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Review Article

Formulation and Evaluation of Orally Fast Dissolving Wafer by Using Natural Gum: Review Article

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ABSTARCT

Oral thin film a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. Fast-dissolving oral thin film is a solid dosage form, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. Oral film includes various ingredients for its formulation. Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drugto the systemic circulation via dissolution when contact with liquid is made. Water-soluble polymers are used as film formers for fast dissolving films. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. Fast-dissolving oral thin film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices

Keywords: Fast dissolving film, Natural gum, Plasticizer, Polymers, Solvent casting method.

INTRODUCTION

Oral administration of drugs is the most prefered way for the delivery of drugs to due to its various advantage, but oral drug delivery system still nedds some advancement to be made because of their drawbacks related to particular group of patients. Many pediatric and geriatric patients are enwilling to take tablet preparation due to fear of choking and its taste even with fast dissolving tablets there is a fear of chocking. The disadvantage in tablets is their size, surface, unpleasant taste and the problem of swallowing tablets was more evident geriatric and pediatric, as well as travelling patients who may not have access to water[2].

Evolution of Dissolving Films

Fast-dissolving drug-delivery were introduced in 1970 as a substitute for tablets, capsules, and syrups for geriatric and pediatric patients who have no problem in swallowing and chocking

Mechanism of action of wafers

Wafers are placed on a patients tongue are any oral mucosal tissue. They are instatntly wet by saliva due to the presence of hydrophilic polymer and other excipients, it rapidly hydrates and dissolves to release the medication for mucosal absorption

Anatomical and physiochemical of oral mucosal cavity

The oral mucosa is composed of an outermost layer of stratified squamous epithelium, lies a basement membrane a lamina pro

Objective of formulating wafers

• To improve patient compliance and provide rapid onset of action

• To reduce the extent of hepatic first pass metabolism.

• To reduce side effects associated with the API by reducing dose.

• To enhance oral bioavailability of molecules.

Special Features of Fast Dissolving films

- Film should be thin and elegant.
- Films are available in various size and shapes.
- It should be Unobstructive.
- It should be easily adhere to the oral cavity.
- Fast disintegration without water and Rapid drug release.

Advantages of Oral Films

- Larger surface area promotes rapid disintegration and dissolution in the oral cavity.
- Oral mucosa is highly vascularized, and it provides improved absorption, increased bio availability, faster onset of action, and bypasses first pass effect.
- They provide dosage accuracy and rapid release with increased patient compliance, and there is no risk of choking.
- When compared to oral dissolving tablet these are less fragile and have excellent adhesion.
- The package of drugs in a blister pack enables ease of transportation and consumption of drug at any place or time needed without water[3].

Disadvantage of Oral Films

• Higher dose cannot be incorporated in this dissolving film, which can be done in the case of orally dissolving tablets.

• Longer preservation is difficult because of hygroscopic nature and the need for special package.

• Drugs that are unstable at buccal pH cannot be administered.

• Restriction of eating and drinking for some time after consumption of the oral dissolving film.

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• Expensive method for the preparation of these films, when compared to oral dissolving tablets[4].

Classifications of Fast Dissolve Technology

• Fast-dissolve technologies can be divided in to three broad groups
• Lyophilized systems
• Compressed tablet-based systems
• Oral thin films

The lyophilized systems

This technology involves taking a suspension or solution of drug with other structural excipients, by using mould or blister pack, which forms tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units are of very high porosity, which allows rapid water or saliva penetration and very rapid disintegration.

Compressed tablet-based systems

The standard tablet technology by direct compression of excipients is used to produce this system. The tablet technologies have different levels of hardness and friability depending on the method of manufacture. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating it using water soluble excipients, super-disintegrate or effervescent components, to allow rapid penetration of water into the core of the tablet.

Oral thin film

It is also called as oral wafers. From the past few years the oral thin films are evolved in confection and oral care markets in the form of breath strips these are novel and widely accepted form by consumers for delivering vitamins and personal care products. Today, FDFs are a proven and accepted technology for the systemic delivery of APIs for over-the counter (OTC) medications and are in the early- to mid-development stages for prescription drugs. This has been attributed to the success of the breath freshener products by consumers such as Listerine Pocket Packs in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50- 200 mm film. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats[5-6].

