

REVIEW ARTICLE

MEDICATED WAFERS AS A NOVEL CARRIERS IN DRUG DELIVERY SYSTEM

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Abstract: In the rising of the hassle for developing a dosage form to improve the patient convince and compliance the particularly drug delivery system. Because of its small size and thickness of a wafer contain the other dosage form is the most acceptable and pleasant. The release of oral wafers is the drug delivery system is an alternative approach of the tablets, capsules, and the liquid oral dosage forms for pediatric and geriatric patients. The most effective attachment with the buccal layers contains buccal wafers as a convenient and suitable dosage form. The semi synthetic and synthetic natural polymer can be used for the preparation of buccal wafers these dosage forms are mostly preferred by patient because of easy handling, effective cost, fast absorption, non-irritating. In oral cavity after the contact of saliva when compared to fast dissolving tablets, it improves the efficacy of the APIs by dissolving within minutes, without chewing and no need of water for administration.

Key words: Medicated Wafer, Flash release, film former

INTRODUCTION:

When compared with other drug delivery systems having the buccal drug delivery is the main and an important extensive acceptable drug delivery in Novel drug delivery system. In marketed available the orally disintegrating tablets are available with appropriate disintegration time of 1 to 2 minutes. In fast dissolving drug delivery systems, Oral flash release wafer drug delivery system is an alternative to tablets, capsules, and syrups for the patients

who feel difficult to swallow the traditional oral solid dosage forms such as paediatric and geriatric patients. For rapid drug release causes its direct systemic circulation in the oral cavity and also this delivery protects of the drug passage through first pass metabolism and also to improve the dissolution system. In oral thin Wafer drug delivery systems are the solid dosage forms, when they kept in the mouth they dissolve in a short period of time without drinking water or chewing. These are also referred as fast dissolving Oral Wafers, wafers, buccal films & Oral strips¹.

Anatomic and Physiological Considerations:

The Four regions are used in the drug administration in the buccal cavity. The four regions have the high different permeability plays an important role in the absorption of drugs across the oral mucosa. The four vital areas are the buccal cavity, the lingual area, the palate and the gingival region. The sites of drug administration in the four mentioned areas above are the Sublingual and the buccal route ². The medicament is the rapidly dissolving wafers are placed under the tongue in sublingual route. The anatomic site for the drug administration between the cheek and gingival area is known as the buccal mucosa. In oral mucosa three layers are present. The first layer is the stratified squamous epithelium underneath this layer the basement Membrane is present.

The basement membrane overlies the lamina propria and the sub mucosa. The different sites of the epithelium structure in the oral cavity show distinction. The gingival and the hard palate are the differences in the permeability amongst the different regions of the oral mucosa. When the cells go through the differentiation from the basal to the flattened keratinous cells, the formation of the MCGs are occur. MCGs are present in both keratinized and no keratinised epithelia, however their composition is different. On the other hand, no keratinised epithelium contains MCGs that are no lamellar and they include cholesterol, cholesterol esters and the glycolspingo lipids³. 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 major role in the cell to cell adhesion for oral lubrication, as well as muco adhesion drug delivery systems. A major feature in the environment of the oral cavity is the presence of 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 sublingual route is however more

suitable for delivery systems formulated either as rapidly disintegrating matrices. These systems create a highly significant drug concentration in the sublingual region prior to systemic absorption across the mucosa ⁴.

