



ADVANCES IN FAST-DISSOLVING ORAL WAFERS FOR RAPID RELIEF IN
MIGRAINE THERAPY

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ABSTRACT

Migraine is a debilitating neurological disorder characterized by recurrent episodes of moderate to severe headache, often accompanied by nausea, photophobia, and phonophobia. Conventional oral dosage forms such as tablets and capsules frequently present limitations in the management of acute migraine attacks, particularly due to delayed onset of action and swallowing difficulties during episodes of nausea and vomiting. In recent years, fast-dissolving oral wafers (FDOWs) have emerged as an innovative and patient-friendly drug delivery platform designed to provide rapid therapeutic onset and enhanced bioavailability through oromucosal absorption. Fast-dissolving oral wafers are ultra-thin polymeric films that disintegrate within seconds upon contact with saliva, releasing the drug for local or systemic absorption without the need for water. These systems combine hydrophilic polymers, plasticizers, saliva stimulants, and taste-masking agents to ensure mechanical strength, rapid dissolution, and acceptable organoleptic properties. The technology is particularly advantageous for pediatric, geriatric, and dysphagic patients, and for drugs undergoing extensive first-pass metabolism. This review highlights the pathophysiology of migraine, the need for rapid drug delivery, and the formulation aspects of fast-dissolving wafers including polymer selection, excipient functionality, manufacturing methodologies such as solvent casting, hot-melt extrusion, and freeze-drying, as well as evaluation parameters like disintegration time, folding endurance, and stability studies. Additionally, it explores the therapeutic potential of oral wafer systems in migraine therapy, emphasizing their rapid onset of action, improved patient compliance, and market growth prospects. In conclusion, fast-dissolving oral wafers represent a promising and evolving drug delivery approach for the acute treatment of migraine, offering rapid relief, convenience, and enhanced patient adherence compared to conventional oral dosage forms.

Keywords: Migraine, Fast-dissolving oral wafers, Orodispersible films, Rapid drug delivery, Bioavailability, Patient compliance, Acute migraine therapy.

INTRODUCTION

Migraine is a genetically influenced complex neurological disorder characterized by episodes of moderate-to-severe headaches, typically unilateral and frequently

accompanied by nausea and heightened sensitivity to light and sound. The word "migraine" is derived from the Greek word *hemikrania*, which was later converted into Latin as *hemigranea*. The French

translation of the term is migraine (Rose, 1995).

Migraine is a common cause of disability and loss of work. Migraine attacks are complex and recurrent neurological events that can unfold for hours to days and significantly impact daily activities and the quality of life of individuals. The most prevalent type of migraine, accounting for 75% of cases, is migraine without aura.

In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. This technology 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, so fast dissolving oral wafer are gaining the interest of large number of pharmaceutical industries. The main advantage of this technology is the administration to pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated. This fast dissolving drug delivery system (FDDS) is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. Orally fast dissolving wafers is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. Fast dissolving oral wafers are very similar to postage stamp in their shape, size and thickness (Garsuch and Breitzkreutz, 2009; Kelodiya *et al.*, 2021). To eliminate the drawbacks of fast dissolving tablet a fast-dissolving wafers can be placed.

Fast dissolving wafers are very similar to ultra-thin strip of postage stamp in their shape, size and thickness. Fast dissolving wafers are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavors, preservatives and colors. Fast dissolving wafers is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the wafers rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Technology Catalysts forecasts the market for drug products in oral thin wafers formulations to be valued at \$500million in 2007 and could reach \$2 billion. More importantly, prescriptions of fast dissolving wafers have been now approved in US, EU and Japan which are the three major regions. These approved wafers, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin wafers market will grow significant (Sushmitha *et al.*, 2014; Dangi *et al.*, 2021).

Fast drug delivery system

The concept of (fast drug delivery system) FDDS emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules

is common among all age groups, especially in elderly and dysphagic patients.

FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast disintegrating tablets, as they may take up to a minute to completely disintegrate. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Most fast dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. These are also called melt-in-mouth tablets, repimelts, porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets.

Anatomic and physiological considerations while preparing wafers

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

called membrane coating granules present at the uppermost 200 micron layer (Yakubov *et al.*, 2014; Bartlett *et al.*, 2012).

Anatomical features of oral cavity

The oral cavity is surrounded by the lips and is composed of two separate regions, the vestibule, the area between the cheeks, teeth, and lips, and the oral cavity proper. The oral cavity proper is mostly filled with the tongue and bounded anteriorly and on the sides by the alveolar processes containing the teeth and posteriorly by the isthmus of the fauces. Anteriorly, the roof forms by the hard palate and posteriorly by the soft palate. The uvula hangs downwards from the soft palate. The mylohyoid muscles constitute the floor of the oral cavity proper. A mucous membrane known as the oral mucosa is composed of stratified squamous epithelium and forms the inner lining of the mouth. Several submandibular and sublingual salivary glands secrete viscous and mucoid fluid to lubricate and keep the oral cavity moist (Johnston, 2015; Yousem and Chalian, 1998).

