrier function and that of the gut, which is highly specialized for adsorptive function. The buccal mucosa is less permeable than the sublingual mucosa within the oral cavity.
- Epithelium thickness:** The thickness of the oral epithelium varies greatly between sites in the oral cavity. The thickness of the buccal mucosa ranges from 500 to 800 μ m
- Blood supply:** The oral cavity is served by a robust blood supply and lymphatic network in the lamina propria, so drug moieties that pass through the oral epithelium are quickly absorbed into the systemic circulation.
- Metabolic activity:** Drug moieties adsorbed via the oral epithelium are released directly into the bloodstream, avoiding the liver's and gut wall's first-pass metabolic effects. As a result, oral mucosal administration may be especially appealing for enzymatically labile drugs such as therapeutic peptides and proteins.
- Saliva and mucus:** The salivary gland's activity implies that a stream of saliva, about 0.5-2L per day, is constantly held against the oral mucosal surfaces. Since the sublingual area is exposed to a lot of saliva, it can improve medication solubility and hence boost bioavailability.
- Retention of delivery system:** Because the buccal mucosa has a smooth and generally immobile surface, it is well suited to the adoption of retentive delivery systems.
- Species differences:** Because rodents have a highly keratinized epithelium, they are not good animal models for investigating buccal medication transport.
- Routes and mechanisms of transportation:** There are two primary routes for drug penetration past the epithelial barrier:
 - The paracellular route:** Between adjacent epithelial cells.
 - The transcellular route:** Across epithelial cells, this can be accomplished through passive diffusion, carrier-mediated transport or endocytic mechanisms.⁸

NOVEL BUCCAL DOSAGE FORMS:

The novel type buccal dosage forms include buccal adhesive tablets, patches, films and semisolids (ointments and gels).

- Buccal mucoadhesive tablets:** Buccal mucoadhesive tablets are dry dosage forms that must be moistened before being placed to the buccal mucosa. A double-layer tablet, for example, with an HPC and polyacrylic acid adhesive matrix

layer and a cocoa butter inner core containing insulin and a penetration enhancer (sodium glycocholate).

B. Patches and Films: Buccal patches consists of two laminates, with an aqueous solution of the adhesive polymer casted onto an impermeable backing sheet, which is then cut into the desired oval shape. A novel film is easily placed on the patient's tongue or mucosal tissue, where it promptly gets wet by saliva and dissolves quickly. The films then quickly disintegrate and dissolve, enabling the drug to be absorbed through mouth.

C. Semisolid Preparations (Ointments and Gels): Bioadhesive gels or ointments have lower patient acceptance than solid bioadhesive dosage forms and they are mostly employed for localized drug therapy within the oral cavity. "Orabase," one of the first oral mucoadhesive delivery methods, is made up of finely ground pectin, gelatin and NaCMC dispersed in a polyethylene and mineral oil gel base that can last for 15-150 minutes at the application site.⁹

Oral dissolving films are novel drug delivery systems that are cost-efficient and have good patient compliance. As the films are designed to adhere to the buccal mucosa, they can be engineered to have both local and systemic effects. In terms of flexibility and comfort, buccal films may be preferred over buccal tablets. ODFs enter the systemic circulation directly through the internal jugular vein, bypassing hepatic first-pass metabolism and promoting high bioavailability. These dosage forms are also self-administrable, pharmaco-economic and have a high level of patient compliance⁶. Buccal drug delivery systems utilize bioadhesion of certain polymers, which become adhesive upon hydration and can thus be used to target a drug to a specific region of the body for an extended period of time. The ability to maintain a delivery system at a specific location for an extended period of time has great appeal for both local and systemic drug bioavailability.¹⁰

The benefits and recent improvements in delivering a variety of compounds outweigh the drawbacks of this route, making

buccal adhesive drug delivery a more significant and viable alternative for future research.

Oral dissolving films (ODF) are a form of oral drug delivery system based on the technology of the transdermal patch for oral drug delivery. This delivery system consists of a thin film that is placed on the patient's tongue or mucosal tissue, gets wet by saliva and then dissolves quickly. The films then quickly disintegrate and dissolve, allowing the drug to be absorbed through the mouth. Pediatrics, geriatrics, emetic patients, abrupt episodes of allergy responses, diarrhoea, coughing or patients with an active lifestyle can benefit from ODFs. It's also excellent for toothaches, old sores, oral ulcers and teething, as well as other local anaesthetics. Oral thin-film technology is still in its early phases, but it has a bright future ahead of it because it focuses on meeting the needs of patients.¹¹

Oral films, also referred to as oral wafers in the literature, are a set of flat films that are administered into the oral cavity. Oral film systems have been around for a while, but they've only recently become a new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable Oral films have evolved from confection and oral care businesses in the form of breath strips over the last several years to become an innovative and well recognized means of delivering vitamins and personal care items to the customers. Companies that have developed polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug administration have jumped at the opportunity to convert their technology to ODF formats. ODFs are a validated and approved technique for systemic delivery of APIs in over-the-counter (OTC) pharmaceuticals and they are still in the early phases of development for prescription drugs.¹²

A diverse comparison of various novel fast dissolving technologies, comprising of numerous characteristics and features are discussed in the **Table 1**.

