Review Article

A Comprehensive Review on Formulation and Evaluation of Herbal Films

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ABSTRACT

Over the past few decades, tendency towards innovative drug delivery systems has majorly increases attempts to ensure efficacy, safety and patient acceptability. Oral route is one of the most preferred routes of drug administration because of ease of administration and increases patient compliance. The pharmaceutical industry is attempting to discover the films as a new oral drug delivery system. Thin films have been described as an alternative approach to conventional dosage forms. These are especially for dysphasia patients, geriatric or bedridden patients. These formulations are suitable for cough, cold remedies, sore throat, allergenic conditions, pain and CNS disorders multi vitamins, snoring aid and sleeping aids are applicable for incorporation in oral films. The present review provides an account of various formulation considerations, method of preparation and advantages and disadvantages and quality control of Herbal films and applications.

Keywords: Herbal Films, Formulation, Evaluation, Solvent Evaporation, Film Former.

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INTRODUCTION

Oral route of drug administration is a most preferred route due to its ease of administration[1], non-invasiveness[2], patient compliance and acceptability[3]. Fast dissolving drug delivery system (FDDS) was introduced in late 1970 as the alternative to conventional capsule and syrups especially for the geriatric and pediatric patients suffering from dysphasia problems[4]. These systems consist of solid dosage form that disintegrate and dissolve quickly in oral cavity without water[5]. Fast dissolving drug delivery system includes orally disintegrating tablets (ODT) and oral thin films (OTFS)[6].

The center for drug and evaluation and research (CDER) defines ODTS as a solid dosage form contains medicinal substance[7]. The first orally dispersible tablets (ODT) form of a drug to get approval from US food and drug administration (FDA) was zydns ODT a formation of charitin (Loratidine) in December this has slowly led to their further advancement and thus fast dissolving films (FDFB) were developed. Chloraseptic, relief strips were the first oral thin film product to incorporate a drug[1]. OTF is an ultra thin film that employs a hydrophilic polymer hydrates or when placed on tongue or in buccal cavity[4].

These films dissolve within seconds to release the active agent without drinking and chewing. The instant bioavailability results from bypassing first pass metabolism, so they are generally designed for the drugs having high first pass metabolism for achieving better availability[4]. The oral film technology is still in the beginning stages and has bright future ahead because of patient compliance.

Phytochemicals can be incorporated in the formulation and development of OFDFs to produce pharmacological activities. Recent studies show that Phytochemicals produce a wide range of therapeutic effects and help in the management of certain disorders. Phytochemicals such as flavonoids, polyphenols, glycosides, saponins, etc. and active constituents present in them are employed in the formulation. Active phytoconstituents such as quercetin, herpetrione, curcumin, etc. can be formulated with film-forming polymers and other ingredients to obtain film.

Certain herbal extracts of peanut, propolis, olive leaf, etc. can also be used as natural active compounds in the formulation and development of OFDFs for therapeutic roles. The extracts are obtained by several extraction techniques such as ethanol extraction, bleaching, decoction and maceration. These natural active compounds have anti-inflammatory, antiviral, immunomodulatory, antimigraine, antiarrhythmic, antioxidant and antibacterial activities. Phytochemical-based OFDFs can be used in the management of Alzheimer's disease, dementia and cerebral insufficiency. Researchers have developed many OFDFs using phytochemicals as an active ingredient[7].

Table 1: General Composition of Herbal films.

S. No	Ingredient	Quantity (w/w)	Example
1.	Drug	5-30%	Thiocolchicoside Sennoside curcumin
2.	Film forming polymer	40-50%	HPMC E3, E5, E15 (synthetic) Pullulan, xanthenes gum, pectin, gelatin, (natural)
3.	Plasticizer	0-20%	Propylene glycol, glycerin, sorbitol.
4.	Sweetening agent	3-6%	Mannitol, sucrose, sorbital.
5.	Saliva stimulating agent	2-6%	Citric acid , ascorbic acid ,
6.	Surfactant	q.s	Sod.lauryl sulfate, tween
7.	Flavouring agent	q.s	Menthol, lemon oil.
8.	Colours, filler etc	q.s	Titanium dioxide, mannitol.

