AN UPDATED REVIEW ON FAST-DISSOLVING SUBLINGUAL FILM FOR TREATMENT OF HYPERTENSION

Mrs. Shital Bidkar[1*], Reshma Bhosale[2], Dr. Shubhrajit Mantry[3], Dr. Kiran Mahajan[4], Dr. Abhishek Meher[5], Dr. Jayant Bidkar[6], Dr. Ganesh Dama[7]

Abstract

Oral administration remains the most popular because of its many advantages such as simplicity, convenience, convenience, adaptability, and ability to be administered in both solid dosage forms (powder, pill, capsule, and tablet form). Squamous epithelium that is stratified makes up the oral mucosa's outermost layer. Lamina propria, the underlayer, and submucosa constitute the basement membrane. off the basal cell layer, the epithelium's mitotically active layer, to the superficial layer, where cells shed off the epithelium's surface, there are a number of unique intermediate layers. The stratified squamous epithelium that covers the remaining area of the body looks similar to this. Drugs may be directly absorbed and may without first-pass hepatic metabolism, access the systemic circulation due to high vascularization of the buccal or buccal mucosa. To treat NDDS, it is necessary to fabricate oral films containing molecules with an increase in oral bioavailability due to the first-pass effect. The third system class, sometimes referred to as oral wafers in the pertinent literature, is a well-known category of systems that has recently attracted renewed interest in the field of quickly dissolving drug administration. Dispensable oral thin films (OTF) or oral strips (OS), originally sold as breath strips in the confectionery and oral care industries, have developed into an advanced and well-liked delivery system for vitamins and personal care products.

Keywords: Hypertension, Oral Film, NDDS, Pathogenesis of Hypertension.

1*,2,3,4,5,6,7 Department of Phamaceutics, SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune, Maharashtra 410504, India, (Email: shitalbidkar@yahoo.com)

***Corresponding Author:** Mrs. Shital Bidkar

*Department of Phamaceutics, SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi (Otur), Tal- Junnar, Dist- Pune, Maharashtra 410504, India, (Email: shitalbidkar@yahoo.com)

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INTRODUCTION-

Oral wafers, also known as oral films in the relevant literature, are flat films that are orally given.. The The oral route is one of the most often used method of medicine administration for systemic effects since it is simplicity, non-intrusive adaptable, and has an excellent level of patient acceptance. Due to their simplicity in manufacturing, transport, and good patient compliance, tablets are the most favoured dose form.[1] A third class, oral film systems, has been around for some time but has just lately gained renewed attention for the delivery of rapidly dissolving pharmaceuticals. In recent years, the confectionary and oral care markets have seen the emergence of breath strips and oral strips, commonly referred to as dissolvable oral films (OTF) or oral strips (OS). A manufacturer of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal medication delivery grasped the chance to transfer this innovation to an OTF format. For over-the-counter medicines (OTC), OTF is currently a validated and accepted technology in early to mid-stage prescription drug development .[2]

The diagrammatic presentation of the oral film is shown in **Figure 1.**

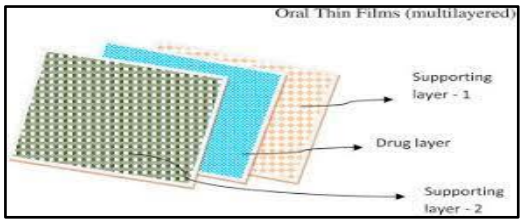

Figure 1: Diagrammatic view of oral film

Due to the popularity of consumer breath fresheners like Pocket Listerine Pack in the consumers in the US, this is a significant accomplishment. These devices produce material films ranging in thickness from 50 to 200 mm using a variety of hydrophilic polymers. Active substances in the film could be soluble, insoluble, or flavor-masked. Large sheets of film are produced before being cut into individual dose multifunction packing units in a number of configurations that are acceptable to the pharmaceutical industry.The most common complaints about tablets are their size and choking hazards. Fast-acting, bioactive, oral fast-dissolving film dosage forms, which consist of both non-pharmacological and pharmacological approaches, can be used when new drug delivery systems seek to alter the treatment of hypertension .[3]Treatment decisions depend on whether a previous CV, DM, or CKD exists. The 2017 AHA/ACC guidelines recommend that a patient with stage 1 hypertension and without these disorders, calculate her 10-year risk of cardiovascular disease. If the risk is less than 10%, it makes sense for him to make only one lifestyle change for 3-6 months. For stage 2 hypertension with pre-existing conditions such as DM, CKD, and a 10-year risk of cardiovascular events greater than or equal to 10%, both lifestyle modifications and medication are recommended.[4,5]