Table 1: Comparative Account on Various Novel Fast Dissolving Technologies.¹³

Properties	Lyophilized systems	Compressed tablet based system	Oral thin films
Composition	Solution or suspension of drug with excipients	Active pharmaceutical ingredient with superdisintegrants	Hydrophilic polymers with drug and other excipients
Technology used	Lyophilization	Direct compression	Solvent casting, hot melt extrusion
Characteristics	High porosity which allow rapid water or saliva penetration and disintegration	Different levels of hardness these result in varying disintegration and packaging needs	Large surface area leads to rapid disintegration
Packaging	Blister pack	High density polyethylene bottles	Blister cards with multiunits.

FEATURES OF ORAL DISSOLVING FILMS:

The following characteristics of oral dissolving films are responsible for improved patient compliance:

1. A thin film in the shape of a postage stamp.
2. Dissolves in the mouth, leaving a pleasant taste and mouth feel.
3. Fast onset of action.
4. When compared to other oral formulations, bypasses first-pass metabolism, increasing drug bioavailability.

5. After oral administration, the films dissolve quickly and leave little or no residue in the mouth.

6. Oral films that dissolve quickly are less sensitive to environmental factors like temperature and humidity.¹⁴

CLASSIFICATION OF ORAL FILMS:¹⁵

Oral films can be divided into three categories:

1. Flash release films
2. Mucoadhesive melt-away films
3. Mucoadhesive sustained-release films.

All these oral dissolving films differ in physical structure, appearance, composition, mode of application, characteristics,

and site of action; summarized in **Table 2**.

Table 2: Classification and Summarization of Properties of Oral Films.¹⁵

Property/Sub Type	Flash release films.	Mucoadhesive melt-away films.	Mucoadhesive sustained release films.
Area (cm²)	2-8	2-7	2-4
Thickness (μm)	20-7	50-500	50-250
Structure (Film)	Single layer	Single or multilayer system	Multilayer system
Excipients	Soluble, highly hydrophilic polymer	Soluble, hydrophilic polymer	Low/nonsoluble polymer
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue	Gingival or buccal region	Gingival (other regions in oral cavity)
Dissolution	Minimum 60 sec Maximum 8-10 hrs.	Disintegration in few mins. forming gel	Maximum 8-10 hrs.
Site of action	Systemic or local	Systemic or local	Systemic or local

ADVANTAGES OF ORAL DISSOLVING FILMS:

The following are some of the benefits of oral dissolving films:

1. Bypassing the first-pass effect, the drug enters the systemic circulation directly. Many drugs, such as insulin and other proteins, steroids and peptides, may be unstable if they come into contact with the digestive fluids of the gastrointestinal tract. Furthermore, the rate of drug absorption is unaffected by food or the rate of gastric emptying.
2. In the oral cavity, a larger surface area facilitates rapid disintegration and dissolution.
3. Oral films are more flexible than ODTs, making them less fragile. As a result, transportation and consumer handling and storage are simplified.
4. Dose administration accuracy.
5. A Pleasant taste is gained by taste-masking technique which is used to avoid the bitter taste of drugs. As a result, these are employed for pediatrics.
6. Longer-term stability due to the fact that the drug is in solid dosage form until it is ingested. As a result, it combines the stability of a solid dosage form with the bioavailability of a liquid dosage form.
7. Increased patient compliance due to the absence of injection-related pain, the administration of pharmaceuticals to unconscious patients and the ease of administration when compared to injections and oral medications.
8. The ease of swallowing and the lack of water demand have led to a higher level of acceptability among dysphagic patients.
9. Dosage forms can be ingested anywhere and at any time, depending on the individual's preferences.
10. Useful in situations requiring a fast onset of action, such as motion sickness, abrupt allergy attacks or coughing, bronchitis or asthma.

11. Increased oral bioavailability of compounds subjected to the first-pass effect.
12. Bypassing the first pass effect results in a decrease in dose, this may lead to a reduction in the molecules' side effects.
13. Thin, flexible strips of polymer, unlike typical solid dosage forms, are not friable, allowing them to withstand the kind of physical degradation that would impair normal solid dosage forms.

