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REVIEW ARTICLE

Polymer Based Wafer Technology: A Review

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ABSTRACT

At all the times there are rising hassle for developing a dosage form which improve patient convince and compliance particularly for Oral/ Buccal drug delivery system. Due to small size, little dose, thickness of buccal wafer over other dosage form is most acceptable and pleasant. Flash release oral wafer drug delivery system is an alternative approach for the tablets, capsules, and liquid oral dosage forms for pediatric and geriatric patients. Effective attachment with buccal layers represents Buccal wafers as convenient and suitable dosage form compared to others. The semi-synthetic and synthetic natural polymer as film former in low concentration can be used for the preparation of Buccal wafers and hence such dosage form are easy to handle, cost effective, fast absorbable, non-irritating and mostly preferred by patient. It improve the efficacy of APIs 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. Wafers formulations are appropriate in allergenic conditions, cough and cold remedies, sore throat, nausea, pain and CNS disorders. Present article overview the advancement in the oral dosage forms, application, formulation composition, method of preparation, evaluation and marketed products of oral flash release wafers.

Key words: Wafer, Flash release, film former.

INTRODUCTION

Among the Novel Drug Delivery system, buccal drug delivery is the main and extensive acceptable drug delivery between the other delivery systems. The orally disintegrating tablets are available in the market providing 1 to 2 minute of disintegration time. Among fast dissolving drug delivery systems, Oral flash release wafer drug delivery system is an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience in difficulties of swallowing traditional oral solid dosage forms [1]. This technology has been used for local action, rapid release of products and for direct systemic circulation in the oral cavity to release drug in rapid fashion. And also this delivery protect drug from first pass metabolism and improve the dissolution. Oral thin Wafer drug delivery systems are solid dosage forms, which dissolve in a short period of time when placed in the mouth without drinking water or chewing. These are also referred d as fast dissolving Oral Wafers, wafers, buccal films/ Oral strips [2].

Anatomic and Physiological Considerations [3-4]:

In the buccal cavity four regions have been used for drug administration. The four regions have varying permeability, which plays a role in the absorption of drugs across the oral mucosa. As seen in the four vital areas are the buccal cavity (**Fig 1 & 2**), the lingual area, the palate and gingival region. The most preferably used sites for drug administration of the four mentioned above are the Sublingual and Buccal route. Using the sublingual route, the medicament is placed under the tongue, usually in the form of a rapidly dissolving wafer. The anatomic site for drug administration between the cheek and gingival is known as the buccal mucosa. The oral mucosa is composed of three layers. The first layer is the stratified squamous epithelium; underneath this layer lies the basement Membrane. The basement membrane overlies the lamina propria and submucosa.

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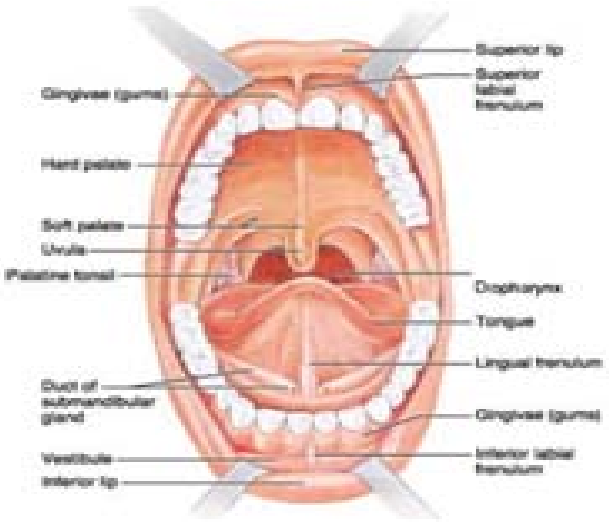
The structure of the epithelium within the different sites of the oral cavity shows distinction. The gingival and hard palate are exposed to mechanical pressure during eating, hence the epidermis is keratinized in a similar manner as the skin. The epithelium in the soft palate, buccal and sublingual area is not keratinized, therefore not containing ceramides and acylceramides which are associated with providing a barrier function [3]. The mucosas of the buccal and sublingual region have only small amounts of ceramide thus it is more permeable when compared to other regions of the oral cavity. The presence of membrane coating granules (MCGs) accounts for the differences in permeability amongst the various regions of the oral mucosa. When cells go through differentiation from basal to flattened keratinous cells, MCGs are formed. MCGs are present in both keratinized and nonkeratinised epithelia, however their composition is different. On the other hand, nonkeratinised epithelium contains MCGs that are nonlamellar and include cholesterol, cholesterol esters and glycospingolipids.



