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Fast Dissolving Films: A Novel Approach in Drug Delivery

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ABSTRACT

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of Active Pharmaceutical Ingredients(API) by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. The FDOFs place as an alternative in the market due to the consumer's preference for a fast dissolving product over conventional tablets / capsules. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postage stamp in their shape, size and thickness. These films have a potential to deliver the drug systemically through intra gastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

***Key Words**: Fast dissolving oral films, Drug Delivery System, and Buccal Route.*

INTRODUCTION

Fast dissolving oral films (FDOFs) are the new type of formulation in FDDDS that provides a very convenient means of taking medications. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms are the oral solid dosage form. The lower bioavailability, long onset time and dysphasia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc.) have the problem of accurate dosing. Mainly and parenterals are painful drug delivery, so most patient incompliance.

Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance. So they formulate the fast dissolving tablets by using super disintegrants and hydrophilic ingredients. Fast- dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [1]. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active lifestyle. It is also useful whether local action desired such as local anaesthetic for toothaches, oral ulcers, and cold sores or teething. OTFs also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture [2].

This unique delivery system holds great promise for use in drug delivery devices designed for application to other moist mucosal surfaces in the body, such as ocular, vaginal, and rectal surfaces.

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General Properties & Release Mechanism:

The Quick-Dissolving film comprises a thin, printable, low-moisture, non-tacky film that is convenient for dosing, suitable for labeling, and flexible for easy packing, handling and application. The thickness of a typical film ranges from 1 to 10 mil and its surface area can be 1 to 20 cm2 for any geometry. Its low dry-tack allows for ease of handling and application. At the same time, the rapid hydration rate facilitates an almost immediate softening of the Quick-Dissolving film upon application in the oral cavity. The wet-tack and muco-adhesive properties of the system are designed to secure the film to the site of application. The flexibility and strength of the film may be selected/ modified to facilitate automatic rewinding, die cutting, and packaging during manufacturing. The flexibility and strength are reflected by the tensile strength, elongation, Young's Modulus, bending length, and tear resistance of the film.

The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick-Dissolving film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick-Dissolving film with a thickness of 2 mm.

The drug is released from the dosage form upon disintegration and dissolution. The disintegration and dissolving times are prolonged as the film thickness increases as shown in the **Fig. 1**. The disintegration and dissolving times may be further influenced, by varying the formulation composition of the film.

In this technique, a solution is prepared containing water soluble film forming polymer (pullulan, hydroxypropyl methylcellulose, carboxy methylcellulose, hydroxyl ethylcellulose, hydroxyl propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which was then allowed to form a film after evaporation of solvent. This film, when placed in mouth, melts or dissolves rapidly, releasing the active drug in mouth. The film is stamp size thin films of size less than 2X2 inches, it dissolve rapidly in mouth within a fraction of seconds [3].

Ideal Characteristics of Fast dissolving Drug Delivery System: [4, 5]

- Require no water for administration
- Cost effective production methods
- Leave minimal or no residue in mouth
- Dissolve within a fraction of seconds
- Have a pleasant mouth feel.

Ideal Characteristics of suitable drug candidates:

- Drugs should have a good taste
- Dose should be low up to 40 mg
- Low molecular weight
- Drug should be stable in water and saliva
- It should be partially unionized at the pH of oral cavity.

Advantage of Fast dissolving films: [6]

- Oral dissolving films can be administered without water, anywhere, any time.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- Suitability for geriatric and pediatric patients and the patients who are un-cooperative.
- Beneficial in cases such as motion sickness, acute pain, where an ultra rapid onset of action required.
- Stability for longer duration of time
- As compared liquid formulations, precision in the administered dose is ensured from each strip of the film and more bioavailability.
- These films avoid first pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and provide new business opportunity like product differentiation, product promotion, and patent extension.
- Ease of administration.
- No special set up required for the industry
- Lower doses
- Site specific action and local action
- Destructive acidic environment of stomach can be avoided
- Minimal side effects

Disadvantages: [7]

- High doses cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.
- Expensive packaging of oral film.
- Dose uniformity is a technical challenge

Formulation Consideration:

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent
- Saliva stimulating agent
- Flavoring agent
- Coloring agent

Formulation of Fast dissolving films involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc. The excipients used in formulation of Fast dissolving films are given below as per their categories. From the regulatory perspectives, all excipients used in the formulation of Fast dissolving films should be generally regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Active pharmaceutical ingredient:

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in OFDFs. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked.