LIMITATIONS OF ORAL DISSOLVING FILMS:

Numerous obstacles have to be faced while delivering the drug via oral dissolving films which can be enumerated as follows:

1. Drug with small dose can only be administered.
2. For local action, rapid drug clearance is caused by continuous saliva secretion (0.5-2L/day), which causes subsequent dilution of the drug, resulting in frequent dosage.
3. This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor.
4. Drugs that are absorbed through passive diffusion can only be administered through this route.
5. Eating and drinking may become restricted.¹⁷

The advantages and recent progress in delivering a variety of compounds render the disadvantages of oral dissolving films which become less significant. Thus, Oral dissolving films are elite for buccal drug delivery systems and are promising option for continued research.

FORMULATION CONSIDERATIONS FOR ORAL DISSOLVING FILMS:

Buccal films having a surface area of 1-3 cm² are most acceptable. The total amount of drug that can be delivered over the buccal mucosa in one day from a 2cm² device is estimated to be around 10-20mg. The shape of the delivery system can also vary, while an ellipsoid shape appears to be the most appropriate for buccal drug administration. The delivery device's thickness is typically limited to a few

millimeters. Aqueous polymer matrixes are extensively used in dissolvable films. These materials are excellent for a number of applications, including buccal drug delivery, due to their water solubility, good film-forming capabilities, safety, molecular weight range diversity and drug compatibility. The delivery device's location must also be considered. The ideal buccal film design would include an API-loaded layer that attaches directly to the buccal site and erodes at a designated rate equal to the time it takes for the total drug concentration to reach the system. Unidirectional drug release ensures maximum absorption and minimal drug loss in the saliva and gastrointestinal tract. Because food and/or beverage consumption may demand removal of the delivery device, the maximum duration of buccal medication retention and absorption is around 4-6 hours. The physiology of the mucus membrane under disease conditions must be taken into consideration (e.g.: Cancer patients suffer from oral candidiasis). Oral mucosal films have a shelf life of 2-3 years, depending on the API, although they are particularly sensitive to environmental moisture.¹⁸

COMPOSITION OF THE FORMULATION:

Oral dissolving film is a thin film containing drug with a surface area of 1-20 cm² (depending on dose and drug loading). Drugs can be loaded up to 30mg in a single dose. Formulation concerns (plasticizers, etc.) have been reported to have a significant impact on the mechanical properties of films.¹⁹

A typical composition contains the following:

1. Drug: 5% to 30% w/w
2. Water soluble polymer: 45% w/w
3. Plasticizers: 0-20% w/w
4. Surfactants: q.s.
5. Sweetening agent: 3 to 6% w/w
6. Saliva stimulating agent: 2 to 6% w/w
7. Fillers, colors, flavors etc.: q.s.

1. Choice of Drug candidate: Antiulcers (e.g. omeprazole), antiasthmatics (salbutamol sulphate), antitussives, antiemetics, expectorants and NSAIDs (e.g.-paracetamol, meloxicam, and valdecoxib) are among the drugs that can be formulated as oral dissolving films. Less bitter, potent and highly lipophilic drug should be preferred for OTF as in case of fast dissolving tablets.²⁰

2. Water Soluble Polymers: Hydroxypropylmethylcellulose (HPMC), hydroxypropyl cellulose (HPC), pullulan, carboxymethyl cellulose (CMC), pectin, starch, polyvinyl acetate (PVA) and sodium alginate are among the film-forming polymers contained in these ODFs. These water-soluble polymers can be used alone or in combination to provide the desired strip qualities. They provide the films' physical structure, ensuring their integrity. The strip's robustness is determined by the type of polymer used and the amount used in the formulation.²¹ Polymers are selected not only for the physical properties they impart to films, but also for their rate of dissolution. The rate at which a dissolving polymer dissolves is inversely proportional to its molecular weight, which determines the rate at which medicine is delivered. As the film forming polymer (which serves as the Oral Film's platform) is the most important and significant component, at least 45 % w/w of polymer should be present based on the total weight of dry Oral Film.²²

3. Plasticizers: The mechanical characteristics of the formulation (tensile strength and elongation) can be improved by adding plasticizers. Mechanical property is plasticizers concentration dependent property. Plasticizers such as glycerol, di-butylphthalate and polyethylene glycols are often employed.²³

4. Surfactants: Surfactants are used in formulations as a solubilizing, wetting or dispersing agent, allowing the film to dissolve in seconds and the active substance to be released immediately. Sodium lauryl sulphate, benzalkonium chloride and tweens are some of the most often used. Poloxamer 407, a solubilizing, wetting and dispersion agent, is one of the most important surfactants.²⁴

5. Sweetening Agents

➤ **Natural Sweeteners:** Sweeteners have become an essential component of nutraceuticals as well as pharmaceuticals that dissolve in the mouth. Sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose are the most common sweeteners. Since fructose is sweeter than sorbitol and mannitol, it is commonly used as a sweetener. Polyhydric alcohols like sorbitol, mannitol, and isomalt can be combined as they offer a pleasant mouthfeel and a cooling effect.²⁵