Structure characteristics of the oral mucosa:

The outermost layer of stratified squamous epithelium makes up the oral mucosa. Lamina propria, the basement membrane, and submucosa, the deepest the most external layer of layer, are located below this. The body's other parts are comparable., the epithelium is that stratified it begins as a basal cell layer that is mitotically active and advances through a number of the middle layers where cells develop into superficial layers that shed off the epithelium's surface. Similar to squamous epithelium. It is estimated that the buccal epithelium has turnover time of 5 to 6 days, possibly represents the entire oral mucosa .[6] The thickness of the oral mucosa varies with localization. The buccal mucosa is 500–800 µm thick, while the mucous membranes of the hard and soft palate, the floor of the mouth, the ventral tongue, and the gingiva are approximately 100–200 µm thick. The composition of the epithelium also depends on its localization in the mouth cavity. Similar to the epidermis, the mucosa of the gums and keratinization of the hard palate and includes neutral lipids called ceramides and acylceramides that play a role in barrier function. .[7] The buccal, sublingual, and soft palate mucous membranes, however, are dekeratinized, comparatively impermeable, and have small amounts of ceramides. Additionally, it has trace levels of polar and neutral lipids, primarily glucosylceramide and cholesterol sulphate. Water is significantly more permeable through non-keratinized epithelium than keratinized epithelium. .[8] The diagrammatic presentation of the oral cavity is shown in **Figure 2.**

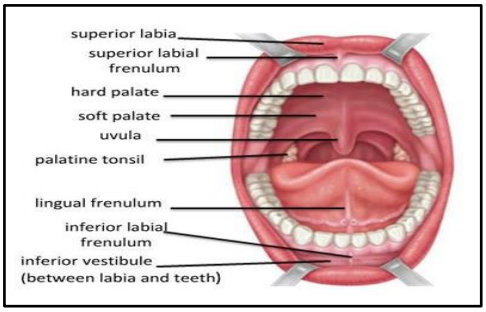

Figure 2: Diagrammatic Oral representation

Hypertension: Elevated blood pressure is sometimes referred to as high blood pressure or hypertension. Depending on your activity, your blood pressure varies throughout the day. High blood pressure may be identified if measures are often greater than normal (or hypertension) .[9]

General Pathogenesis of hypertension-

95% and 5%, respectively, of patients with hypertension have primary (or essential) HTN and secondary hypertension. are two types of hypertensions. The cause of absolutely necessary hypertension is unfamiliar; however, generally manifests by the age of 5 or 6, is frequently linked to a high salt consumption and weight gain, and has a strong genetic component. bringing up the potential for a genetic predisposition to this disease .[10] On the other hand, secondary hypertension has a number of known causes, including chronic kidney disease, sleep apnea, renal artery stenosis, and adrenal insufficiency. Both scenarios possess a phenomenon known as the perturbation of various mechanisms necessary to maintain normal blood pressure. Extensive research has been done on endothelial function, sodium retention, water retention, the sympathetic nervous system, and the renin-angiotensin-aldosterone system in order to pinpoint these pathways. [11] At the onset of the disease, given the aforementioned age-related modifications to blood pressure, any discussion of the pathophysiology of hypertension in the elderly must focus on the primary cause of increased systolic blood pressure, which differs from that in young people. Typical hemodynamic findings associated with elevated pulse pressure vary with age [12]. Hyperactive circulation with increased heart rate and cardiac output increased left ventricular ejection fraction, and normal global peripheral resistance is common findings in individuals younger than 40 years. Heart rate and cardiac output tend to decrease in people over the age of 65, and vascular resistance increases [13,14] The natural history of mild hypertension is similar to these observations, with a gradual progression from hyperactivity to increased systemic resistance and normal or decreased cardiac output. Two of his classic findings relevant to this progression are decreased arterial baroreflex sensitivity and increased peripheral vascular resistance, and the specific role of these factors in hypertension in the elderly is the focus of this study [15]. General pathogenesis of the hypertension is presented in **Figure 3.**