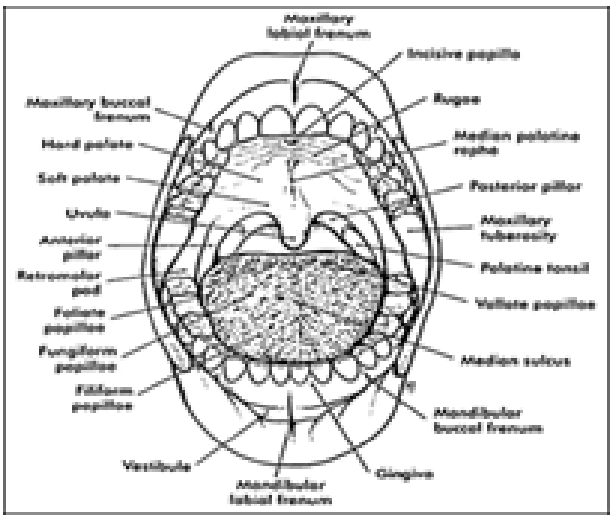


Figure 1 & 2: Anotomical sites of oral cavity

A layer of mucus is present on the surface of the epithelial layer of cells (**Fig 3**). This plays a major role in cell-to-cell adhesion, oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems .A major feature in the environment of the oral cavity is the presence of saliva. The salivary glands produce saliva, responsible for protecting the soft tissues from abrasion during the mastication of food Saliva plays an essential role in facilitating the disintegration of quick-disintegrating drug delivery systems.

The Buccal and sublingual regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a drug delivery system for a desired duration. Although the buccal mucosa is less permeable than the sublingual mucosa and does not yield a rapid onset of action as seen with sublingual delivery, mucosa of the buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of a retentive system. In case of buccal drug delivery, adhesion to the oral mucosa allows the intimacy of contact and the improved drug absorption. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs. The sublingual route is however more suitable for delivery systems formulated either as rapidly disintegrating matrices or soft gels. These systems create a highly significant drug concentration in the sublingual region prior to systemic absorption across the mucosa.

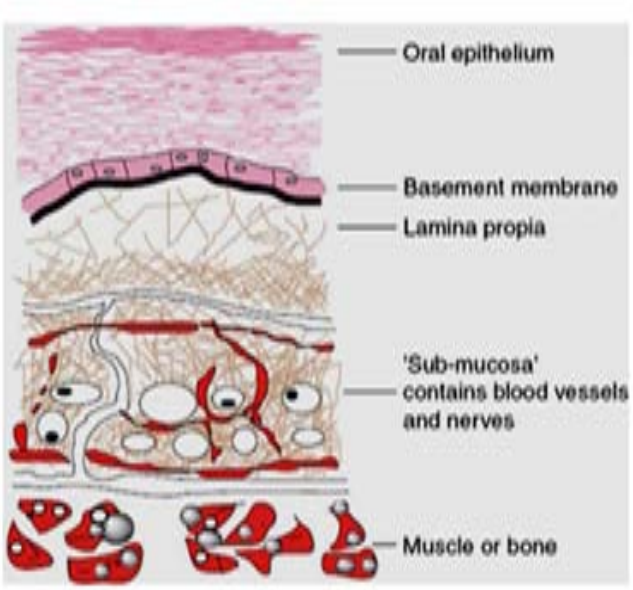


Figure 3: Layers of Oral mucosa

Why Buccal Delivery [5-6]?

The mucous membrane permeability provides a convenient route for the systemic delivery of new

and existing therapeutic drugs. Different mucosal regions like oral mucosa, nasal, rectal, vaginal, ocular may facilitate bioavailability by avoiding the hepatic metabolism. Transmucosal drug delivery is being considered as an attractive delivery route for new and existing drug compounds, some of which are only available today through parentral delivery.

Among the various sites available for transmucosal drug delivery, the buccal mucosa and the sublingual area are the best-suited sites for local as well as systemic delivery of drugs, due to their physiological features.

The buccal mucosal site offers a smooth, immobile surface with high vascular perfusion, in contrast to the sublingual mucosal site, which lacks an immobile mucosal surface. The lack of an immobile surface derives from the fact that the sublingual space is constantly washed by saliva from the sublingual salivary ducts. However, the sublingual mucosal membrane is much thinner (190μm) than the buccal mucosal membrane (580μm). The difference in thickness may explain the difference in permeability (Kp) of the mucosal membranes, 579 x 10-7 cm/min *vs* 973 x 10-7 cm/min for the buccal mucosa and floor of the mouth, respectively. When compared to other mucosal areas, the buccal mucosa is more tolerant to potential allergens, with less impact for irreversible damage, and relatively lower enzymatic activity. For compromised patient populations where swallowing is difficult or where a potential choking hazard is present, a buccal delivery device presents an elegant and effective dosage format with improved bioavailability when compared to other oral formats.

Buccal devices offer advantages to caregivers for administration, in that the Buccal area is easily accessible and generally a well-tolerated site by patients as it does not require swallowing for the device to deliver an efficacious systemic dose with rapid onset. A number of buccal products are emerging for the treatment of chronic conditions, as well as breakthrough treatments for central nervous conditions and pain therapies in the form of oral sprays, buccal films or tablets, and sublingual films or wafers. As with transdermal applications, formulators are limited by the ability to deliver higher molecular weight (Mw) compounds through buccal mucosal tissue. This is because the buccal and sublingual membranes contain a stratified (multilayered) epithelium that demonstrates differentiation of various cell layers in the form of keratinisation. This is different from the single epithelium cell layer lining the gastro-intestinal tract, thereby resulting in less resistance to permeability.

Several approaches can be taken to increase the permeation of a drug through the buccal mucosal membrane. One of these approaches is to improve the bioadhesion properties to increase residence time and drug release of the device in the oral cavity. Modification of the drugs partition coefficient can be used as an approach. A third approach, which is also used in transdermal drug delivery, is to employ the use of chemical permeation enhancers.