Anatomy of Oral Mucosa:

Oral mucosa contains following three layers of cells

1. Stratified squamous epithelium - It's the outermost layer of the oral cavity. Basement membrane is the interface between connective tissue and epithelium
2. Lamina propria - It's a connective tissue present below basement membrane
3. Sub mucous membrane - It is the innermost layer of the oral cavity. [4]

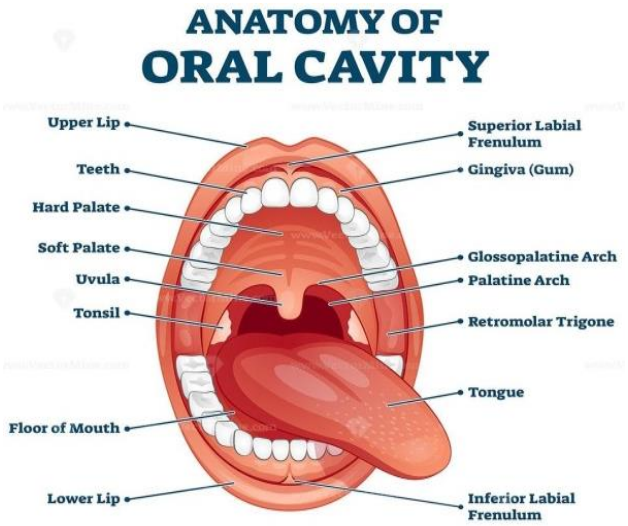

Figure 1: Oral Cavity

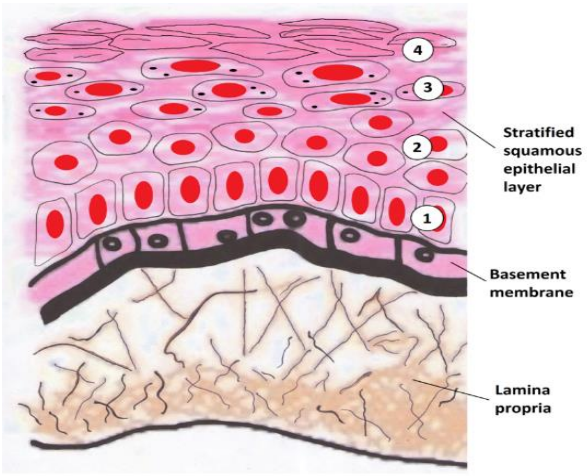

Figure 2: Structure of Oral Mucosa

Advantages of Oral Films

1. Ease of administration for mentally ill and non compliant[8]
2. Pleasing and fresh mouth feel
3. No risk of choking
4. Easy application no swelling and chewing difficulties[7]
5. To avoid first part metabolism
6. Rapid onset of action
7. Good stability
8. No requirement of water[4]
9. Dose precision
10. It masks bitter taste
11. Administration of an accurate dose is possible
12. Reduce gastrointestinal irritation

Disadvantages of Oral Films

1. Dose uniformity if difficult to maintain[8]
2. Sometimes so the fragile and granular property
3. Drugs with high dose cannot be incorporated into the film[7]
4. Drugs which causes irritation to the mucosa cannot be administered
5. Eating and drinking may be restricted
6. Drug unstable at the buccal ph can be administered[4]
7. Require special packaging for the product stability and safety
8. OTF are not in official to the pharmacopeia

Limitations of Oral Films[3]

1. High doses cannot be incorporated
2. Excessive bitter drugs are not feasible
3. Dose uniformity is a technical challenge

4. To require special packaging for the products stability and safety
5. Drugs which irritate the oral mucosa cannot be administered by this route

Classification of Oral Films

There are three different subtypes

- Mucoadhesive sustain release wafer
- Mucoadhesive melt away wafer
- Flash release

APPLICATIONS OF ORAL FILMS

Oral films are preferred for local action and also to manage pain, allergies, sleeping difficulty and CNS disorders. [3]

Topical Applications

The use of dissolvable films may be feasible in this delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other application, [1]

Gastroretentive Dosage Systems

Dissolvable films are being considered in the dosage forms for which water soluble and poorly soluble molecules of varies molecular weights are contained in a film format. Dissolution films could be trigger by pH or enzyme secretion of the gastrointestinal tract, and used to treat gastrointestinal disorders. [9]

Diagnostic Devices

Dissolvable films may be loaded in sensitive agents to allow controlled release when exposed to biological fluid of to create isolation barriers for separating multiple reagents to enable timed reactions with in a diagnostic device. [1]