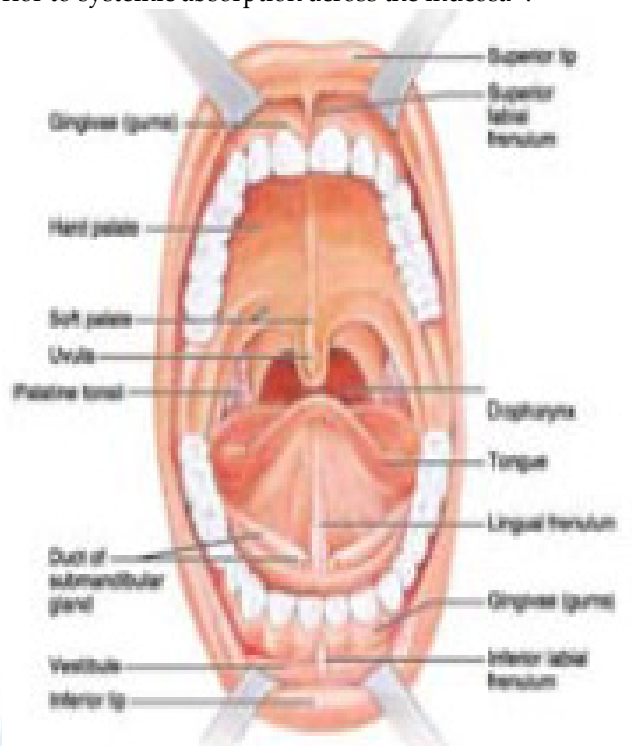


Figure No. 1 the vital areas are the buccal cavity

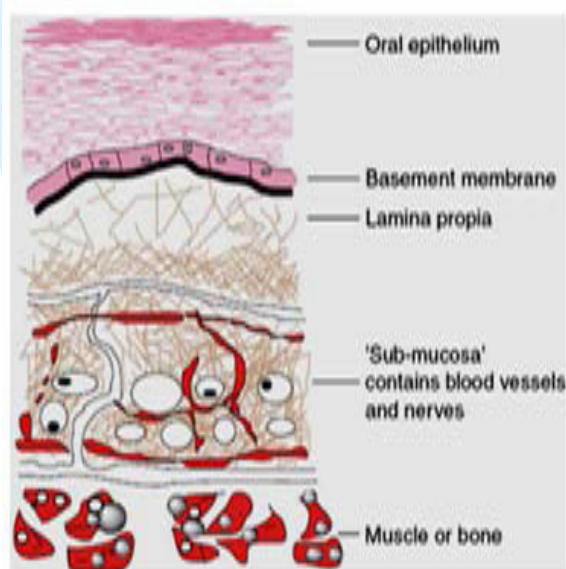


Figure No.2 Surface of the epithelial layer of cells

Why Buccal Delivery: The mucous membrane having a permeability to provide a convenient route for the systemic delivery of new therapeutic drugs. The mucosal regions like oral mucosa, nasal, rectal, vaginal, ocular may facilitate bioavailability by providing the hepatic metabolism. Trans mucosal drug delivery is an attractive delivery

route for new and existing drug compounds, some of which are only available through parental delivery. Among the various sites available for transmucosal drug delivery, the best suited sites for local as well as systemic delivery of drugs, due to their physiological features. The lack of an immobile surface derives from the fact that the sublingual space is constantly washed with saliva from the sublingual salivary ducts. 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 ⁵.

From the single epithelium cell layer lining to the gastrointestinal tract, there is gradual decrease in resistance to the permeability. Several approaches can be taken to increase the permeation of a drug through the buccal mucosal membrane to improve the bio adhesion properties to increase residence time and drug release pattern in the oral cavity. Modification of the drugs partition coefficient can be used in some approaches.

Physicochemical properties of the oral mucosa: The surface of buccal cavity comprises of stratified squamous epithelium which is essentially too separated from the underlying tissue of lamina propria and sub mucosa. 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. Hence the Buccal delivery serves as an excellent platform for absorption of molecules having poor dermal penetration. 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.

Mechanism of Fast Dissolution in Oral cavity: Fast dissolution represents that these dosage forms dissolve rapidly and disintegrate into smaller particles in saliva. 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 ⁶.

The wafer quickly dissolves in the oral cavity, and the active ingredient can be absorbed into the blood via the oral mucosa. Once absorbed in the oral mucosa, thus bypasses the liver in first pass effect, which improves the bioavailability. It will base upon the selected wafer the active ingredient release may also be delayed. 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.

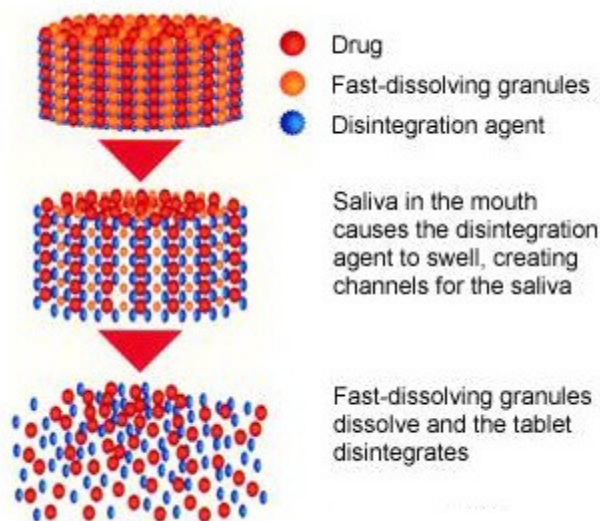


Figure: 3 Mechanism of Fast Dissolution in Oral cavity

Wafer - A novel oral dosage form: The wafers created by new possibilities for action profiles and patient compliance. The wafers are the paper-thin polymer films used as carriers for pharmaceutical agents.