Film forming polymers:

A variety of polymers are available for preparation of Fast dissolving films. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation.

The robustness of the strip depends on the type of polymer and the amount in the formulation [8]. The various polymers available, pullulan, gelatin and hypromellose are most commonly used for preparation of Fast dissolving films. Pullulan is a natural polymer obtained from non-animal origin and does not require chemical modification. Modified starches are also used for preparation of Fast dissolving films. Due to low cost of this excipient it is used in combination of pullulan to decrease the overall cost of the product. About 50 to 80 % w/w of pullulan can be replaced by starch in the production of Fast dissolving films without loss of required properties of Pullulan. Combination of microcrystalline cellulose and maltodextrin has been used to formulate Fast dissolving films.

Plasticizers:

Plasticizer is a vital ingredient of the for Fast dissolving films formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer [8,9] Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight [11]. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.

Sweetening agents:

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, and iso-malt can be used in combination as they additionally provide good mouth-feel and cooling sensation.

Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) has more than 200 -300 time sweetness [11].

Saliva stimulating agent:

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

Flavoring agents:

It was observed that age plays a significant role in the taste fondness. Flavoring agents can be selected from 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. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Coloring agents:

Pigments such as titanium dioxide or FD & C approved coloring agents are incorporated (not exceeding concentration levels of 1 % w/w) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form.

Technologies for Fast Dissolvingfilms:

1. Soluleaves:

In this technology the film is produced in order to release the active ingredients on coming in contact with saliva. This method is especially useful for pediatric and geriatric patients who may have difficulty swallowing conventional tablets. SOLULEAVES are designed in such a way that they adhere to mucous membrane in order to release the drug slowly in 15mins [12].

2. Foamburst:

FOAMBURST is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honey combed structure results in capsules that dissolve rapidly, causing a melt-in-the mouth sensation [12].

3. Xgel:

X Gel film Technology developed by Bio Progress was causing a revolution in the product offerings and manufacturing methods, which was now available to the pharmaceutical industry. X Gel film, potentially enhance the product stability. The films may be coloured or printed during manufacture for branding and coding which is a useful mechanism to enhance product identification and has also been developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices [13, 14].

4. Wafertab:

Wafer Tab is a unique, innovative, and highly stable edible film dose form. Wafer Tab is a drug delivery system which incorporates pharmaceutical actives into an ingestible film strip. It provides rapid dissolution and release of active pharmaceutical ingredient, when the strip comes into contact with saliva in the mouth. The Wafer Tab film strip can also be flavoured for additionally improved taste-masking. The active ingredient is integrated into the body of a fused. The film can be prepared in a variety of shapes and sizes and is an ideal method for delivering medicines which require fast release and also for use by patients who have difficulty swallowing [15].

Manufacture of ODFs:

One or a combination of the following process can be used in the manufacturing of ODFs:

a) Solvent casting,
b) Semisolid casting,
c) Hot-melt extrusion (HME),
d) Solid-dispersion extrusion, and
e) Rolling (1, 4).

The most commonly used methods of film manufacturing are solvent casting and HME.

Solvent-casting method.

The ODF is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear, viscous solution. The API and other agents are dissolved in smaller amounts in the solution, and combined with the bulk drug. This mixture is added to the aqueous, viscous solution. The entrapped air is removed by vacuum. Deaeration is necessary to obtain uniform film property and thickness. The resulting solution is cast as a film, allowed to dry, and cut into pieces to the desired size. The properties of the API play a critical role in the selection of a suitable solvent. The physicochemical properties of the API should be considered. These properties include compatibility of the API with other film-forming excipients, compatibility with solvents, the polymorphic nature of the API selected, and temperature sensitivity. Manufacturing and packaging ODFs requires special precaution to be taken to control the effect of moisture. Stability of the film and its mechanical properties are significantly affected by the presence of moisture. Another factor requiring strict control is temperature. Controlled temperature conditions are required for maintaining the viscosity of the solution and temperature sensitivity of the API [16].