Classification of Oral thin film

Following are the subtypes of oral fast dissolving films:

• Flash release.
• Mucoadhesive melt-away wafer.
• Mucoadhesive sustained release wafers.

Ideal characteristics of a drug to be selected

• The drug should have pleasant taste.
• The drug should have small or moderate molecular weight.
• The drug should have good stability and solubility in water and in saliva.
• It should be partially unionized at the pH of oral cavity.
• It should have the ability to permeate oral mucosa[7].

Formulation aspects for fast dissolving films

• Drug Category
• Film Forming Polymers
• Plasticizers
• Sweetening Agents
• Saliva Stimulating Agents
• Cooling Agent
• Flavoring Agent
• Coloring Agent
• Surfactants
• Stabilizing and thickening agents

Formulation of Wafers

Drug or active pharmaceutical ingredients

Generally, 5-30 % of API can be incorporated in film. Water soluble APIs are present in the dissolved state in the film. Micronized API will improve the texture of the film and also for better dissolution and uniformity in film.

Wafer forming polymers

The polymers form the majority of formulation i.e. they are used 45% (w/w), alone or in combination to obtain the desired properties. The wafer should be tough enough so that there won't be any damage while handling or during transportation used in alone or in combination to improve hydrophilicity. Some examples of polymers are methyl cellulose, pullulan, gelatin, gum acacia, tragacanth, etc.

Plasticizers

Plasticizers used should be compatible with the polymer and also with the type of solvent employed. It is added up to 20% (w/w) of the formulation. It improves the flexibility of the strip and reduces the brittleness. It reduces the glass transition temperature of the polymer used in the range of 40-60 degree Celsius for the non-aqueous solvent system and below 75 °C for the aqueous system. However, inappropriate use of plasticizers may lead to cracking, splitting and peeling of wafers. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. The commonly used plasticizers are glycerol, dibutyl phthalate, polyethylene glycols, etc.[8].

Saliva stimulating agent

The saliva stimulating agents are the excipients that increase the saliva production rate, aids in the faster disintegration of the wafer when used in a concentration of 2-6% (w/w). The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at the equal time under the same condition. The stimulant action of sweeteners depends on the sweetness value. Sweeteners used as saliva stimulating agents are fructose, xylose, maltose, lactose and glucose. Certain flavoring agents are also used like peppermint, cinnamon, nutmeg, vanilla, cocoa, coffee, chocolate, apple, cherry, etc.

Surfactant

It acts as solubilizing, wetting and dispersing agents in the formulation so that the wafer gets dissolved within seconds and release active agent quickly. Some of the commonly used surfactants are sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, etc.

Sweetening agents

Sweeteners play an important role in improving compliance wafers in the pediatric population. Natural sweeteners and artificial sweeteners play an important role in improving the palatability of oral dissolving formulations. The uses of natural sweeteners are restricted in people with diabetics and thus artificial sweeteners are used. The classical source of sweetness is sucrose which is

Table 1: Evolution of Dosage Form.

First	Conventional oral solid drug dosage form
Second	Modified release tablets or capsules
Third	Fast action solid dosage forms (sublingual tablets)
Fourth	Fast action solid dose form (fast dissolving oral thin films

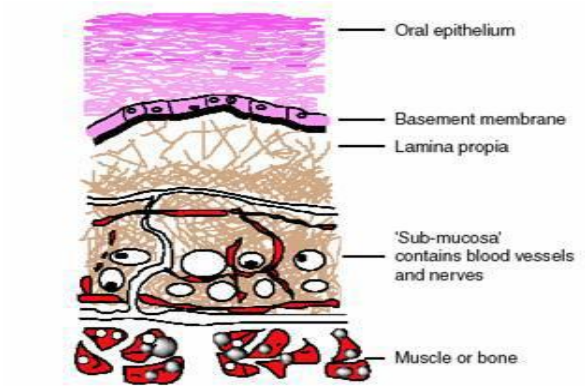

Figure 1: Tongue Layer

derived from cane or beet in the form of liquid or dry state; dextrose, fructose, glucose and maltose are also used. Saccharin, cyclamate and aspartame are the first generations of artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. All of the artificial sweeteners have toxic and carcinogenic effects, so natural sweeteners like rebiana is used[9].