➤ **Artificial Sweeteners:** The artificial sweeteners have gained more popularity in culinary and pharmaceutical preparations. Artificial sweeteners are divided into two groups: I generation and II generation sweeteners. Acesulfame-K and sucralose have 200-fold and 600-fold sweetness, respectively. When compared to sucrose, neotame and alitame have a sweetening capacity of over 2000 and 8000 times, respectively. Rebiana, a natural sweetener derived from the South American plant, Stevia rebaudiana which has more than 200 to 300 times sweetness.²⁶

6. Saliva Stimulating Agent: More saliva production aids in the faster disintegration of fast dissolving film formulations, hence the formulations may include salivary stimulants such as acids used in food preparation. Salivary stimulants include citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid, with citric acid being the most popular among them.²⁷

7. Flavors: Any flavor that approved by the US Food and Drug Administration (FDA) can be added, such as strong mints, sour fruit flavors or sweet confectionary flavors¹⁵. The amount of flavor required to mask the taste is determined by the type and strength of the flavor.²⁸

METHODOLOGIES FOR PREPARATION OF ORAL DISSOLVING FILMS:

Manufacturing processes involved in making mucoadhesive buccal patches/films, namely solvent casting, hot melt extrusion and direct milling.

1. Solvent Casting Technique: Buccal films are formulated using the solvent casting method (as shown in **Figure 2**), in which the water soluble ingredients are dissolved to form a clear viscous solution and the drug, along with other excipients, is dissolved in a suitable solvent, then both solutions are mixed and finally casted in to the petri plate, which is then dried and cut into pieces of the desired size. The qualities of the API are crucial in determining which solvent to use. Hydroxyl propyl methyl cellulose (HPMC), Hydroxyl propyl cellulose (HPC), pullulan, sodium alginate, carboxy methyl cellulose (CMC), polyvinyl alcohol (PVA), pectin, guar gum and polyvinylpyrrolidone are examples of water-soluble polymers used to formulate buccal films. The final stage is to dry the film,

which removes the solvent and aids in the development of the final result. In most cases, an inert base for film casting is made of glass, plastic or Teflon plates. Several issues might arise when manufacturing technology is scaled up from the laboratory to the production level. The casting of the film, obtaining equal thickness of the film and adequate

drying of the sample are all examples of challenges faced. In the final process of drying, right type of dryer is selected. Once the films are dried, cutting, stripping and packaging is done. Films of appropriate size and shape can be cut. 3x2 cm² and 2x2 cm² are the most popular film sizes available.²⁹