Effective absorption of active ingredient: The wafer quickly dissolves in the oral cavity and the active pharmaceutical ingredient can be absorbed into the blood via the oral mucosa. The active ingredient, absorbed in the oral mucosa, thus by passes the liver first pass effect, in which improves bioavailability. Depending on the selected wafer type, the active ingredient's release may also be delayed ⁷.

Classification of oral Wafer: There are three subclasses

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

Formulation consideration:

Composition of the oral thin Wafer: Mouth dissolving Wafer is a thin Wafer with an area of 5-20 cm² 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 have been reported as important factors affecting mechanical properties of the Wafers, such as changing the glass transition temperature to lower temperature ⁸.

1. Drugs: Different classes of drugs can be formulated as mouth dissolving Wafers including Antiulcer (e.g. Omeprazole), Antiasthmatics (Salbutamol sulphate),

Antitussives, Expectorants, Antihistaminics, NSAID'S (e.g. Paracetamol, Meloxicam).

Table: 5 Formulation details

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	Flavours, Colours, Fillers	Q.S

2) Water soluble polymers: 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 Wafers⁹.

3) Plasticizers: Formulation considerations 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, dibutyl phthalate, and polyethylene glycols etc¹⁰.

4) Penetration enhancers: 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, surfactants and, among these, bile salts, azone and alcohols ¹¹.

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 etc¹¹.

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. Flavouring agents can be selected from synthetic flavour oils, oleo resins, extract derived from various

parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg is examples of flavour oils while vanilla, cocoa, coffee and chocolate ¹¹.

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

8) **Saliva stimulating agents:** 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
Flavouring agents: may be selected from syn. Flavour oils, oleoresins, from plant parts. 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 ¹¹.

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 paediatric 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 ¹¹.

10) **Taste Masking Agents:** 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.

Manufacturing methods: One or combination of the following process can be used to manufacture the mouth dissolving Wafers ¹².

1) **Solvent casting method:** In solvent casting method having water soluble polymers are dissolved in a water hsving the drug along with 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 a 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.

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, which was prepared in sodium or ammonium hydroxide. 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 ¹³.

3) **Solid dispersion extrusion:** 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.

4) **Hot melt extrusion:** In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture.

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

1) Organoleptic evaluation 2) Mechanical properties a) Thickness b) Dry test/tack test c) Tensile Strength 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 Wafers¹⁴.

2) Mechanical properties: Mechanical properties of Wafers are evaluated using 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 calculated¹⁵.