Physicochemical properties of the oral mucosa:

The surface of Buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane. It is interesting to note that the permeability of Buccal mucosa is greater than that of the skin, but less than that of the intestine. It is also reported that the permeability of the Buccal mucosa is approximately 4–4000 times greater than that of the skin. Hence the Buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 micron layer. The epithelia of oral cavity are also composed of an intercellular ground substance called as mucus which basically consists of proteins and carbohydrates. It maintains hydrated condition of the oral cavity, provides adequate lubrication, concentrates protective molecules such as secretory immunoglobulin and reduces the attachment of microorganisms. The saliva and salivary mucin contribute to the barrier properties of oral mucosa.

While the major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth sub-mandibular (tongue regions), and the sublingual ducts, the minor salivary glands are located in the lips, Buccal mucosa and in linings of the mouth and throat. Total turnover rate of the total whole saliva (output from the major and minor salivary glands) at normal physiological conditions has a flow rate of 1–2 ml/min. Drug absorption through the Buccal cavity can take place either by the transcellular route (or intracellular route, crossing

across the cell membrane and entering the cell) or paracellular pathway (passing between the cells). The mucosa in sublingual region is relatively more permeable leading to rapid absorption with improved bioavailability.

Mechanism of Fast Dissolution in Oral cavity [7]**:**

The term "fast dissolution" represents that these dosage forms dissolves rapidly and disintegrates into smaller particles by saliva and swallowed into the stomach. The time to reach from mouth to the stomach is estimated to be between 5 and 10 minutes. Therefore fast dissolving drug delivery system has the advantage of liquid dosage form i.e. convenient drug administration.

The wafer quickly dissolves in the oral cavity, and the active ingredient can be absorbed into the blood - stream via the oral mucosa. The active ingredient, once absorbed by the oral mucosa, thus bypasses the liver's first-pass effect, which improves bioavailability. Depending on the selected wafer type, the active ingredient's release may also be delayed. In this case, it is absorbed after swallowing via the gastrointestinal tract.

The fast passage of dissolved dosage form to the stomach provides a better opportunity for the medication to be absorbed through the membrane of the Buccal cavity, Pharynx and Esophagus for improved bioavailability and quick onset of drug action.[7]

Wafer – a novel oral dosage form:

The wafers created new possibilities for action profiles and patient compliance. Wafers are paper-thin polymer films used as carriers for pharmaceutical agents. The innovative dosage form is taken orally but does not require water or swallowing.

Effective absorption of active ingredient:

The wafer quickly dissolves in the oral cavity, and the active ingredient can be absorbed into the blood - stream via the oral mucosa. The active ingredient, once absorbed by the oral mucosa, thus bypasses the liver's first-pass effect, which improves bioavailability. Depending on the selected wafer type, the active ingredient's release may also be delayed. In this case, it is absorbed after swallowing via the gastrointestinal tract.

Positive aspects with wafers (industrial point of view):

- Attractive dosage form with new active ingredients.
- Improvement of established products.
- Access to new indications by means of a new absorption profile even for existing active ingredients.
- Optimization of bioavailability.
- Increase patient compliance.
- Innovative technology for product.
- Increase of product appeal through innovative format.
- Exclusivity and cutting edge technology position in the market through a step forward.

Special features of mouth dissolving Wafers

- Thin elegant Wafer
- Available in various size and shapes
- Fast disintegration and Rapid release
- The drug to be incorporated should have low dose up to 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Advantages of oral dissolving Wafers [8-9]**:**

Table 1: Differences in Mouth dissolving wafers and Oro-dispersible tablets

Sr. No	Mouth Dissolving Wafers	Oro-dispersible Tablet
1	High dissolution due to a large surface area	Lesser dissolution due to less area
2	Better durable than Oro-dispersible tablet	Less durable as compared with Wafers
3	More patient compliance	Less patient compliance than Wafers
4	Low dose can only be incorporated	High doses can be incorporated
5	No risk of choking	It has a fear of choking

Classification of oral Wafer [10]**:**

There are three subclasses

(1) Flash release wafers
(2) Mucoadhesive melt-away wafers
(3) Mucoadhesive sustained-release wafer

Pharmacopoeial Status of Oral Wafers

Pharmacopoeias provide the Monographs of common dosage forms. Even though Oro-dispersible tablets, medicated chewing gums, Oro-mucosal lyophillites are included but the monographs and specifications for oral Wafers of different dissolution kinetics has not so far been established. There are insufficient pharmaceutical technical processes for analysis in development and quality control of Wafers as well.

Objective of Formulation of Wafers:

The aim of the present research work is development and characterization of mouth dissolving oral Wafers of a suitable drug candidate so as to achieve following objectives:

- To improve patient compliance and provide a rapid onset of action.
- To reduce the extent of hepatic first pass metabolism.
- To reduce side effects associated with the API by reducing its dose
- To enhance the oral bioavailability of molecules.