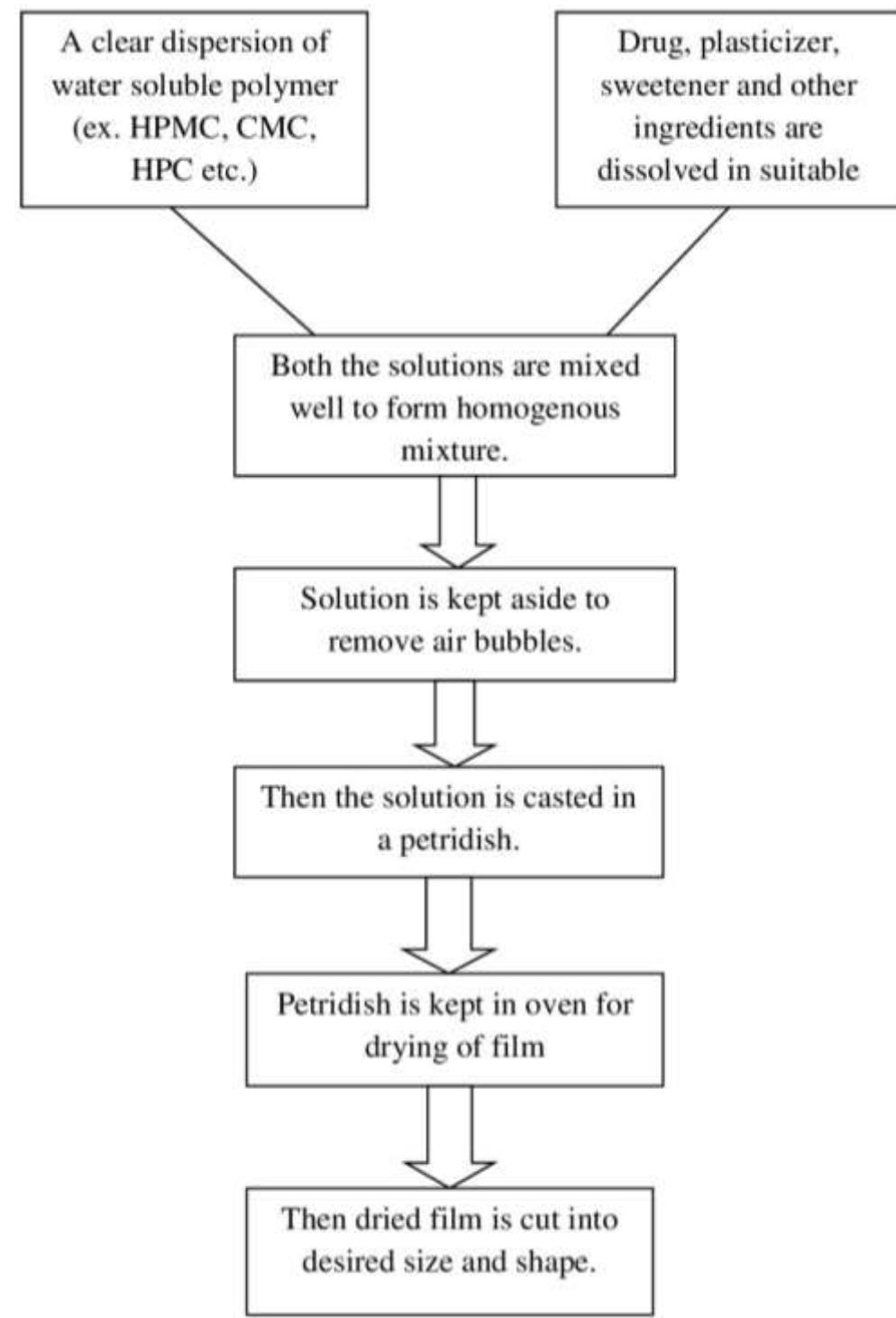


Figure 2: Steps Involved in Solvent Casting Method²⁹

2. Semisolid casting: A solution of water-soluble film forming polymer is prepared first in the semisolid casting procedure. 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 added, resulting in a gel mass. Finally, heat-controlled drums are used to cast the gel mass into the films or ribbons. The acid insoluble polymer should be used in a 1:4 ratio with the film forming polymer.³⁰

3. Hot melt extrusion: Granules, sustained-release pills and transdermal and transmucosal drug delivery systems are all made by hot melt extrusion. The drug is initially combined with carriers in solid form in the hot melt extrusion process. The mixture is then melted in an extruder with heating. The melt is finally moulded into films by the dies. Polymers with low molecular weight or viscosity, such as HPMC E5 or pullulan PI.20, are usually preferred when designing films. To obtain desired physical qualities, a combination of several grades of polymers might be employed. When high and low viscosity polymers are combined, a film with strong mechanical strength and high drug solubility is created.

In the pharmaceutical sector, the manufacturing process for films is divided into several steps: Typically, the mass is prepared first, with temperature and steering speed controlled. The films are then coated and dried in a drying tunnel, where the temperature, air circulation and line speed are all carefully monitored. After that, the wafers are punched, pouched and sealed in the final process.³¹

4. Solid dispersion extrusion: Solid dispersion extrusion refers to the solid dispersion of one or more APIs in an inert carrier in the presence of amorphous hydrophilic polymers employing methods like Hot melt extrusion. Immiscible components are extruded with the drug in this process and subsequently solid dispersions are made. Dies are then used to form the solid dispersions into films.³²

5. Rolling method: A solution or suspension containing drug is rolled on a carrier in the rolling method. Water or a combination of water and alcohol is used as the solvent. On the rollers, the film is dried before being cut into the appropriate shapes and sizes.³³

EVALUATION OF ORAL DISSOLVING FILMS

- 1. Weight variation:** Weight variation is calculated by weighing any five films from the formulation individually on a digital balance and then computing the average weight.³⁴
- 2. Thickness:** The thickness of the films is calculated by selecting five films at random and then determining the thickness of each film after calibration using a standard digital Vernier Caliper. The thickness of the film is measured at various crucial points and average values are reported.³⁵
- 3. Folding endurance:** Folding endurance is a critical method for determining a film's mechanical qualities. It is determined by folding the film repeatedly at the same point until it breaks. The folding endurance value is calculated as the number of times the oral dissolving films can be folded without breaking. The greater the folding endurance value, the greater the film's mechanical strength.³⁶
- 4. Surface pH:** The film's surface pH is determined by soaking it with 10ml of distilled water in a petridish and then measuring it with a pH metre electrode by touching the film surface and noting the pH value.³⁷
- 5. Moisture uptake and moisture loss:**³⁸

The original weight of the film is determined first and then the film is placed in a desiccator (including calcium carbonate) for three days to determine the percentage moisture loss. The films are removed and weighed again after three days and the moisture loss is calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

A film's percentage moisture uptake is calculated by exposing it to an atmosphere with a relative humidity of 75% at room temperature for seven days and then using the following method to calculate the moisture uptake:

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

6. Disintegration time: Placing the film in a beaker containing 20ml of distilled water is used to determine the disintegration time. The disintegration time is the time it takes for the film to totally dissolve.³⁹