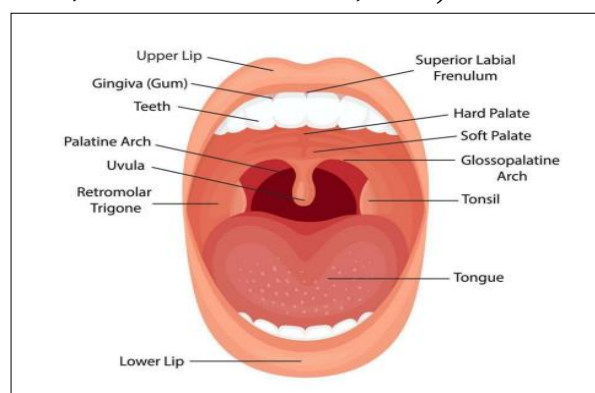


Figure 1: Anatomy of oral cavity
Oral wafers

Oral wafers/oro-dispersible wafer strips. These are paper thin polymer films of typically 2-8 cm² area and 20-500 µm thickness, containing typically less than 50

mg of API. They are administered directly on the tongue (Galey *et al.*, 1976).

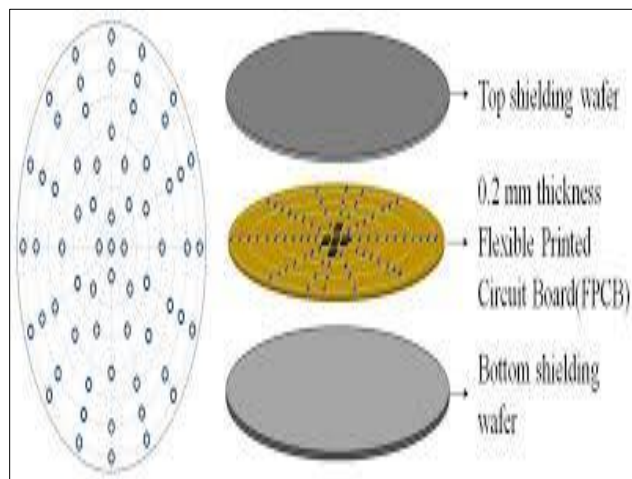


Figure 2: Structure of Oral Wafer

Benefits

- Increasing the bioavailability of the oral administered drugs that otherwise undergo hepatic firstpass metabolism
- It improved the patient compliance due to the elimination of pain with injections.
- Drug absorption can be terminated in case of the emergency.
- It offers passive system, which does not require any activation process.

Salient Features

- Thin elegant film
- Available in various size and shapes
- Excellent mucoadhesion
- Fast disintegration
- Quick dissolution
- Rapid release
- Adaptable and amenable to existing processing and packaging machinery
- Cost effective (Arunkanth, 2013).

Mechanism of action of wafers

Wafers are placed on a patient's tongue or any oral mucosal tissue. They are instantly wet by saliva due to the presence of hydrophilic polymer and other excipients; the film rapidly

hydrates and dissolves to release the medication for mucosal absorption (Agarwal *et al.*, 2011).

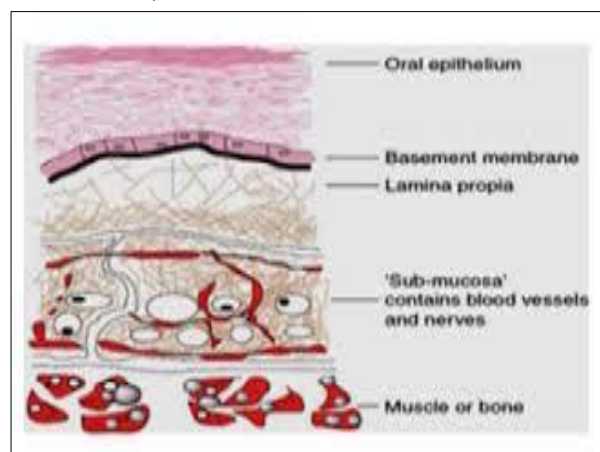


Figure 3: Mechanism of action of wafers
Advantages of wafer technology for migraines

- **Rapid action:** The wafer formulation allows for fast disintegration and absorption, leading to a quicker onset of action compared to conventional tablets.
- **Convenience:** As they can be taken without water, wafers are highly convenient for patients who need to take medication anywhere, anytime.
- **Alternative for nausea:** This delivery method is ideal for migraine sufferers who experience nausea and vomiting, as swallowing a pill can be difficult or aggravate symptoms.
- **Enhanced compliance:** The ease of use and rapid relief can increase patient adherence to their treatment regimen.