Vaccines

Fast dissolving films can be delivered in the form of vaccine which is stable at room temperature so it is quickly dissolved in mouth and in saliva. Rotavirus vaccine prepared in united states in room temperature stable fast dissolving buccal film delivery system for vaccines: [3]

- Oral films are applicable to enhance the bioavailability of poorly bioavailable drugs
- Taste masking of bitter drugs
- Dissolvable films are loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.[3]

FORMULATION OF ORAL FILMS

Fast dissolving oral films include various ingredients for its formulations such as

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Super disintegrants
- Sweetening agents
- Saliva stimulating agent
- Surfactants
- Flavoring agent
- Coloring agent[10]

Formulation of FDFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of OS should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms. A typical composition includes various ingredients[3].

Table 2: Typical composition of Herbal Film contains the following ingredients.

S NO	Agents	Concentration
1	Plant Extract	1-25%
2	Water soluble polymer	40-50%
3	plasticizers	0-20%
4	Fillers, colors, flavors etc	0-40%

ACTIVE PHARMACEUTICAL INGREDIENT

The film composition contains 1-30% w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredients because high dose of drug are difficult to incorporate in fast dissolving film. (A number of drugs can be used as fast dissolving oral film including anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, antiemetic, etc.[4]

Ideal characteristics of a drug to be incorporated.

- Drug should have pleasant taste.
- Should have low dose up to 40 mg.
- Drugs with smaller and moderate molecular weight are preferable.
- Drug should have good stability and solubility in water as well as in saliva.
- Should be partially unionized at the pH of oral cavity.
- Should have the ability to permeate oral mucosa

Common examples of drugs incorporated into ODEs are salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron. dexamethasone, rofecoxib. cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc. Phytochemicals such as flavonoids, polyphenols, glycosides, saponins, etc. and active such as quercetin, herpetrione, curcumin, etc. can be formulated[3].

FILM FORMING POLYMERS

Polymers are the most important ingredient of the on-fat dissolving film. Robustness of the film depends on the amount and type of polymer. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. Generally, 45% w/w of polymer is used which is based on total weight of dry film. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva. The polymers can be used alone or in combination to obtain the desired film properties. The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the film.[3,4]

Ideal Properties of Film Forming Polymer

- Should be non-toxic and non irritant.
- Must be hydrophilic.
- Should have excellent film forming capacity.
- Should have good wetting and spread ability property.
- Should be readily available & should not be very expensive.
- Should have low molecular weight.
- Should have sufficient shelf-life. Must be tasteless, colorless.
- Should not cause any secondary infection in oral mucosa.
- Should exhibit adequate peel, shear and tensile strengths.

Currently used, both natural & synthetic polymers for the preparation of oral films are as follows

Table 3: Polymers used in the preparation of Oral Films

S.NO	Natural polymer	Synthetic polymer
1	Pullulan	Hydroxypropylmethyl cellulose
2	Starch, gelatin	Polyvinyl pyrrolidone
3	Pectin	Polyvinyl alcohol
4	Sodium alginate	Carboxymethyl cellulose
5	Maltodextrin	Poly ethylene oxide
6	Polymerized rosin	Kollicoat
7	lycoat RS 720, NG 73	Hydroxypropyl cellulose
8	xanthan	Hydroxyl ethyl cellulose

Plasticizers

Formulation considerations (plasticizer etc) have been reported as important factors effecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers are glycerol, di butylpthallate and poly ethylene glycols etc (3).

Superdisintegrants:

Superdisintegrants, when added to Oral Film formulations, provide rapid disintegration as a result of the combined effect of both water absorption and swelling. Superdisintegrants accelerate disintegration and dissolution by providing absorption and swelling owing to their excessive water absorption. Powerful interaction with saliva is very important for disintegration. Some of the commonly used superdisintegrants and their concentrations are shown in Table 4

Table 4: Superdisintegrants used in oral films and their concentrations

Superdisintegrants	Commercial name	Concentration w/w %	Disintegration mechanism
Sodium starch glycollate	Explotab, primogel	2-8	Fast water absorption and subsequent fast swelling
Cross povidone	PolyplasdoneXL10	2-5	Absorption and swelling go together
Polacrillin potassium	AmberliteIRP88 Indion294	0.5-5	Fast water absorption and subsequent fast swelling