Formulation consideration [11]

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

Composition of the oral thin Wafer [12-20]**:**

Mouth dissolving Wafer is a thin Wafer with an area of 5-20 cm^2 containing an active ingredient. The instant dissolution, in water or saliva correspondingly, is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 15mg. Formulation considerations (polymer, sweetener, plasticizers etc.) have been reported as important factors affecting mechanical properties of the Wafers, such as changing the glass transition temperature to lower temperature.[12]

Table 2: Formulation details

S. No	Ingredients	Amount(s) (w/w)
1	Drug substances (API)	5-30%
2	Wafer forming Polymer	45%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Surfactant	Q.S.
6	Sweeteners	3-6%
7	Flavors, Colors, Fillers	Q.S

1) **Drugs** [21,22]:

Different classes of drugs can be formulated as mouth dissolving Wafers including Antiulcer (e.g. Omeprazole), Antiasthamatics (Salbutamol sulphate), Antitussives, Expectorants, Antihistaminics, NSAID'S (e.g. Paracetamol, Meloxicam).

The ideal characteristics of a drug to be selected [22]

- Drug should have pleasant taste.
- Incorporated drug should have low dose (up to 40 mg)
- Posses smaller and moderate molecular weight
- Good stability and solubility in water as well as in saliva
- Partially unionizes at the pH of oral cavity
- Ability to permeate oral mucosal tissue

The oral flash release wafer technologies have the prospective for delivery of variety of API. But as the high dose cannot be incorporated into the Wafers, only 5mg to 30mg of API can be incorporated into the Wafer. Insoluble API is dispersed uniformly in the Wafer. API s can also be added as milled, micronized and also in the form of nanocrystals or particles depending upon the release profile. Several APIs that can be potentially used for oral Wafer technology are with bitter taste, makes the formulation unpleasant, especially for pediatric formulations. This leads to the very significance unit operation – taste masking, before incorporating the API in the oral dissolving Wafer. Various methods are used to improve the palatability of the formulation.

- **Simplest method**
  It includes the mixing and blending of Drug with bitter taste with pleasurable taste which is termed as obscuration technique.
- **Barrier method**
  This method is applicable to mask the bitter taste which includes complexation, polymeric coating and micro particle and coated particle.

2) Water soluble polymers [23-26]**:**

Water-soluble polymers are used as Wafer formers. The use of Wafer forming polymers in dissolvable wafers/films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the Wafers. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer Wafers/ strip/film bases.

Some of the water soluble polymers used as Wafer former are

- HPMC E-3 and K-3
- Methyl cellulose A-3, A-6 and A-15
- Pullulan*
- Gelatin
- Sodium Alginate

- Hydroxy propyl cellulose
- Polyvinyl alcohol
- Maltodextrin and Eudragit
- Polymerized rosin* is a novel Wafer forming polymer

The primary intention of developing of Oral Wafer dosage forms relies on their disintegration in the saliva of the oral cavity, is necessarily be water soluble. In order to prepare a thin Wafer formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and exceptional Wafer forming capacity. It should have passes properties like good wetting and spread ability. The polymer should show satisfactory peel effect and tensile strengths. The polymer should be widely available and economic. Many different polymers for use in oral Wafers are proposed in the literature, and various research groups have introduced different materials.

The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouthfeel and solubility characteristics of fast dissolving Wafers. The type of polymer and the amount of polymer in the formulation affects the stiffness of wafers. Polyvinyl pyrrolidone Wafers are brittle in nature and therefore Cross Povidone is mixed with Poly Vinyl Pyrrolidone for preparation of flexible fast disintegrating Wafers. In this case, microcrystalline cellulose is used to render the Wafer non-sticky and smooth. Microcrystalline cellulose was also used to decrease the disintegration time and improve the dissolution of drug from the Wafers.

Water soluble polymer that may be used include natural gums such as those derived from Guar, Xanthun, Acacia, Arabic or Tragacanth, other available polymers are, polyethylene oxide, acrylic based polymer and several types of Sodium Carboxymethyl Cellulose (CMC), several types of Hydroxypropyl Methyl Cellulose (HPMC), a synthetic copolymer of polyethylene glycol–polyvinyl alcohol (Kollicoat IR) and sodium alginate. Cellulose ethers are widely available and economical. Pullulan, an a-1,6-linked maltotriose produced from the fungus Aureobasidiumpullulans, has also been used. Five starches and maltodextrin have also been investigated as alternative Wafer formers. The physicochemical characteristic of the polymer or polymers selected for Wafer formulation play a vital role in determining the resultant disintegration time of the cast thin Wafer oral dosage form.

Ideal properties of the Wafer forming polymers [27,28]**:**

- Non-toxic, nonirritant and devoid of leachable impurities
- Good wetting and Good shelf life
- Pleasant mouth feel
- Devoid of secondary infections in the oral mucosa or dental regions
- Local enzyme inhibition action along with penetration enhancing property

3) **Plasticizers:**

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of Wafers. The mechanical properties such as tensile strength and elongation to the Wafers have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, dibutylphthalate, and polyethylene glycols etc.

4) **Penetration enhancers** [29-31]**:**

Penetration enhancers are also required when a drug has to reach the systemic circulation to exert its action. These must be non-irritant and have a reversible effect: the epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids (that act by disrupting intercellular lipid packing), surfactants and, among these, bile salts (by extracting membrane protein or lipids, by membrane fluidization, by producing reverse micellization in the membrane and creating aqueous channels), azone (by creating a region of fluidity in intercellular lipids) and alcohols (by reorganizing the lipid domains and by changing protein conformation). Recently, chitosan and its derivatives, polymers already known for their mucoadhesive properties, have been shown to be the potential penetration enhancers for trans-mucosal.