Flavoring agents

Perception of flavors changes according to individual's ethnicity and liking. The acceptance of the oral disintegrating or dissolving formulation by an individual, by and large, depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which tastes for at least about 10 min. Flavors can be used alone or in combination. The amount of flavour needed to mask the taste depends on the flavour type and its strength. Flavoring agents can be selected from synthetic flavour oils, oleo resins and extract derived from various plants. Various flavor oils added are peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg, etc.

Coloring agents

Pigments or FD&C approved coloring agents are incorporated like titanium dioxide, natural colour and custom pantone-matched colour are also used.

Thickening agent

It improves the viscosity and consistency of dispersion or solution before casting of wafers. Agents like gum, carrageenan and cellulosic derivatives in the concentration of 5% (w/w) are used as thickening agents.

Taste masking agents

Examples of taste masking agents are sorbitol, mannitol, xylitol, dextrose, etc. The various approaches for taste masking of bitter drugs:

• Polymer coating solution of drug or its suspension applied to a substrate.
• Particles or entities of active drugs are coated directly.
• Granulation with compatible excipients followed by a polymer coating[10].

Definition of Gums

The most common theories says that gums are formed as a natural phenomenon of the plant in which internal plant tissues disintegrate through a process called gummosis. This in turn form cavities, which exudes transformed carbohydrates called gums.

Classification of Gums

Gums are present in high quantities in varieties of plants, animals, seaweeds, fungi and other microbial sources, where they perform a number of structural and metabolic functions; plant sources provide the largest amounts. The different available Gums can be classified as follows[11].

According to the charge

Anionic Polysaccharides

Natural: Pectin, Xanthan gum, Hyaluronic acid, Chondroitin sulfate, Gum Arabic, Gum Karaya, Gum Tragacanth

Semi-Natural: Carboxymethyl, Chitin, Cellulose gum.

Cationic Polysaccharides

Natural: Chitosan

Semi-Natural: Cationic Guar gum.

Cationic- Hydroxyethylcellulose (HEC).

Nonionic Polysaccharides

Natural: Starch, Dextrin's, Guar gum.

Semi-Natural: Cellulose Ethers (e.g. hydroxyethyl cellulose, Methylcellulose, Nitrocellulose).

Table 2: Three types of oral films are differentiated from each other.

Type /Property	Flash Release Wafer	MucoadhesiveMelt-away wafer	Mucoadhesive Sustained release Wafer
Area (cm2)	2 – 8	2 – 7	2 – 4
Thickness (μm)	20 – 70	50 – 500	50 – 250
Structure	Film: single layer	Single or multilayer system	Multilayer System
Excipients	Hydrophilic polymers	Hydrophilic polymers	Low / Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspension	Suspension or solid Solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival or other region in oral cavity
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8 – 10 hr.

Table 3: Comparison of Orodispersible film and Orodispersible tablet.

Orodispersible film	Orodispersible tablet
It is a film	It is a tablet
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Better durable than Orodispersible tablets	Less durable as compared with orodispersible film
More patients compliance	Less patient compliance than film
Low dose can be incorporated	High dose can be incorporated

Table 4: Ingredient used in formulation.

S.no.	Ingredient	Amount
1	Drug(API)	5-30%
2	Water Soluble polymer	45%
3	Plasticizer	0-20%
4	Saliva Stimulating Agent	2-6%
5	Surfactant	Q.S.
6	Sweetening Agent	3-6%
7	Flavors, Colours, Fillers	Q.S.

Table 5: List of a few plants, which are commercially tapped for, gums with their product names.