Sweetening Agent

Sweeteners are the important component used in the oral film generally sweeteners are used for the taste masking of bitter drugs so that drugs are palatable sweeteners are used alone or in combination between the concentration of 3-6%w/w .natural sweeteners used are xylose, ribose, glucose, sucrose maltose, sreviosides, dextrose, fructose, lipid glucose in isomaltose .fructose is sweeter than sorbitol and mannitol and thus widely used as sweet artificial sweeteners used in oral films are sodium are calcium saccharine salts cyclamats salts acesulfame k etc. Acesulfame k and sucralose have more than 200 and 600 times sweet. Neotame and altitame have more than 2000 - 8000 times sweetening power as compared to sucrose. Di peptide based sweeteners: aspartame. Protein based sweetener; thaumatin 1 and 2. [1]

Saliva Stimulating Agent

The purpose of using saliva stimulating agent is to increase the rate of production of saliva that would aid in the faster disintegration of the FDF Generally acid are used as salivary stimulants. Citric, Malic acid lactic acid ascorbic acid and tartaric acid are the few examples of salivary stimulants,

citric acid being the most preferred among them. These agents are used alone or in combination between 2 to 6%.[9]

Surfactants

They are generally used to increase the solubility, wettability a like and dispersibility of the film so that the film gets dissolved within seconds and release the drug rapidly. Commonly used surfactants are sodium lauryl sulphate; surfactants are polaxamer 407 benzalkonium chloride, benzathonium chloride, tweens etc. [4]

Flavoring Agents

Flavoring agents can be selected from the synthetic flavor oils oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Any flavor can be added such as essential oils or water soluble extract of menthol, intens mints such as peppermints, sweet mint, separmint, wintergreen, cinnamon, clove sour fruit flavor such as lemon, orange or sweet confectionary flavor such as vanillin, chocolate, or fruit essence like apple, raspberry, cherry pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength. [3]

Colouring Agents

Pigments like silicon dioxide, titanium oxide or FD$C approved coloring are most commonly used. Their concentration level should not exceed 1%.[4]

MANUFACTURING METHODS OF HERBAL FILMS

1. Solvent casting
2. Semi solid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling

Solvent Casting:

Fast dissolving buccal films are preferably formulated using the solvent casting method,) whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred. [3]

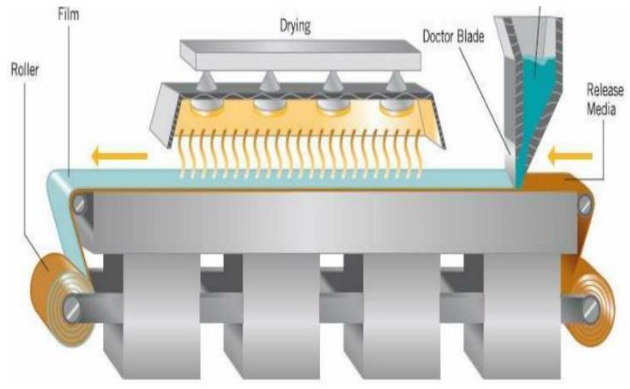

Figure 3: Solvent Casting Method

Semisolid casting:

Solution of water soluble film forming polymer is prepared. Resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate of force necessary for tearing is generally found near the tearing onset which is ranked as tear resistance value (Bhyan et al., 2011). [4]

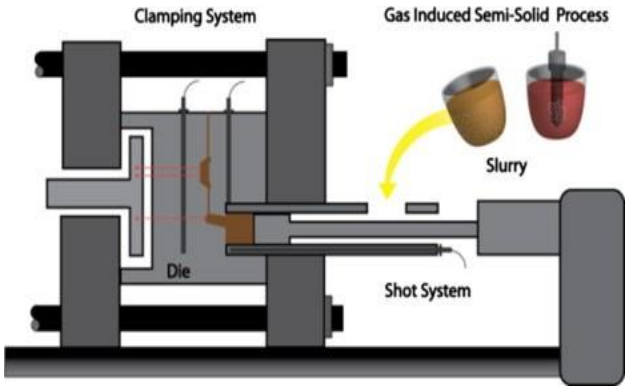

Figure 4: SEMI SOLID CASTING METHOD

Hot melt extrusion:

Hot metal extrusion is commonly used to granules, sustained release tablets, transdermal and transmucosal drug delivery systems, Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. [2]

Solid Dispersion Extraction:

Solid dispersion of Domperidone using beta-cyclodextrin, PEG 400 and HPMC E15 was successfully prepared and films were casted using solid dispersion extrusion method). [2]

Rolling Method:

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug Add pre mix to master batch feed tank. Fed it via a 1st metering pump and control valve to either or both of the 1st and 2nd mixer. Add required amount of drug to the desired mixer. Blend the drug with master batch pre mix to give a uniform matrix. Then a specific amount of uniform matrix is then fed to the pan through 2nd metering pumps. The film is finally formed on the substrate and carried away via the support roller. The wet film is then dried using controlled bottom drying.[3]

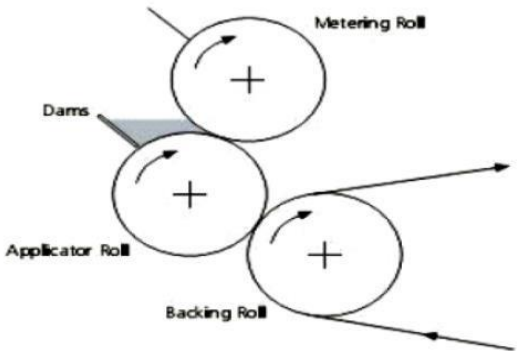

Figure 5: Rolling Method

EVALUATION OF HERBAL FILMS:

Thickness:

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations. [3]

Dryness/tack test:

Tack is defined as the tenacity with which the strip gets adhered to an accessory like a piece of paper that has been pressed into contact with strip. Eight stages of film drying process have been identified and these are set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through (dry to handle), dry to recoat and dry print free. Various instruments are available to perform this test. [4]

Tensile strength:

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below[9]

Tensile strength =Load at failure x 100
Film/Thickness x Film width

Percentage Elongation:

When a pulling force is applied, the tensile increases. This tensile continues until the integrity of the film form deteriorates. The percentage of elongation can be determined by measuring the final size of the film before its integrity deteriorates. This rate increases as the amount simulate of plasticizer is enhanced. Elongation percentages of OTF formulations are calculated by the formula below: [5]

E%= L - L0/ L0× 100

Where L0 is the initial length of the specimen and L is the length at the moment of rupture.

Young's Modulus:

Young's modulus or elastic modulus is the measure of rigidity or toughness of film. It is given as the ratio of applied stress over strain in the region of elastic deformation as follows: [7]

Young's Modulus = force at corresponding strain/cross-sectional area 1/corresponding strain

Tear resistance:

Tear resistance of film is the intricate function of its ultimate resistance to rupture. Maximum force required to tear the film is measured as tear resistance value. This test is typically attributed to plastic industry. The rate of loading employed is 2 in/ min which is planned to determine the magnitude of force required to initiate tearing in the film specimen. The maximum amount of force necessary for tearing is generally found near the tearing onset which is ranked as tear resistance value. [2]

Weight Variation:

Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight. [3]

Folding Endurance:

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value. [3]

Surface pH Test:

Surface pH of film may cause irritation to the oral mucosa. It is necessary to check the surface pH of the film. Surface pH of the film should be neutral i.e. 7 or should be close to 7. A combined pH electrode can be used for this purpose. The film is made slightly wet with water and the pH is measured by bringing electrode in contact with film and the pH reading is noted. This test is applied on at least 6 films and the mean ± SD can be calculated which the final value of surface pH. There is one more method to determine the surface pH i.e. 1.5%w/v agar gel is prepared and the prepared films were placed on it. The surface pH can be measured using pH paper. It is placed on the surface of the film and change in colour of pH paper gives the value of surface pH of the film. [4]

Swelling Property:

Simulated saliva solution is used to check the swelling studies of films. Initial weight of film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more increase in weight. Degree of swelling is determined by these parameters (2)

Degree of swelling = final weight (wt)- initial weight (wo)/initial weight (wo)

Wt = weight of film at time interval t; wo= weight of film at time 0.