Specific types of equipment such as rollers are required for pouring the solution on an inert base. The clearance between the roller and the substrate determines the required thickness of the film. The final step, drying the film, removes the solvent and helps to obtain the finished product. Usually, glass, plastic, or teflon plates are used as an inert base for film casting. When the manufacturing technology is transferred from laboratory scale to production scale, several problems can be encountered. These problems can include the casting of the film, obtaining uniform thickness of the film, and proper drying of the sample. The selection of the proper type of dryer is needed in the final step of drying.

Once the films are dried, cutting, stripping, and packaging is done. Suitable size and shapes of films can be cut. The commonly available sizes of films are 3 x 2 cm^2 and 2 x 2 cm^2. Selection of the packaging container is an equally important parameter for the ODF. The packaging container should provide sufficient mechanical strength to protect the film during shipping and from external factors such as temperature and humidity. Depending upon the characteristics of the film, single-unit containers and multiple-unit dispensers can be selected. The packaged films are inspected before being packed into a secondary packaging container [16].

Hot-melt extrusion: [17, 18]

HME is commonly used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug-delivery systems. The HME process recently has gained popularity in the pharmaceutical industry. Based on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers, and plasticizers into various final forms to achieve desired drug-release profiles. Processing films by this technique involves shaping a polymer into a film *via* the heating process rather than through the traditional solvent-casting method.

Advantages of HME for film formation include the following:

- No need to use solvent or water
- Fewer processing steps
- Compressibility properties of the API may not be of importance
- Good dispersion mechanism for poorly soluble drugs
- More uniform dispersion of the fine particles because of intense mixing and agitation
- Less energy compared with high-shear methods
- Minimum product waste
- Possibility of scale-up
- Good control of operating parameters.

In the HME process, the API and other excipients are mixed in a dry state, the heating process is started, and the molten mass is extruded out of the hot-melt extruder. The advantage of this process is the complete elimination of the solvent. The films are allowed to cool and are cut to the desired size. The high temperature used in the process makes it suitable for thermostable drugs. Drugs that are sensitive to temperature cannot be used in this process.

Solvent casting is a hydrous process suitable for thermo labile and thermostable drugs in comparison to HME, which is anhydrous and requires thermostable drugs. Repka *et al*. studied the influence of chlorpheniramine maleate (CPM) on topical HPC films by HME. CPM has been reported to function as an effective plasticizer, thereby increasing percent elongation and decreasing tensile strength in a concentration-dependent manner. CPM also acts as a processing aid in the extrusion of hot-melt films by allowing film processing at lower temperatures.

An evaluation of HME and the *in vivo* bio-adhesive properties of HPC films containing seven polymer additives on the epidermis of human subjects was performed. HPC films containing additives with and without plasticizers were prepared by HME. Incorporation of a carbomer (Carbopol 971P NF, Lubrizol, Cleveland, OH) and polycarbophil into HPC films increased bio-adhesion significantly. Many studies were conducted using HME for preparing solid dispersions. It was reported that melt extrusion of miscible components resulted in amorphous solid-solution formation, whereas extrusion of an immiscible component led to the amorphous drug dispersed in a crystalline excipient. The process has been useful in preparing solid dispersions in a single step. An extruder consists of two distinct parts. The first part consists of a conveyer system that transports the material and imparts a degree of distributive mixing. A second part, a dye system, forms the materials into the required shape. The drug-carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die shapes the melt in the required form such as granules, pellets, films, or powder, which can be further processed into conventional tablets or capsules. Oxygen and moisture should be completely eliminated for substances susceptible to oxidation and hydrolysis.

Semisolid Casting:

In the semisolid-casting method, a solution of the water-soluble, film-forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate and cellulose acetate butyrate), which is previously prepared in ammonium or sodium hydroxide. The appropriate amount of plasticizer is added to obtain a gel mass. The prepared gel mass is cast into films or ribbons using a controlled heat source. The thickness of the film is controlled between 0.015–0.05 in. [19].

Solid-dispersion extrusion:

The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers using methods such as HME. In solid-dispersion extrusion, immiscible components are extruded with drug, and solid dispersions are prepared. The solid dispersions are shaped into films by means of dies. The drug is dissolved in a suitable liquid solvent. This solution is incorporated into the melt of polyols such as polyethylene glycol, obtained below 70 °C, without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. The polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used [19, 20].