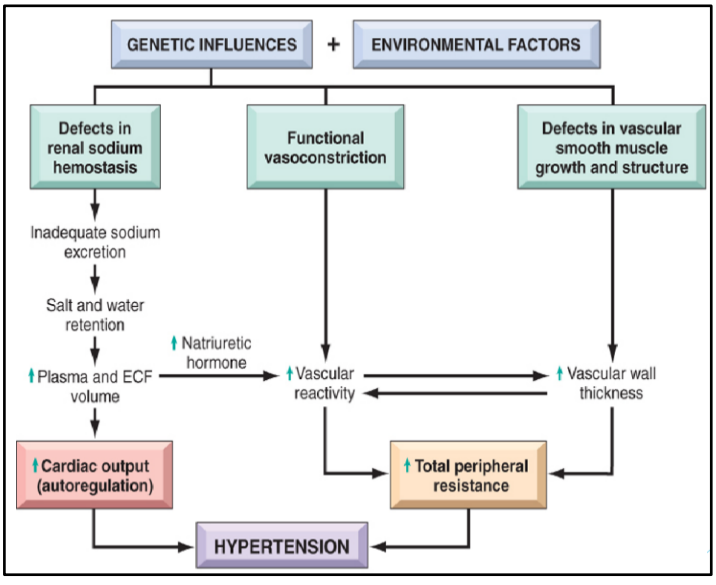

Figure 3: General Pathogenesis of Hypertension

Oral films Formulation consideration:

Oral films Formulation consideration: a thin film with a medicine that can range in size from 1 to 20 cm2 (concerning to dose and drug loading). A medicine can only be loaded with a maximum of 30 mg. The the films' mechanical characteristics are significantly influenced by formulation factors (plasticizers, etc.). [21]

Film Forming Polymers

There are numerous polymers available of the production of rapidly-dissolving films. Polymers can be utilized on unique to them. or collectively, to provide the required tape characteristics. The resulting film must be tough to avoid damage during handling or shipping. The type and amount of polymer are factors that contribute to the robustness of the strip [22]. A fast-dissolving strip dosage form, on the other hand, must have the ability to dissolve quickly after it is placed in the mouth, providing instant drug distribution to the buccal cavity. The streak-forming polymer, which makes up the majority of the fast-dissolving film, should typically make up at least 45% by weight of the total dry weight of the film. Pullulan, gelatin, and hypromellos [23,24,25] are the most often utilised polymers for creating fast-dissolving films.List of film forming polymers is presented in **table 2.**

Table 2: List of film-forming polymers in preparation of film [24-27]

Natural polymer	Synthetic polymer
Starch	Hydroxy propyl methyl cellulose
Pectin	Polyvinyl pyrrolidone (PVP)
gelatin	Polyvinyl alcohol (PVA)
Sodium Alginate	Sodium Carboxymethylcellulose
Maltodextrin	Polyethylene oxide (PEO)
Pullulan	Kollicoat IR
Xanthan	Hydroxypropyl cellulose (HPC)
Polymerized rosin	Hydroxy ethyl cellulose (HEC)

Plasticizers

The plasticizer chosen will depend on how well it works combined with the polymer and the kind of solvent used in the casting of the strip. It promotes to making the strip more flexible and less brittle. The plasticizer considerably improves the characteristics of the strip by decreasing the polymer's glass transition temperature to below 75ºCfor aqueous systems and between for non-aqueous solvent systems, the plasticizer significantly enhances the strip's properties. Ordinarily, plasticizers are used at a concentration of 0 to 20% by weight of the dry polymer [26,27,28]

Surfactants:

Surfactants can function as wetting, dispersing, or solubilizing agents. In the formulation process, the film dissolves in a matter of seconds and swiftly releases an active ingredient. Sodium lauryl sulphate, benzalkonium chloride, tweens, polyethylene glycol, and others are some of the surfactants that are frequently utilized. One of the most significant surfactants utilised as solubilizing, wetting, and dispersion agents is poloxamer 407 [29]

Natural Sweeteners:

Sweeteners are now a vital component of both pharmaceutical and nutraceutical products. Sweeteners will disintegrate around the mouth. Dextrose, fructose, glucose, liquid glucose, and isomaltose are some examples of sugars. some of the sweetener sources. Since sorbitol and mannitol are less sweet than fructose, it is frequently used as an alternative to sugar. Additionally, they offer a cooling sensation and good mouthfeel. You can combine polyhydric alcohols like sorbitol, mannitol, and isomalt. The main benefits of polyhydric alcohols are that they are less carcinogenic and have no aftertaste, which is important when creating oral preparations [30]

Agent for Stimulating Saliva:

For the fast-dissolving film formulations to disintegrate more quickly, more saliva must be produced. As a result, the formulations might contain acids that are employed during food preparation as stimulants for saliva. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are a few examples of salivary stimulants. Among this group, citric acid is the most important. [31]

Flavor:

Any flavor that has received US FDA approval may be included in the recipeintense mints, sour fruit flavours, or sweet flavours of dessert for instance. The type and strength of the flavor determine how much is required to cover the taste. The main purpose of using coloring agents is to give a pharmaceutical dosage form a unique appearance. The full spectrum of colors— FD and colours as

well as EU colours and naturally occurring colours like curcumin and chlorophyll [32]

Manufacturing Methods

Mouth-dissolving films can be manufactured by combining one of the following processes.