7. Drug content: Dissolving the strip in 100ml of water with continuous stirring for 4 hours determines the amount of drug present in an oral dissolving film. After that, a whatman filter paper is used to filter the solution and the drug content is evaluated using a UV Spectrophotometer.⁴⁰

8. In-vitro drug release: The USP rotating paddle method is used for conducting the dissolution studies on the films. Distilled water, 6.8 pH phosphate buffer (300ml), 0.1N HCl (900ml) are commonly used as dissolution medium. The release rate is determined at 37±5°C temperature, with a rotation speed of 50 rpm. The oral dissolving film is then added to the dissolution medium. The samples (2 ml) of drug dissolved are withdrawn at predetermined interval i.e., at every 30 seconds and are replaced with fresh medium. The samples are then filtered and analysed for drug release using UV spectrophotometer.

NOVEL TECHNOLOGIES USED FOR PREPARATION OF ORAL DISSOLVING FILMS:

- 1. Wafertab™:** This is a patented drug delivery system that allows active ingredients to be administered in the form of ingestible filmstrips. In this delivery system, a pre-measured amount of drug is incorporated into the body of an Xgel™ film that has already been made. This is done to keep the active ingredient stable while also preventing it from being exposed to excessive heat and moisture. They're usually made to be taken orally or applied topically. As soon as the drug comes into contact with saliva, it dissolves quickly.
- 2. Soluleaves™:** This technology is used to keep the active component in the oral cavity and is commonly used in flavor-release products such as mouth fresheners and vitamins. When these films come into contact with saliva, they breakdown quickly by instantly releasing the medication in the oral cavity.⁴¹
- 3. Foamburst™:** Soluleaves are a type of foamed film. During the production of these films, an inert gas is forced inside, resulting in the construction of a honeycombed structure that allows for quick release, resulting in a novel mouth sensation that is similar to melting in the mouth.⁴²

MARKETED FORMULATIONS:

A number of companies have commercialized films as a drug delivery platform and have marketed their products successfully. Some of the approved marketed products of oral film forming technology are enlisted in the **Table 3**.

TABLE 3: SOME APPROVED MARKETED PRODUCTS OF ORAL FILMS. 43

Formulations	Brand name	Manufacturer/marketed	Country
Fast dissolving oral films	Zolmitriptan Rapid film®	Labtec's production site in Hamburg Germany	Europe
Ondansetron ODF	Setofilm®	BioAlliancePharma	Europe
Ondansetron ODF	Zuplenz®	Marketed by: Strativa Pharmaceuticals united	States
Oral films of;	-	Hughes Medical Corp.	-
1.Methylcobaln			
2.Diphenhydramine HCL			
3.Dextromethorn			
4.Loratadine			
d-Amphetamine	KP106	Monosol Rx and KemPharm	-
Listerine Pocket Packs	-	Monosol Rx	-
Buprenorphine/Naloxone films	Suboxone	Monosol Rx	-
Donepezil film	Donepezil Rapidfilm®	Labtec	Europe as well as in US
Vitamins, Hormones, Nutraceuticals films.	-	Paladin labs	Canada and the US
Midazolam Maleate	-	Pharmaceutical	China