5) **Surfactants:**

Surfactants are used as solubilizing or wetting or dispersing agent so that the Wafer is getting dissolved within seconds and release active agent immediately. Some of the commonly used are Sodium Lauryl Sulfate, Benzalkonium chloride, Bezthonium chloride, Tweens etc. One of the most important surfactant is Polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

6) **Flavor:**
Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors. Flavoring agents Perception for the flavors changes from individual to individual depending upon the ethnicity and liking. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. The selection of flavor is also dependant on the type of drug to be incorporated in the formulation. For example, mint flavor is generally added in products used for gastric related ailments like indigestion. The acceptance of the oral disintegrating or dissolving formulation by an individual by and large depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about10 min.

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, spearmint oil, oil of nutmeg is examples of flavor oils while vanilla, cocoa, coffee and chocolate.

7) **Color:**
A full range of colors is available, including FD & C colours, EU Colours, Natural Colours and custom Pantone-matched colors.

8) **Saliva stimulating agents** [32-34]**:**
Saliva stimulating agents Increases the saliva production rate, aids in faster disintegration of wafers (Conc. - 2-6 % w/w). Examples citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid Flavoring agents: may be selected from syn. Flavor oils, oleoresins, from plant parts. Amount depends on the flavor type and strength important flavors: peppermint, cinnamon, nutmeg, vanilla, cocoa, coffee, chocolate, citrus, apple, cherry, raspberry, pineapple.

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 Wafer formulations. 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. These agents are used alone or in combination between 2 to 6%w/w of weight of the Wafer. Other buccal Wafer ingredients such as sweeteners also act as salivary stimulants. Food grade sugars as well as synthetic sugars are useful salivary stimulants along with acidulate. Glucose, fructose, xylose, maltose, lactose are few examples of such sweeteners.

The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at equal time under same conditions. The stimulant action of sweeteners is dependent on the sweetness value. Fructose has the sweetness value of 1.1 as compared to 0.7 of glucose and 1.0 of sucrose. The artificial sweetener is preferred over natural sugars because lower concentration is required and multiple uses don't result in dental caries in individuals.

9) 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. Sweetness plays important role for improving compliance wafers in pediatric population. Natural sweeteners and artificial sweeteners, plays vital role to improve the palatability of the oral dissolving formulations. 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. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, 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. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) is about 200–300 time sweet than other. Stevia plant is best alternative to synthetic one. All artificial sweeteners have toxic and carcinogenic effects.

10) **Taste Masking Agents** [35]:
Taste masking of bitter or objectionable tasting drug substances is critical for any orally administered dosage form. There are various approaches of taste masking of bitter drugs for fast dissolving dosage forms:

- Polymer coating to the Solution of drug or its suspension applied to a substrate

- Particles or entities of active drug are coated directly.
- Granulation with compatible excipients followed by the polymer coating.

Sugar based excipients are used for taste masking and as bulking agents. Sorbitol, mannitol, xylitol, dextrose, fructose are mainly used.

Manufacturing methods:

One or combination of the following process can be used to manufacture the mouth dissolving Wafers.

1) Solvent casting method [36,37]:

In solvent casting method water soluble polymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. Fast dissolving Wafers 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 finally casted in to the Petri plate and dried, which is then cut into pieces of the desired size.

The properties of the API play a critical role in the selection of a suitable solvent. Water-soluble hydrocolloids used to prepare RDFs include: hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), pullulan, sodium alginate, pectin, carboxy methyl cellulose (CMC), polyvinyl alcohol (PVA). Solvents used for the preparation of solution or suspension should ideally be selected from ICH Class 3 solvent list.

Specific types of equipment used at large scale production (**Fig 4**) as well as rollers are used for pouring the solution on an inert base. The clearance between the roller and the substrate determines the required thickness of the Wafer. The final step, drying the Wafer, removes the solvent and helps to obtain the finished product. Usually, glass, plastic, or Teflon plates are used as an inert base for Wafer 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 Wafer, obtaining uniform thickness of the Wafer, and proper drying of the sample. The selection of the proper type of dryer is needed in the final step of drying. Once the Wafers are dried, cutting, stripping, and packaging is done. Suitable size and shapes of Wafers can be cut. The commonly available sizes of Wafers are 3 x 2 cm^2 and 2 x 2 cm^2.

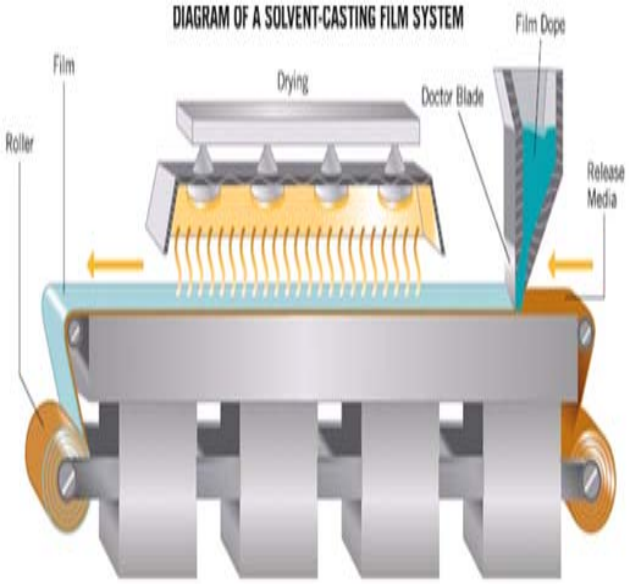


Figure 4: Solvent casting technique

Advantages:

1. Better uniformity of thickness and better clarity than extrusion.
2. Wafer has fine gloss and freedom from defects such as die lines.
3. Wafer has more flexibility and better physical properties.