Rolling method:

In the rolling method, a solution or suspension containing the drug is rolled on a carrier. The solvent is mainly water and a mixture of water and alcohol. The film is dried on the rollers and cut into desired size and shapes. The film is made by preparing a premix and adding the API, and film is subsequently formed [21]. The premix or master batch containing the film-forming polymer, polar solvent, and other excipients, except the API, are added to the master-batch feed tank. A predetermined amount of the master batch is controlled and fed through a metering pump and control valve to the mixers. The required amount of the drug is added to the desired mixer through an opening. After blending the API with the master batch to provide a uniform matrix, the matrix is fed to the pan using metering pumps. The thickness of the film is controlled using a metering roller. The film is finally formed on the substrate and carried away *via* the support roller. The wet film is dried using controlled bottom drying, preferably in the absence of external air currents or heat on the surface of the film.

Evaluation of Fast Dissolving Filmss:

The ODF is evaluated by various parameters such as thickness, the mechanical properties of the film, folding endurance, assay/drug content as well as by studies of *in-vitro* disintegration, *in-vitro* dissolution, surface morphology, and taste [22, 23].

Thickness:

The thickness of strip can be measured by a micrometer at different locations. This measurement is essential to ascertain uniformity in the thickness of the film as this thickness is directly related to the accuracy of the dose in the strip.

Fourier transfer infra red spectroscopy (FTIR):

The identification of drug and polymer was done by Fourier transfer infra-red spectrophotometer, (Jasco, FTIR model 6100, Japan). The infra red (IR) spectra of the sample was compared with the IR spectra of the reference.

Mechanical properties of the film:

The mechanical properties are tensile strength, percentage elongation, and elastic modulus.

Tensile Strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

Tensile strength=Load at failure/(Strip thickness x strip width).....Eq.1

Percentage elongation:

When stress is applied, a film sample stretches, and this stress is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the sample. As the plasticizer content increases, the elongation of film is observed.

Percentage elongation = Increase in length of strip/Initial length of strip X 100.....Eq.2

Tear resistance:

The tear resistance of a plastic film is a complex function of its ultimate resistance to rupture. A very low rate of loading of 51 mm/min is employed. It is designed to measure the force to initiate tearing. The maximum stress or force (usually found near the onset of tearing) required to tear the specimen is recorded as the tear resistance in newtons.

Young's modulus or elastic modulus:

Young's modulus or elastic modulus is the measure of the stiffness of the film. It is represented as the ratio of applied stress divided by the strain in the region of elastic deformation:

Young's modulus = Slope/Strip thickness x crosshead speed X 100 ...Eq.3

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with less percentage elongation.

Folding endurance:

Folding endurance is determined by repeated folding of the film at the same place until the film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value.

Assay/drug content:

Assay/drug content is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia.

In-vitro disintegration:

Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. For this study, the film, as per the dimensions required for dose delivery, was placed on a stainless-steel wire mesh containing 10 ml of distilled water. The time required for the film to break was noted as *in-vitro* disintegration time.

Surface morphology:

A study of surface morphology of the ODF is performed using the environment-scanning-electron microscopy method. The uniformity of the film and absence of pores and striations indicate the good quality of the ODF.

Taste evaluation:

A taste evaluation study can be performed using a panel of human volunteers. The ODF should possess the desired sweetness and flavor acceptable to the patient. *In-vitro* methods using taste sensors, a specially designed apparatus, and drug release by modified pharmacopoeial methods are used for this purpose. Experiments using electronic-tongue measurements also have been reported to distinguish between the sweetness levels in taste-masking formulation.

In-Vitro Dissolution:

In-vitro dissolution studies can be performed using the modifications to the standard basket or paddle apparatus described in any of the pharmacopoeia because a conventional paddle apparatus may lead to floating of the film. The dissolution medium will be selected as per the sink conditions and the highest dose of the API.