CONCLUSION

In current scenario, it has become really important for the formulators to bring novelty and provide consumer's satisfaction concurrently. So, for the same Oral dissolving films have been found as one of the promising and novel approach for maximizing the therapeutic action of drug and enhancing the patient compliance as well. It has been found more advantageous over conventional dosage form. They have the potential to deliver active ingredient both locally and systemically. Accessibility of excipients and ease of preparation makes it a better choice for formulators. It provides accuracy in administered dose without being vulnerable for chocking or suffocation. Various novelties have been introduced in the preparation methodologies of ODF's like Wafertab™, Soluleaves™ and Foamburst™ which provides more precision and thus helps in enhancement of patient compliance.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siah-Shabdar MR, Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: Effect of fillers, Farmaco 59: 155-161. DOI: <https://doi.org/10.1016/j.farmac.2003.11.011>.
2. Rathborne M, Drummond B, Tucker I, Oral cavity as a site for Systemic drug delivery, Adv Drug Deliv Rev 13: 1-22. DOI:[10.1016/0169-409X\(94\)90024-8](https://doi.org/10.1016/0169-409X(94)90024-8).
3. Venkat S, Mucoadhesive films: An over review, Asian Journal of Science and Technology, 2017; 8:4790-4802.
4. Harris D, Robinson JR, Drug delivery via the mucous membranes of the oral cavity, J. Pharm. Sci., 1992; 81:1-10. DOI: [10.1002/jps.2600810102](https://doi.org/10.1002/jps.2600810102).
5. Ehtezazi T, Algellay M, Islam Y, Roberts M, Dempster NM, Sarker SD, The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films, J. Pharm. Sci., 2018; 107(4):1076-1085. DOI: [10.1016/j.xphs.2017.11.019](https://doi.org/10.1016/j.xphs.2017.11.019).
6. Wertz PW, Squier CA, Cellular and molecular basis of barrier function in oral epithelium, Crit. Rev. Ther. Drug Carr. Sys., 1991; 8:237-269.
7. Patel KV, Patel ND, Dodiya HD, Shelat PK, Buccal bioadhesive drug delivery system: An Overview, Int J Pharm Bio Arch 2011; 2(2):600-9.
8. Gupta SK, Singhvi IJ, Shirasat M, Karwani G, Agrawal A, Buccal adhesive drug delivery system: A Review, Asian Journal of Biochemical and pharmaceutical research, 2011; 2(1):105-114.
9. Lee JW, Park J, Robinson J, Bioadhesive-based dosage forms: the next generation, J. Pharm. Sci., 2000; 89(7):850-66. DOI: [10.1002/1520-6017\(200007\)89:7<850::AID-JPS2>3.0.CO;2-G](https://doi.org/10.1002/1520-6017(200007)89:7<850::AID-JPS2>3.0.CO;2-G).
10. Miller NS, Johnston TP, The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery, Rev 2005; 57:1666-91. DOI: [10.1016/j.addr.2005.07.003](https://doi.org/10.1016/j.addr.2005.07.003).
11. Hussain MW, Kushwaha P, Rahman MA, Akhtar J, Development and Evaluation of Fast Dissolving Film for Oro-Buccal Drug Delivery of Chlorpromazine, Indian Journal of Pharmaceutical Education and Research, 2017; 51:S539-S547. DOI:[10.5530/ijper.51.4s.81](https://doi.org/10.5530/ijper.51.4s.81).
12. Shojaei Amir H, Buccal Mucosa as A Route for Systemic Drug Delivery: A Review, J Pharm Pharmaceutical Sci., 1998; 1 (1):15-30.