Disadvantages:

1. The polymer must be soluble in a volatile solvent or water.
2. A stable solution with a reasonable minimum solid content and viscosity should be formed.
3. Multiple casting techniques may be selected on the basis of the fluid rheology, desired applied mass, and required dosage uniformity.

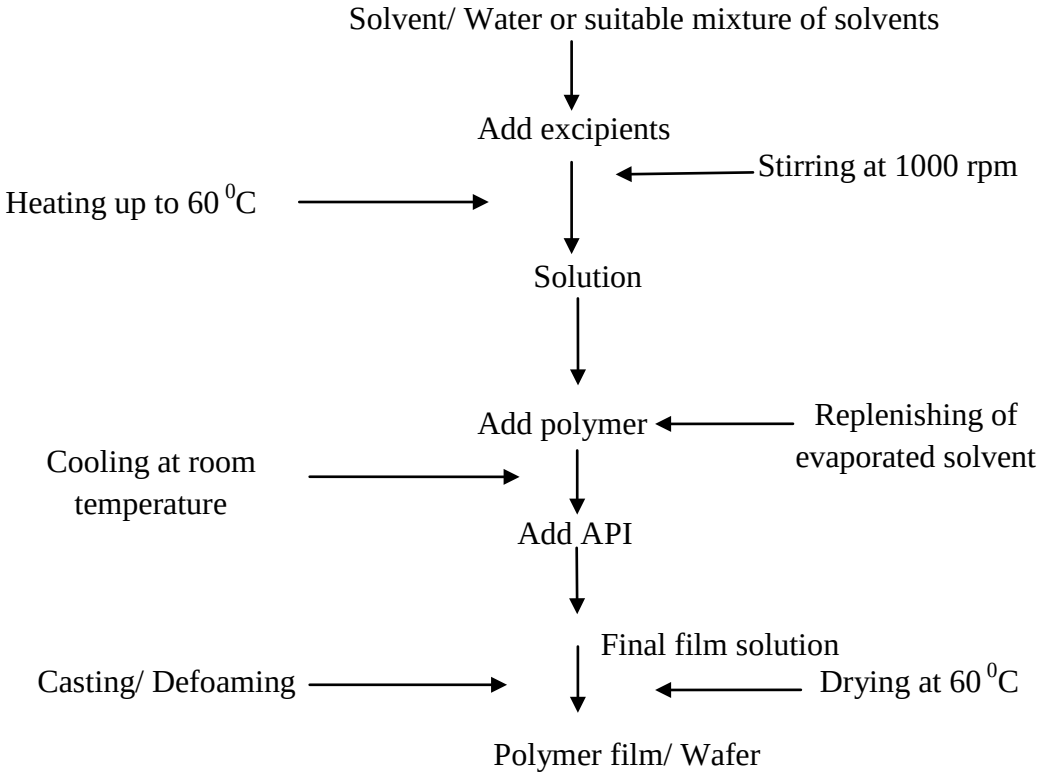


Fig 1: Flow Chart of Solvent casting method for Preparation of Flash release wafer

2) Semisolid casting:

In semisolid casting method, solution of water soluble Wafer forming polymer is prepared. Then obtained solution is further added to acid Insoluble polymer solution (e.g. Cellulose acetate phthalate, Cellulose acetate butyrate), which was prepared in sodium or ammonium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the Wafers or ribbons using heat controlled drums. The thickness of the Wafer is between 0.015-0.05 inches.

The ratio of the acid insoluble polymer to Wafer forming polymer should be 1:4. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution. Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor. Both mixtures are mixed to form homogenous viscous solution and degassed under vacuum. Bubble free solution is coated on non-treated casting Wafer coated Wafer is sent to aeration drying oven. Wafer is cut in to desired shape and size.

3) Solid dispersion extrusion [38]**:**

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to Wafers by use of dies.

Advantages:

1. Fewer processing steps
2. More uniform dispersion of the fine particles because of intense mixing and agitation

4) Hot melt extrusion [39-41]:

In hot melt extrusion method (**Fig 5**) firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to Wafers by the dies.

Advantages:

1) Improved bioavailability of poorly soluble compounds.
2) During Processing solvents and water are not required.
3) Cost-effective process with reduced production time and number of unit operations.
4) Sustained, modified and targeted release capability, Superior stability at varying pH and moisture levels.
5) Better content uniformity was obtained among granules of different size ranges.

Disadvantages:

1) Thermal degradation due to use of high temperature
2) Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
3) Higher-melting-point binders require high melting temperatures and can contribute to

volatility problems especially for heat-labile materials.