Name of the source	Family	Exudate/Product
A. senegal (L.) Willd	Leguminosae	Gum Arabic
Astragalus gummifer	Leguminosae	Gum tragacanth
Cochlospermum gossypium L	Cochlospermaceae	Gum karaya Lannea
Azadirachta indica A. Juss	Meliaceae	Neem gum

Table 6: List of plants which yield seed gum

Plant names	Family	Product
Ceratonia siliqua L. (Carob tree)	Leguminosae	Locust bean gum
Cyamopsis tetragonolobus (L.) Taub.	Leguminosae	Guar gum
Tamerindus indica	Leguminosae	Tamarind gum

Amphoteric Polysaccharides

Semi-Natural: Carboxymethylchitosan, N-hydroxyl-Dicarboxyethylchitosan, Modified Potato starch.

Hydrophobic Polysaccharides

Semi-Natural: Cetylhydroxyethylcellulose, Polyquaternium.

According to the source

Marine origin/algal (seaweed) gums: Agar, Carrageenan, Alginic acid, Laminarin.

Plant origin

Shrubs/tree exudates—Gum Arabica, Gum Ghatti, Gum Karaya, Gum Tragacanth, Khaya and Albizia gums;

Seed gums—Guar Gum, Locust bean Gum, Starch, Amylose, Cellulose

Extracts -Pectin, Larch gum;

Tuber and roots—Potato starch.

Animal origin: Chitin and chitosan, Chondroitin sulfate, Hyaluronic acid.

Microbial origin (bacterial and fungal): Xanthan, Dextrin, Curdian, Pullulan, Zanflo, emulsan, Baker's yeast glycan, schizophyllan, lantana, Kerstin, scleroglucan.

Prepared gums

- Biosynthetic gums Xanthan, scleroglucan, dextrin.
- Starch and its derivatives, dextrin.
- Cellulose derivatives.

Semi-synthetic

Starch derivatives: Heta starch, Starch acetate, Starch phosphates.

Cellulose derivatives: Carboxymethyl cellulose (CMC), Hydroxyethyl cellulose, Hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), microcrystalline cellulose (MC)

According to shape

- Linear: Aligns, Amylose, Cellulose, pectin.
- Branched:

Short branches—Xanthan, Xylan, and Galactomannans;

Branch-on-branch—Amylopectin, Gum Arabic, Tragacanth.

According to Monomeric units in chemical structure

Homoglycans— Amylose, Arabinanas, Cellulose;

Diheteroglycans— Algins, Carrageenan's, Galactomannans;

Tri-heteroglycans—Arabinoxylans, Gellan, Xanthan;

Tetra-heteroglycans—Gum Arabic, Psyllium seed gum;

Penta-heteroglycans—Ghatti gum, Tragacanth.

Natural Gum

Natural gums (gums obtained from plants) are hydrophilic carbohydrate polymers of high molecular weights, generally composed of monosaccharide units joint by glucocidic bonds. They are generally insoluble in oils or organic solvents such as hydrocarbons, ether or alcohols. Gums are either water soluble or absorb water and swell up or disperse in cold water to give a viscous solution or jelly. On hydrolysis they yield aarabinose,galactose, mannose and glucuronic acid[12-13].

Advantages of Natural Gums in pharmaceutical science

- Biodegradable
- Biocompatible and non-toxic
- Low cost
- Environmental-friendly processing
- Local availability
- Better patient tolerance as well as public acceptance
- Edible sources

Disadvantages of Natural Gums in pharmaceutical science

- Microbial contamination
- Batch to batch variation
- Uncontrolled rate of hydration
- Reduced viscosity on storage

Manufacturing methodologies of wafer

Various approaches to manufacturing of rapid dissolving wafers are classified as follows:

Casting and drying
- Solvent casting
- Semi-solid casting

Extrusion
- Hot-melt extrusion
- Solid dispersion extrusion

Freeze dried wafers

Rolling method[14-15]

Solvent casting method

Fast dissolving 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 exicipients are dissolved in suitable solvent then both the solution are mixed and stirred and finally casted in to the petri plate and dried. water Soluble ingredients are dissolved in water and API and other agents are dissolved in suitable solvent[16-17].