Solvent casting:

Solvent casting was used to create the films. The polymer was precisely weighed, dissolved in water, and then glycerine was added to the mixture (solution I). With the aid of a magnetic stirrer, combine the drug and additional ingredients with water in a different beaker to create solution II. To release all trapped air bubbles, the color, and flavor are added to the mixture and continuously stirred for 15 minutes. The solution was then transferred into a Petri dish and left to dry for 24 hours at room temperature. Following their drying, these films were taken off the Petri dish and cut into predetermined sizes and shapes. Films are wrapped in aluminum foil and put in desiccators for additional evaluation [33] The solvent casting system is presented in **Figure 4.**

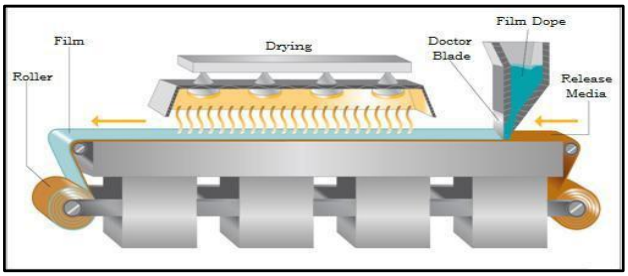

Figure 4: Solvent casting system

Semisolid casting:

A solution of a polymer that forms films in water is conditioned initially in the casting that is semisolid process. The resultant remedies is then added to a polymer solution produced in ammonium or sodium hydroxide to dissolve an acid-resistant polymer (such as cellulose acetate phthalate or cellulose acetate butyrate). The proper the quantity of plasticizer there is subsequently utilised, which causes a gel mass to develop. In the end, the gel mass is cast with the use of heat-controlled drums into the films or ribbons. The film is between 0.015 and 0.05 inches thick. For optimal results, use a 1:4 ratio for the film-forming materials and acid-insoluble polymer [34]

Solid dispersion extrusion:

In this process, the medication is distributed along with immiscible components to create solid dispersions. After that, dies are used to form films from the solid dispersions [35].

Hot melt extrusion:

The mass is first created using the current approach, which also regulates temperature and steering speed. A tunnel for drying out, where the temperature, airflow, and accelerate lines are once again restrained, the film is finally coated and evaporated. The films are then punched and sealed in the final step, after which comes the slitting. In the Drugs and carriers, the hot melt extrusion process is first combined in solid form. A heater-equipped extruder then melts the mixture. At the very least, the dies to form the melt into films[36]. The hot melt extrusion system is presented in **Figure 5.**

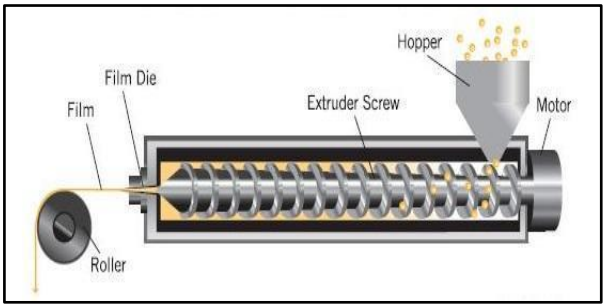

Figure 5: Hot Melt Extrusion Method.

Rolling Technique:

The rolling technique entails rolling a solution or suspension encompassing the drugs on the carrier. The majority of the solvent is composed of water and an alcohol-water combination. After the film has dried on the rollers, it is cut into the preferred

sizes and shapes. Additional materials, such as active substances, were solube in a tiny amount of an applying a high-shear processor to an aqueous solvent. Water-soluble hydrocolloids are dissolved in it to produce a uniformly viscous mixture [37]. The rolling method is presented in **Figure 6.**

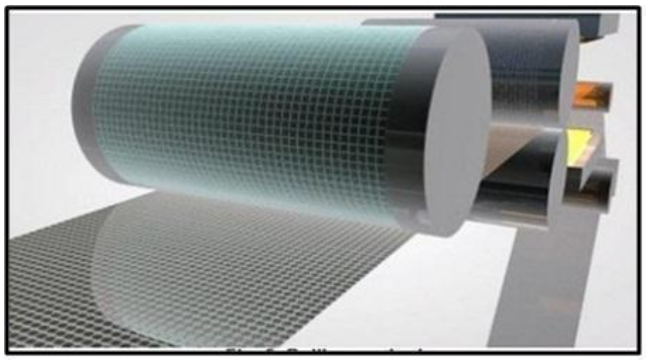

Figure 6: Diagrammatic representation of the Rolling method

Fast-dissolving film evaluation:
The physical characteristics, surface quality, and other following parameters of all the produced films were assessed.