***In Vitro* Disintegration Time**:

In vitro disintegration time is determined visually in a glass dish with 10 ml distilled water with swirling every 10 seconds. The disintegration time is the time when the film starts to break or disintegrate. [8]

***In Vitro* Dissolution Study:**

The drug release studies are performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus is thermo stated at the temperature of a 37 +1°C and stirred at rate of 50 revolutions per minute. Each film is fixed on a glass slide. Then the slide is immersed in the vessel containing 500 ml of phosphate buffer solution. [8]

Packaging of Orally Disintegrating Films

Packing considerations are critical for storage, protection and stability of dosage form. Packaging for oral thin films includes foil paper or plastic pouches, single pouch, aluminum pouch. Blister packaging with multiple units and barrier films. Barrier films are most commonly used for those drugs are extremely moisture sensitive (Patil et al., 2014). Rapid film technology developed by Labtec GmbH describes primary packaging made of a sealing pouch affords enough space for logos, codes, instructions or other information. The films are manufactured by a laminating process and packaging costs are comparable to tablets.[2]

MARKETED PRODUCTS:

Large number of OTF formulations is available in market. First, breath freshener films were introduced into market. Then, over-the-counter (OTC) and nutraceutical film formulations which incorporated active ingredients such as vitamins, herbal extracts and non-herbal extracts. Pfizer introduced Listerine pocketpaks in 2001 for as breath fresher. The brand augmentation started after this was fairly successful for several popular OTF products from Novartis and J&J Consumer (Triaminic, Theraflu", Benadryl, and Sudafed). Biofilm is utilizing OTF for the brand extension of the existing products in pharmaceuticals as well as nutraceuticals with a range of aphrodisiac, energy boosters, vitamins and appetite suppressors. Some marketed OTC product. [6,8]

Table 5: List of some marketed oral films

Product Name	API	Use
Listerine	Cool mint	Mouth fresheners
Triaminic	Dextromethorphan HBr	Cough suppressants
Suppress	Menthol	Mouth fresheners
Chloraseptic	Benzocaine Menthol	Local anesthetic
Gas-X	Simethicone	Anti Flatulating
Theraflu	Dextromethorphan HBr	Anti allergic
Setofilm	Ondansetron	Prevention of Nausea and Vomiting
Sudafed PE	Phenylephrine	Relieving Congestion
Klonopin Wafer	Clonazepam	Treatment of anxiety

PATENTED ORAL FILMS:

Inventor	Title	Patent number	Year of patent
Abeer M. Al-ghananeem	Compositions and methods for transmucosal delivery of lofexidine	US12410114	2009
Hao Zhang	Oral transmucosal drug dosage using solid solution	US6264981	1999
Michael S. Balkin	Oral transmucosal delivery tablet and method of making it	US5656284	1995
Brian Hague	Sugar-free oral transmucosal solid dosage forms and uses thereof	US10771046	2004
Hao Zhang	Dissolvable backing layer for use with a transmucosal delivery device	US7276246	2007
Kazuyoshi Furusawa	Fentanyl compound-containing edible patch to be applied to oral mucosa	US10668284	2003
Janet Anne Halliday	Oral transmucosal delivery	US6488953	2001
Christopher N. Jobdevairakkam *et al.*	Composition of fentanyl citrate oral solid transmucosal dosage form	US11271767	2005
Roy L. Mcquinn *et al.*	Transmucosal drug delivery device	US5780045	1996
Stelios Tzannis *et al.*	Bioadhesive drug formulations for oral transmucosal delivery	US11650227	2007
Vikas Agarwal *et al.*	Oral transmucosal nicotine dosage form	US11986097	2007
Mirja Huhtinen *et al.*	Transmucosal veterinary composition comprising detomidine	US1667100	1993
Matthew T. Scholz *et al.*	Bioadhesive composition and patch	US5750136	1995
Kauko Kurkela *et al.*	Transmucosal formulations of levosimendan	US6399610	2000
Roy L. Mcquinn	Non-invasive transmucosal drug monitoring method	US5113860	1991
Adel Pinhasi *et al.*	Solid composition for intra-oral delivery of insulin	US11887653	2006
Paul C. Wilhelmsen	Tablet giving rapid release of nicotine for transmucosal administration	US6248760	1999
James E. Biegajski *et al.*	Water-soluble pressure-sensitive mucoadhesive and devices provided therewith	US5700478	1995
John M. Pinney *et al.*	Two-stage transmucosal medicine delivery system for symptom relief	US6358060	2002
Katsumi Ihara *et al.*	Phentanyl-containing adhesive patch for application to oral-cavity mucosa	US10524024	2006
Leah M. Lehman *et al.*	Method and apparatus for transdermal or transmucosal application of testosterone	US11441311	2005
Sonia J. Heiber *et al.*	Buccal delivery of glucagon-like insulinotropic peptide	US5766620	1998

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