***In- Vivo* Animal & Human Safety Studies:**

Local oramucosal irritation studies performed on animals and humans were conducted to demonstrate the safety of the Quick-Dissolving films. An animal safety study was conducted using the hamster cheek pouch model. In the hamster cheek pouch study, the film was given to the animal twice a day for 4.5 consecutive days (9 doses in total). For each application,Quick-Dissolving film was retained in the pouch for 10 minutes and subsequently rinsed off using distilled water. The pouch was observed for any irritation prior to and after each application and 24 hours following the last application (9th dose). No irritation was observed during the course of the entire animal study.

A clinical acute oramucosal irritation test for Quick-Dissolving films was conducted on healthy human volunteers to ensure and demonstrate the clinical safety of the fast-dissolving system. Six

Quick-Dissolving film placebo samples were placed on the tongue of the volunteers, one every 10 minutes over a 1-hour time period. Each volunteer was asked to apply one Quick-Dissolving film every 10 minutes. The site of application and the oramucosae were evaluated for any acute irritation prior to and following each application, as well as at 1 hour and 24 hours following the last application. No irritation was observed at the site of application or the surrounding oramucosal tissues upon evaluation at the various time points.

Stability studies:

Stability study was carried out for all the batches at accelerated condition 65% relative humidity and 35 ºC (temperature) in the humidity chamber for the three months. After 3 months the films were evaluated for the drug content, disintegration time and physical appearance observation.

Packaging:

A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. Which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the Mouth dissolving Films. The Rapid Card is exactly the same size as a credit card and holds three Mouth dissolving Films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available.

Clinical and regulatory requirement:

To indicate bio equivalency of a product to that of existing oral drug, an abbreviated new drug application is required. *In-vitro* dissolution studies and therapeutic equivalence are considered. Comparative bioequivalence between an orally disintegrating tablet and an ODF can be evaluated. If the ODF exhibits a different target pharmacokinetic profile compared with the existing marketed product, the ODF is considered a new dosage form. For a new dosage form, a new clinical study is required. A new clinical study offers the advantage of three years of marketing exclusivity to the product. Preclinical toxicity studies are not required if the molecule is the same as that of the approved product. Safety, tolerability, and efficacy features are to be demonstrated in such trials. Oral mucosa-irritation testing is carried out in both animal models and humans. The hamster-cheek pouch is the most appropriate model for predicting irritation criteria before testing in humans.

Table No. 1: Marketed Preparation of Fast Dissolving Oral Films [23]

Product	Manufacturer	Active Pharmaceutical Agent	Strength (mg)
Triaminic	Novartis	Dextromethorphan HBr	7.5
Triaminic	Novartis	Diphenhydramine HCl	12.5
Theraflu	Novartis	Dextromethorphan HBr	15
Gas-X	Novartis	Simethicone	62.5
Sudafed	Pfizer	Phenylephrine HCl	10
Benadryl	Pfizer	Diphenhydramine HCl	12.5
Chloraseptic	Prestige	Benzocaine Menthol	3/3
Suppress 2.5	InnoZen	Menthol	2.5
Orajel	Del	Menthol/Pectin	2/30
Listerine	Pfizer	Cool mint	-
Theraflu Thin Strip Long Acting Cough	NOVARTIS	Dextromethorphan	-
Theraflu Thin Strip Multi-Symptom	NOVARTIS	Diphenhydramine	-
Thaminic Thin Strip Long Acting Cough	NOVARTIS	Dextromethorphan	-
Triaminic Thin Strip Cough and Runny Nose	NOVARTIS	Diphenhydramine	-
Gas-X Thin Strip Anti Gas	NOVARTIS	Simethicone	-
Little Colds Sore Thorat Strips	Prestige Brands	Pectin	-
Suppress Cough Strips	InnoZen	Dextromethorphan	-
Chloaseptic Relief Strips	Prestige Brands	Benzocaine: Menthol	-

CONCLUSION

Our review concludes that, many of the pharmaceutical companies are switching their product franchise from ODTs to ODFTs. This technology option can also provide a good platform for patent non-infringing product development. ODFT allows brand extension for products. The ODFT is a good tool for product life cycle management for increasing the patent life of existing molecules or products. Compared to some of the complicated and expensive process (like lyophilization) used to manufacture ODTs, the ODFT is relatively easy to fabricate; thus reducing the overall cost of the therapy.

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