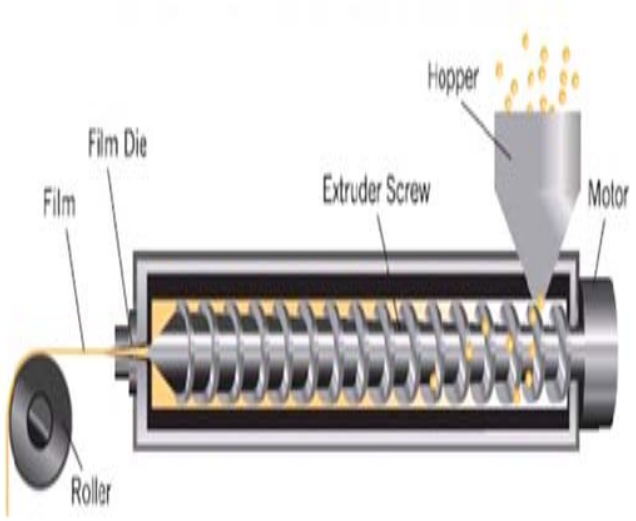


Figure 5: Film extrusion Technique

5) Rolling Method:

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The Wafer is dried on the rollers and cut in to desired shapes and sizes. Other ingredients including active agents dissolved in small portion of aqueous solvent using High shear processor. Water soluble hydrocolloids Dissolved in water to form homogenous viscous Solution.

Evaluation of Fast Dissolving Wafers [42,43]

1) Organoleptic evaluation
2) Mechanical properties
   a) Thickness
   b) Dry test/tack test
   c) Tensile Strength
   d) Percent Elongation
   e) Tear Resistance
   f) Folding endurance
3) Swelling properties
4) Transparency
5) Taste evaluation
6) Assay/Content uniformity
7) Disintegration time
8) In-vitro Dissolution test
9) Stability testing

1) Organoleptic evaluation:

For evaluation of the product, special controlled human taste panels are used. *In-vitro* methods of utilizing taste sensors are being used for this purpose. These *In-vitro* taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral Wafers.

2) Mechanical properties:

Mechanical properties of Wafers are evaluated using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Wafers are held between two Clamps positioned between 3cm. During Measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when Wafer breaks. Three mechanical properties namely tensile strength, elastic modulus and % Elongation are calculated.

Thickness:

The thickness of wafer can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the Wafer as this is directly related to the accuracy of dose in the wafer.

Dryness test/tack test:

Tack is the tenacity with which the wafer adheres to an accessory (a piece of paper) that has been pressed into contact with the wafer.

Tensile Strength:

It is the maximum stress applied to the point at which the Wafer sample breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the wafer as given in the equation below:

$$\textbf{Tensile strength} = \frac{\{\textbf{Load at failure} \times \textbf{100}\}}{\{\textbf{wafer thickness} \times \textbf{wafer width}\}}$$

Percent Elongation:

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

$$\%\ \textbf{Elongation} = \frac{\{\textbf{Increase in length of wafer} \times \textbf{100}\}}{\{\textbf{Initial length of wafer}\}}$$

Tear Resistance:

Tear resistance of plastic Wafer or sheeting is a complex function of its ultimate resistance rupture. Basically very low rate of loading 51mm (2 in)/min is employed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newtons (or pounds-force).

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 Wafer is folded without breaking is computed as the folding endurance value.

3) Swelling property:
Wafer swelling study is conducted using simulated saliva solution. The Wafer sample is weighed and placed in a stainless steel wire mesh. The mesh containing Wafer sample is submerged into 15ml medium in a plastic container. Increase in the weight of the Wafer is determined at predetermined time interval until a constant weight is observed. The degree of swelling is calculated using formula-

$$\alpha = (w_t - w_o)/w_o$$

w_t is weight of Wafer at time t, and w_o is weight of Wafer at time zero.

4) Transparency:
The transparency of the Wafers can be determined using a simple UV spectrophotometer. Cut the Wafer samples into rectangles and placed on the internal side of the spectrophotometer cell. Determine the transmittance of Wafers at 600 nm. The transparency of the Wafers can be calculated as follows:

$$\text{Transparency} = (\log T600)/b = - €c$$

Where, T600 is the transmittance at 600 nm, b is the Wafer thickness (mm), c is concentration

5) Taste evaluation:
Taste acceptability was measured by a taste panel consisting of human volunteers(n=6) with 10 mg drug and subsequently Wafer sample containing 10 mg Drug held in mouth until disintegration, then spat out And the bitterness level was recorded. The volunteers were asked to gargle with distilled water between the drug and sample administration. Following scale was Used for the indicating taste masking values: + = very bitter, ++ = moderate to bitter, +++ = slightly bitter, ++++ = tasteless/taste masked [15, 17,18].

6) Assay/ Content uniformity:
This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is85–115 percent.

7) Disintegration Time:
The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strip. Although, no official guidance is available for oral fast disintegrating Wafers/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.

8) *In-vitro* 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 dissolution test can be difficult due to tendency of the strips to float on the dissolution medium where paddle system is used.

9) Stability test:
A piece of wafer preparation was stored in an Aluminum package at 25 ^{0}C with 50-60% humidity (normal condition) or at 40 with 75% humidity (accelerated condition) for 4-24.

Packaging of oral Wafer [44]:
In the pharmaceutical industry, it is vital that the package selected adequately should preserve the integrity of the product. Expensive packaging, specific processing and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving Wafers. Single packaging is mandatory for Wafers. An aluminum pouch is the most commonly used packaging format.

Selected characteristics packaging material:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper resistant requirements.
- They must be non-toxic and must not be reactive with the product.
- They must not impart to the product taste or odor.

1) Single pouch:
Soluble Film Drug Delivery Pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and Moisture. The package provides a flexible thin film alternative for nutriceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection.