Form a clear viscous solution

↓

Both the solution are mixed

↓

Degassed under vacuum

↓

Resulting solution is cast as a film

↓

Film is dried in drying oven and collected

Hot melt extrusion

Hot melt extrusion method has various benefits; those are fewer operation units, minimum product wastage, better content uniformity, an anhydrous process, absence of organic solvents.

In hot melt extrusion method[18-19].

Drug is mixed with carriers in solid form

↓

The extruder having heaters melts the mixture

↓

Finally the melt is shaped in films by the dies.

Freeze-dried wafers

A polymer of concentration 1% (w/w) and lactose as a bulking agent of concentration 6% (w/w) was added to deionized water and mixed for 45 min. 1.5 ml of the various polymer solutions was pipetted out into the cylinder cavities pre-oiled with mineral oil. The formulation was subjected to a freeze-phase in a freeze-dryer at-60ºC for 2h & the dying phase was executed at a pressure of 25 m-tor for 24 h. Wafers were stored in glass jars with 2g of desiccant sachets[20].

Table 7: List of a few sea weeds used as sources of gum.

Plant names (Red Algae, Rhodophyceae)	Product
Chondrus crispus	Carrageenan
G. cartilagineum	Agar
F. spiralis	Alginate

Table 8: Biosynthetic gums (microbial gum)

Name of the organism	Product
Xanthomonas compestris	Xanthan
Aureobasidium pullulans	Pullulan
Leuconostoc mesenteroides	Dextran

Rolling method

Asolution or suspension containing drug is rolled on a carrier. The solvent is mainly water or a mixture of water and alcohol. The wafer is dried on the rollers and cut into desired shapes and sizes. Other ingredients including active agents dissolved in a small portions of aqueous solvent using the high-shear processor. Water soluble hydrocolloids
are dissolved in water to form homogeneous viscous solution[21-22].

Application

Oral mucosal delivery via buccal, sublingual, and mucosal route by use of ODFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. ODF evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products[23].

Gastro retentive dosage systems

Dissolution of film could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could
Potentially be used to treat gastrointestinal disorders.

Diagnostic devices

Dissolvable films may be 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 within a diagnostic device[24].

Taste masking

An important aspect of thin film drug delivery technology is the masking of the often bitter and poor taste of drug formulations.

Vaccination

Rotavirus vaccines is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as freshening yours breath.

Evaluation of formulation

Physical characteristics observation

Charcterisatics such as homogenecity,colour,transparency,flexibility,brittleness and surface of the oral films were evaluated by visual inspection[25].

Thickness

The thickness of film is measured by micrometer screw guage at different strategic locations.This is essential to

Table 9: Pharmaceutical Application of gums.

Common name	Botanical name	Family	Pharmacutical application
Khaya gum	Khaya grandifolia	Meliaceae	Binding agent
Gum acacia	Acacia arabica	Leguminosae	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient in cosmetic
Gum tragacanth	Astragalus gummifer	Leguminosae	Suspending agent, emulsifying agent, demulcent, emollient in cosmetics and sustained release agent
Carragennan	Chondrus cryspus	Gigarginaceae	Gelling agent, stabilizer in emulsions and suspensions, in toothpaste, demulcent and laxative
Sodium alginate	Macrocytis pyrifera	Lessoniaceae	Suspending agent, gelation for dental films, stabilizer, sustained release agent, tablet coating