Weight variation:
To account for weight, three films of each formulation were taken and weighed independently on a digital balance variance; the average weight was then determined [38]

Film thickness:
Each film's thickness was measured using a micrometre screw gauge at various points on the film, and the average thickness was calculated[39].

Surface pH:
With the assistance of water, the film is slightly moist. By applying the electrode against the oral film's surface, the pH is determined. Three films of each formulation were used in this study, and the ±S.D. was determion. [40]

Folding endurance:
By folding a single film repeatedly until it broke, the folding endurance was put to the test. How many times the film could be folded in the same position without breaking determines the value of folding endurance ·

Drug content:
A circular piece of film with a diameter of 1.5 cm was cut, dissolved in 100 cc of 0.1N HCl, and then filtered. transferring the material to a 100 ml volumetric flask. After the proper dilution, the medication is identified spectroscopically

Disintegration time:
The USP disintegration time test instrument was used for the disintegration test. The disintegration apparatus IP tubes each received one film from the formulation. The tube received a disc. The apparatus was operated while suspended in 0.1 N HCl until the film disintegrated

***In-vitro* dissolution studies:**
The fast-dissolving film's in-vitro dissolution was investigated using 0.1N HCl as the dissolution a medium in a USP paddle dissolution test apparatus. The experiment was achieved at a constant temperature of 37± 0.5°C. At every two minutes, a 5 ml sample was taken out and replaced with 0.1 N HCl in the same quantity. A UV-visible spectrophotometer was used to determine the total percentage of drugs released at 205

Stability studies:
Stability testing aims to identify the ideal storage settings, follow-up testing intervals, and shelf life by demonstrating how the quality of a drug substance or product varies over time as a result of several environmental factors, such as temperature, humidity, and light. At 40°C and 75% RH for three months, stability studies were conducted in accordance with ICH International Conference of Harmonization guidelines. The improved film formulations were placed in amber-colored bottles with cotton plugs that were tightly sealed and caps. They were then kept at 40oC and 75% RH for three months, and at predetermined intervals, their in-vitro dispersion, drug content, and physical characteristics time were assessed

FTIR's Study on Drug-Excipient Compatibility:
The IR spectra of the purely drug and formulations were used to determine compatibility using the KBr Disc method on the Shimadzu FTIR-8400S Spectrophotomete. Marketed film formulations are presented in **Table 3.**

Table 3: List of Marketed Films [47-50].

Product	**Manufactured By**
Donepezil rapid dissolving films, Ondansetron rapid dissolving films	Labtec Pharma
Altoid cinnamon strips, Boots vitamin strips, Cool shock peppermint strips, Benzocaine films, and Caffeine films.	Dow chemical company
Listerine Pocket Paks, Breath Freshening Strips	Pfizer's Warner-Lambert consumer healthcare division
Klonopin Wafers	Solvay Pharmaceuticals
Listerine Cool Mint Pocket Paks	Pfizer, Inc.
Triaminic	Novartis

Conclusion:

The most popular delivery method is oral route of administration of drugs for systemic effects due to its simplicity, non-invasiveness, adaptability, patient compliance, and acc Adaptability, non-intrusiveness, patient acceptance, and compliance. The most commonly used dose form is tablets because of their easy to manufacture, transport, and high Patient adherence. In related literature, an oral film, also known as an oral wafer, is a collection of flat films that are placed in the mouth. As the search for better dosage forms to meet patient needs and promote acceptance continues, oral film technology will remain a delivery system that should not be ridiculed or prematurely discarded. To fully realise the potential that this innovative delivery system has to offer, the existing information and prescribing capabilities must be updated. There is great interest in noninvasive drug delivery strategies to achieve and prevent rapid onset of action. The sighting range is reduced but improved. Therefore, current oral films have received much attention, versatility, and availability for delivering many drugs to pediatric, geriatric, dysphagic, and bedridden patients. This is an advantage over similar oral solid dosage forms.

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