2) Blister card with multiple units:

The blister Container consists of two components: the blister, Which is the formed cavity that holds the product, and The lid stock, which is the material that seals to the blister. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture

3) Polyvinyl Chloride:
The most commonly used blister material is polyvinyl chloride (PVC). This material, which provides a nominal or zero barriers to moisture, is used when the product does not require Effective moisture protection.

4) Barrier Films:
Many drug preparations are extremely sensitive to moisture and therefore require High barrier films. Several materials may be used to provide moisture protection such as Poly-chlorotrifluoroethylene (PCTFE) film, Polypropylene.

5) Continuous roll dispenser:
An automatic drug tape Dispensing and metering device and a disposable Cassette containing a roll of drug tape housed in a Small reusable portable dispenser unit. The dispenser contains a measurement device for carefully measuring the length of tape as it is dispensed. A Counter monitors the remaining doses of drug tape remaining within the dispenser. A timer device may be provided to alert the patient that it is time for the Medicament to be dispensed. As the lid of the dispenser unit is opened, the measured length of drug Tape is severed from the roll by a cutter blade incorporated into the lid.
The administration of the dose to the patient may be set by adjusting the tape length Released for each single dose and selecting the time Intervals between dosages. The invention comprises also ingestible tapes of medicament.

APPLICATIONS OF ORAL FILM DELIVERY SYSTEM [45]:

a) Taste masking:
Taste masking of the drugs becomes critical to patient compliance because the Oral film systems dissolve or Disintegrate in patient's mouth, thus releasing the Active ingredients which come in contact with the Taste buds. An important aspect of wafer drug delivery is the Masking of the often bitter and poor taste of drug Formulations. One method of taste-masking is Encapsulation, the coating of drug particles with a Polymeric covering sufficient to mask the taste of the Drug particle while maintaining the ability to release the drug for absorption.

b) Vaccination:
Oral thin film is delivered in the form of vaccine which is stable at room temperature so that is quickly dissolves in mouth and in saliva. Rotavirus Vaccine is prepared in United States by Johns Hopkins University in 2006. Rotavirus vaccine is a Room temperature stable quick-dissolving oral thin Film delivery system for vaccines that will make Vaccinations almost as simple as freshening your Breath. This delivery system exhibits many Advantages not available in current products: Improved patient compliance, improved Bioavailability, reduction in the costs associated with Storage, distribution, handling and administration.

Sustained release film:
Sustained release Strip is applicable in hospital preparations and drug carriers. Polymer like Chitin and Chitosan derivatives are used as excipient and drug carriers in the pharmaceutical area.

List of marketed wafers [46-48]

Product	Manufactured by
Doneprezil and Ondansatron rapid dissolving films	Labtec Pharma
Altoid cinnamon strips, Boots vitamin c strips, Benzocaine films, Caffeine films	Dow chemical company
Listerine Pocket Paks, Breath Freshening Strips	Pfizer
Gas-X(Simethicon), Triaminic	Novartis
Orajel (menthol)	Del
Sudafed(Phenylephrine)	Wolterskluwer health, Inc.

Future Prospects and Challenges [49,50]:

Historically, drug delivery has taken the form of injection, infusion, ingestion, and inhalation, with additional variations of each category. For example ingestion may be in tablet, capsule or liquid form; inhalation may be via use of a dry powder inhaler, an MDI, or a nebulizer. The challenge for both drug and drug delivery companies is to deliver both existing and emerging drug technologies in a manner that improves the benefits to the patients, healthcare workers and the healthcare system. Areas that are being targeted for improvements through device development includes improved efficiency, minimized side effects , continuous dosing (sustained release) , reduced pain from administration , increased ease of use , better compliance , contribution of healthcare workers decreased, improved safety for healthcare workers.

In addition, due to the well-known fragility and hygroscopicity of lyophilized products, an appropriate packaging system for the wafers need to be developed to ensure that the dosage form reaches the patient and is administered intact. The modification of this technology to provide a prolonged release mucoadhesive system seems promising. It is envisaged that this system will be applicable to many drugs requiring the extended release of bioactive material. Therefore, the lyophilized wafer matrices developed in this study are highly effective in the rapid delivery of drugs, using the oral route as a site of administration. A number of unique opportunities are presented for the formulation of a controlled release drug delivery system.

Wafers may be used for the oral delivery of drugs such as protein and peptide-based active agents that have limited bioavailability when administered by conventional tablets. The protein and peptide-based products frequently degrade rapidly in the stomach.

CONCLUSION

Wafers as novel drug delivery systems have better patient compliance and may offer improved Biopharmaceutical properties, improved efficacy and better safety compared with conventional oral dosage forms. In future, Flash release wafer is promising due to the availability of modern technologies combined with well-built market acceptance. Future possibilities for improvements in fast dissolving drug delivery system are bright. The present report concludes that Flash release oral Wafer is most acceptable and accurate oral dosage form which bypass the hepatic system and show more therapeutic response. Fast dissolving Wafers have several advantages over conventional dosage forms and fast dissolving tablets. The pharmaceutical companies prefer this dosage form due to both patient compliance (especially pediatric and geriatric) as well as industrial acceptability. Oral Wafers can replace the over-the-counter (OTC) drugs, generic and name brand from market due to lower cost and consumer‘s compliance.

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