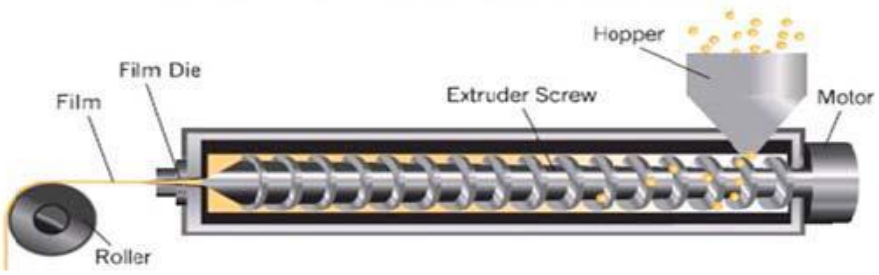

Figure 2: Hot melt extrusion

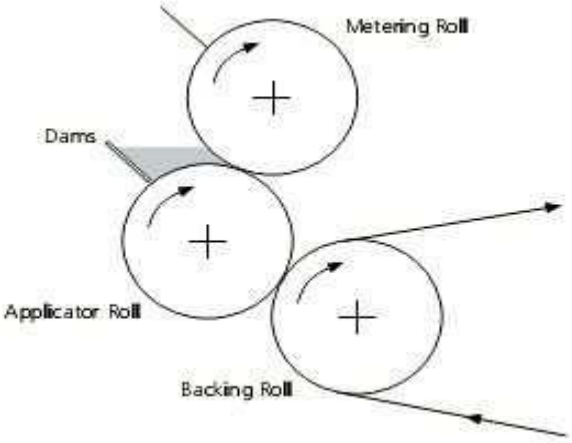

Figure 3: Rolling method

ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film[26].

Folding endurance

Folding endurance is determined by repeated folding of the film at the same place till the film breaks.The number of times the film is folded without breakings is computed as the folding endurance[27].

In vitro disintegration studies

The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to or dispersible films.Although,no official guidance is available for oral disintegrating films,this may be used as a guideline for quality control test or at development stage.Typical disintegration time for films is 5-30sec.The film as per the dimensions (2*2cm)required for dose delivery was placed in petridish containing 10ml phosphate buffer (pH6.8)[28-29].

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the film to float onto the dissolution medium when the paddle apparatus is employed. But once film gets wet it goes into the solution. Both apparatus are suitable to use and have evidence to be use. The in vitro dissolution test was carried out in a paddle dissolution apparatus[30-31].

Surface pH

A FIilm with too much acidic or basic pH, affects the area of application and causes damages to oral mucosal membrane leading to patients discomfort.It is likely that the chemical nature of the drug and excipients influences

the ph of the prepared film. In this, the surface pH of prepared film was measured after allowing it to wet by keeping it in contact with distiiled water for short period at room temperature. It was measured by touching tool the bulb of pH-meter[32-33].

Drug content and uniformity

Content uniformity is determined by estimating the API content in individual film. Limit of content uniformity is 85-115%. The film was cut in 2x2 cm in size dissolved in 50ml of phosphate buffer pH 6.8 sonicated for 15 minute filter using whattmann filter paper. This solution was used for U.V analysis and then concentration of drug is determined for checking drug uniformity[34].

Weight variations

For weight variation, individual films are weighed and the average weights are calculated. Then the average weight of the films is subtracted from the individual weight of the films. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content. This test was carried out for three films of size 2×2 cm in size cut from single film[35].

Tensile strength

Orodispersible film should possess moderate tensile strength, high % elongation (%E), low Young's Modulus, and high percent of drug release. Tensile strength is the maximum stress applied to a point at which the film specimen breaks. For the tensile strength Brookfield's TexturePro CT V1.4 CT3 Texture Analyzer was used[36].

Formula given below is used for determination of Tensile strength:

Tensile strength=Load at failure × 100/Strip thickness × Strip width.

Percent Elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases[37].

% Elongation =Increase in length of strip × 100 /Initial length of Strip.

CONCLUSION

The oral dissolving film is an advanced technology that can be of tremendous use especially in geriatric and pediatric patients as they combine the stability of a solid dosage form and the ease of use in a liquid preparation. Mouth-dissolving oral films have several advantages over the conventional dosage forms and hence are of great importance particularly during the emergency situations such as allergic reactions and asthmatics attacks. And more importantly, mouth dissolving films are travel-friendly dosage forms where water is not needed for dissolution of the drug. The mouth dissolving film promises to be a unique, selective, and needful dosage delivery system and will be of great use in dentistry and medicine in the future[38-39].

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