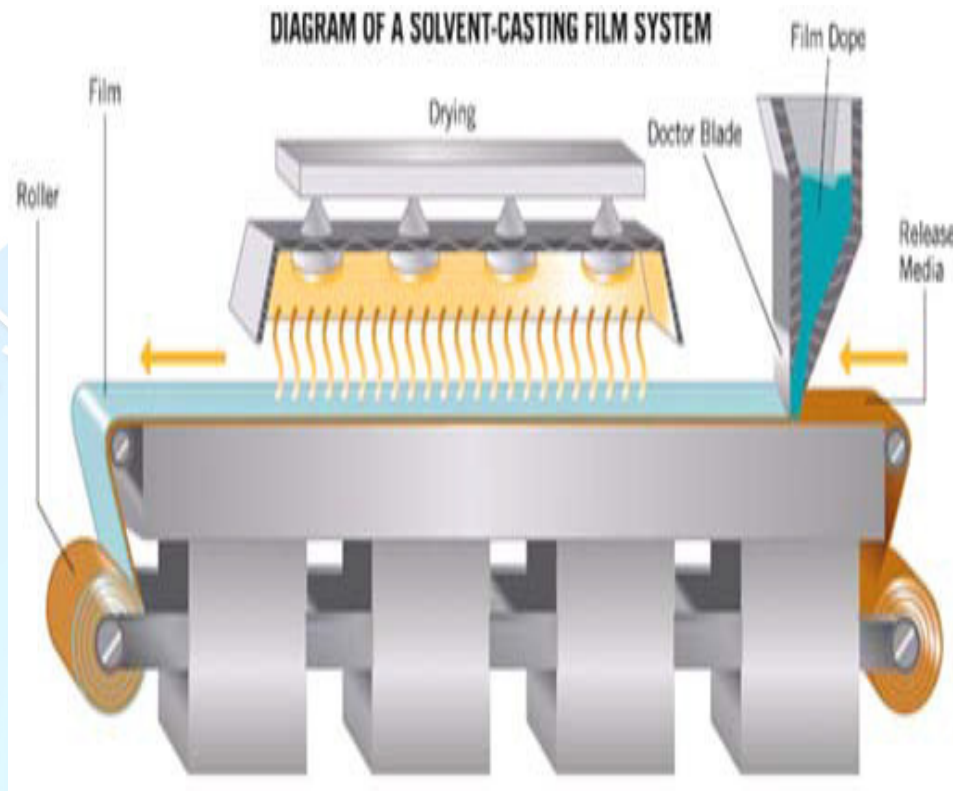


Figure 4: Solvent casting techniques

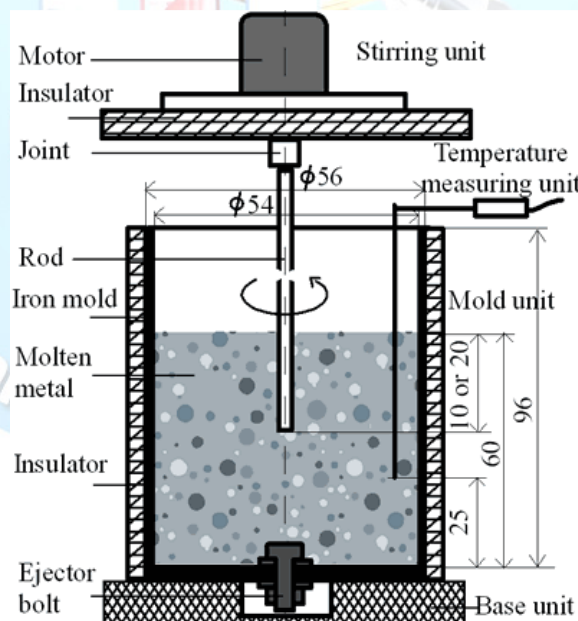


Figure 5: Solid dispersion extrusion techniques

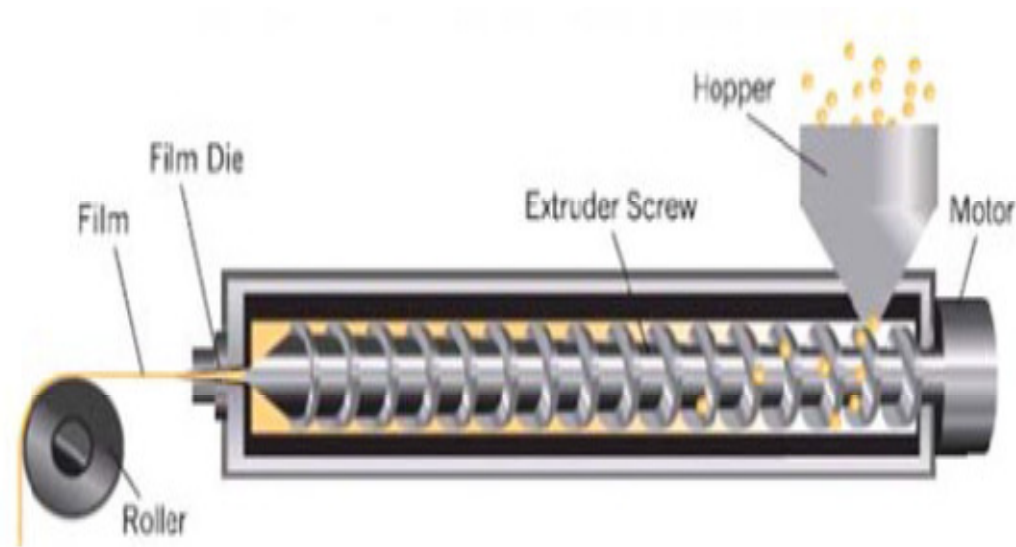


Figure 6: Film extrusion Technique

b) 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.

c) 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 wafer¹⁶.

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 observed¹⁷.

The degree of swelling is calculated using formula:

$$\alpha = (w_t - w_0) / w_0$$

w_t is weight of Wafer at time t ,

w_0 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.

5) Taste evaluation: Taste acceptability was measured by a taste panel consisting of human volunteers 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 administration¹⁸.

6) 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 strip¹⁹.

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 stage¹⁹.

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 API¹⁹.

Packaging of oral Wafer: 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 aluminium pouch is the most commonly used packaging format.

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 nutraceutical 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 aluminium 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 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:

a) Taste masking: Taste masking of the drugs becomes critical to patient compliance because the Oral film sys-

tems dissolve or Disintegrate in patient’s mouth, thus releasing the Active ingredients which come in contact with the Taste buds²⁰. 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 saliva²¹. 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. The 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.

Conclusion: Medicated Wafers as novel drug delivery systems having a better patient compliance and may offers to improve biopharmaceutical properties, improved efficacy and better safety compared with the conventional dosage forms. The 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. 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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