13. Niyaz USH, Elango K, Oral fast dissolving films: An innovative drug delivery system, *World Journal of Pharmacy and Pharmaceutical Sciences*. 2018; 7:881-907.
14. Dixit RP, Puthli SP, Oral strip technology: Overview and future potential, *Journal of Controlled Release*, 2009; 139:94-97. DOI: [10.1016/j.jconrel.2009.06.014](https://doi.org/10.1016/j.jconrel.2009.06.014).
15. Patil P, Shrivastava, Fast Dissolving Oral Films: An Innovative Drug Delivery System, *International Journal of Science and Research*, July 2014; 3(7)2088-2093.
16. Jain A, Harish C, Ahirwar, Tayal S, Mohanty PK, Fast Dissolving Oral Films: A Tabular Update, *J. Drug Delivery and Therapeutics*, 2018; 8 (4):10-19. DOI: <https://doi.org/10.22270/jddt.v8i4.1724>.
17. Patil BS, Tate SS, Kulkarni U, Hari Prasanna RC and Wadageri GV, Development and In-vitro evaluation of mucoadhesive buccal tablets of Tizanidine hydrochloride using natural polymer Xanthan gum, *Inter. J. Pharm. Sci. Rev. and Res.*, 2011; 8(2):140-146.
18. Khatoon N, Raghavendra Rao NG, Reddy BM, Overview on Fast Dissolving Oral Films, *International Journal of Pharmaceutical Sciences and Drug Research*, 2013; 1(1):63-75. DOI: <https://doi.org/10.25004/IJPSDR.2016.080101>.
19. Kulkarni AS, Deokule HA, Mane MS, Ghadge DM, Exploration of different polymers for use in the formulation of oral fast dissolving strips, *J. Current Pharmaceutical Res.*, 2010; 2(1):33-35.
20. Murthy AV, Ayalasomayajula LU, Earle RR, Jyotsna P, Formulation and Evaluation of Tramadol Hydrochloride Oral Thin Films, *IJPSR*, 2018; 9:1692-1698. DOI: [10.13040/IJPSR.0975-8232.9\(4\).1692-98](https://doi.org/10.13040/IJPSR.0975-8232.9(4).1692-98).
21. Rajat P, Ravi S, Pravin S, Darwhekar GN, A Review on Mouth Dissolving Film, 2019; 9(6):206-10. DOI: [10.22270/jddt.v9i6.3676](https://doi.org/10.22270/jddt.v9i6.3676).
22. Sau-hung S, Robert S, Lori, Fast dissolving orally consumable films, U.S. Patent 6, 596, 298.
23. Prakash I, DuBois GE, Clos JF, Wilkens KL, Fosdick LE, Development of rebiana, a natural, non-caloric sweetener, *Food and Chemical Toxicol.*, 46(S2):S75-S82. DOI: [10.1016/j.fct.2008.05.004](https://doi.org/10.1016/j.fct.2008.05.004).
24. Israel K, Leo M, Salivary stimulant, U.S Patent, 1989; 4820506.
25. <http://www.Patent storm.us /patents/ 6740332/claims. Html>.
26. Chapdelaine AH, Zyck DJ, Dzija M, Edible film formulations containing maltodextrin, US Patent, 2009.
27. Technical Brief: Particle Sciences Drug Development Services, Vol 3 2010.
28. Coppens KA, Hall MJ, Mitchell SA, Read MD, Hypromellose, Ethyl cellulose and Polyethylene oxide used in hot melt extrusion, *Pharmaceutical Technol.*, 2005; pp: 1-6.
29. Mahesh A, Shastri N, Sadanandam M, Development of Taste Masked Fast Disintegrating Films of Levocetirizine Dihydrochloride for Oral Use, *Current Drug Delivery*, 2010; 7(1):21-27. DOI: [10.2174/156720110790396454](https://doi.org/10.2174/156720110790396454).
30. Devaraj H, Venkatachalam S, Radhakrishnan A, Research Article A Review on Formulation of Oral Dissolving Film, 2018; 10(4):151-9. DOI: [10.35629/7781-0603370378](https://doi.org/10.35629/7781-0603370378).
31. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L, Fast dissolving films made of maltodextrins, *European Journal of Pharmaceutics and Biopharmaceutics*, 2008; 70: 895-900. DOI: [10.1016/j.ejpb.2008.06.032](https://doi.org/10.1016/j.ejpb.2008.06.032).
32. Frey, Film Strips and Pharmaceuticals, *Pharmaceutical Manufacturing and Packaging Sources*, 2006; pp: 92-93.
33. Bilal Q, Unhale SS, A review on mouth dissolving films, 2020; (March).
34. Elsayed, I, EL- Dahmy RM, Elshafeey AH, Gawad EL, Gazayerly EL, Tripling the bioavailability of rosuvastatin calcium through development and optimization of an in situ forming nanovesicular system, *Pharmaceutics*, 2019, Jun 11; 11(6):275. DOI: [10.3390/pharmaceutics11060275](https://doi.org/10.3390/pharmaceutics11060275).
35. Niyaz U, Elango K, Oral Fast Dissolving Films: An Innovative Drug Delivery System, *World Journal of Pharm. and Pharmaceutical Sci.*, 2018; 7(11):881-907. DOI: [10.4274/tjps.galenos.2020.76390](https://doi.org/10.4274/tjps.galenos.2020.76390).
36. Ammar HO, Ghorab MM, Mahmoud AA, Shahin HI, Design and In Vitro/ In Vivo Evaluation of Ultra-Thin Mucoadhesive Buccal Film Containing Fluticasone Propionate, *AAPS PharmSciTech*. 2017; 18:93-103. DOI: [10.1208/s12249-016-0496-0](https://doi.org/10.1208/s12249-016-0496-0).
37. Bala R, Sharma S, Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment Bulletin of Faculty of Pharmacy, Cairo University, 2018; 56(2):159-158. DOI: [10.1016/j.BFOPCU.2018.04.002](https://doi.org/10.1016/j.BFOPCU.2018.04.002).
38. Chavan DU, Marques SM, Bhide PJ, Kumar L, Shirodkar RK, Rapidly dissolving Felodipine nanoparticle strips: Formulation using design of experiment and characterization, *J. Drug Deliv. Sci. Technol.*, 2020, 60, 102053.
39. Bharti K, Mittal P, Mishra B, Formulation and characterization of fast dissolving oral films containing buspirone hydrochloride nanoparticles using design of experiment, *J. Drug Deliv. Sci. Technol.*, 2019, 49, 420-432. DOI: [10.1016/j.JDDST.2018.12.013](https://doi.org/10.1016/j.JDDST.2018.12.013).
40. Naik S, Hemanth H, Vageesh N, Basavaraju K, Formulation and in vitro evaluation of rizatriptan benzoate oral disintegrating film, *Innovat International Journal Of Medical & Pharmaceutical Sciences*, 2018; 3(1). DOI: [10.24018/10.24018/ijmps.2018.v1i1.22](https://doi.org/10.24018/10.24018/ijmps.2018.v1i1.22).
41. Reddy Usha Kiran T, Reddy Sunil Kumar K, Manogna Katta, Prof. Thyagaraju K, A detailed review on fast dissolving oral films, *Indo-American Journal of Pharmaceutical Research*, 2018; 8(6):1315-1326.
42. Kumar RS, Yagnesh Naga Satya T, Oral dissolving films: an effective tool for fast therapeutic action, *Journal of Drug Delivery and Ther.*, 2019; 9(1-s): 492-490. DOI: <https://doi.org/10.22270/jddt.v9i1-s.2395>.
43. Wasilewska K, Winnicka K, How to assess orodispersible film quality? A review of applied methods and their modifications, *Acta Pharmaceutica*, 2019; 69:155-176.