Ingredients used for forming oral wafers

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 watersoluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the Wafers (Finch, 2013).

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) (Costa *et al.*, 2019).

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 (Pathan and Setty, 2009).

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 (Lawrence, 2015).

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 (Bhattarai and Gupta, 2015).

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 (Douroumis 2007).

Colour

A full range of colours is available, including FD and C colours, EU Colours, Natural Colours and custom Pantone-matched colours (Tao *et al.*, 2018).

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 (Emmelin and Engstrom, 1960; Fox *et al.*, 2004).

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 (Ali and Quadir, 2007).

Manufacturing Methodologies of Wafer

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. It includes advantages like fewer processing steps and more uniform dispersion of the fine particles because of intense mixing and agitation (Kolter and Maschke, 2009).

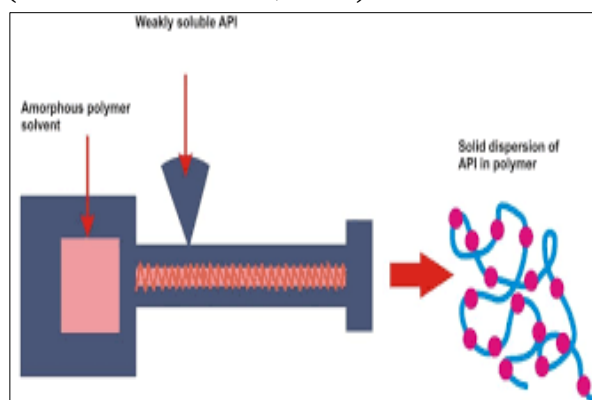


Figure 4: Solid dispersion extrusion

Semisolid Casting

In this method a solution of water soluble film forming polymer should be prepared and the resulting solution should be added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was made in ammonium or sodium hydroxide. Then suitable amount of plasticizer should be added to form a gel mass. Finally, the gel mass should be casted in to the films or ribbons using heat controlled

drums. The thickness of the film formed will be in the rapid of 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer must be 1:4 in this method.

Rolling method

A solution 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 portion of aqueous solvent using the high-shear processor. Water soluble hydrocolloids are dissolved in water to form homogeneous viscous solution (Frey, 2006; Mandeep *et al*, 2013).

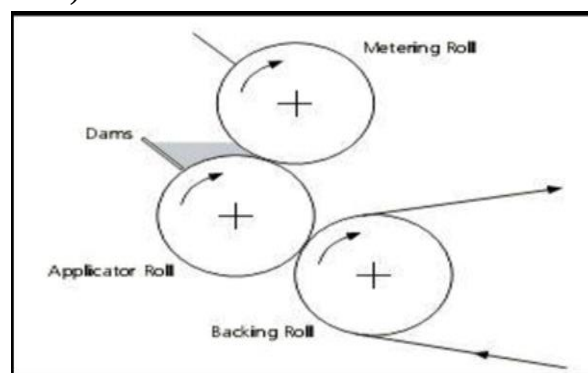


Figure 5: Rolling method

Hot-melt extrusion

The active moiety and other ingredients are mixed in a dry state, subjected to the heating process and then extruded out in a molten state. The solvent is completely eliminated. The strips are further cooled and cut to the desired size. The high temperature used in this process may degrade thermolabile APIs (Repka *et al.*, 2007).

Solvent Casting Method

This technique is employed to manufacture fast dissolving wafers of size 3x2 cm² and 2x2 cm². Water soluble polymers are dissolved in the aqueous vehicle. The drug along with other excipients is dissolved in

suitable solvent, and both are mixed and stirred. It is finally casted on Petri dish or plate made up of glass, plastic or Teflon and dried. Specific types of equipment are used at large scale production as well as rollers are used for pouring the solution on an inert base. Entrapped air is removed by vacuum. The final step is drying the wafer, removes the solvent and helps to obtain the finished product. Wafers are dried after which cutting, stripping and packaging is done (Maniruzzamam *et al.*, 2012).

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 pipette out into the cylinder cavities pre-oiled with mineral oil. The formulation was subjected to a freeze-phase in a freeze-dryer at -60°C for 2h and the drying phase was executed at a pressure of 25 m-tor for 24 h. Wafers were stored in glass jars with 2g of desiccant sachets (Bhalla, 1999; Boateng *et al.*, 2009).

Evaluation of Wafers

Color

It should be attractive and good patient compliance.

Weight

The wafers were subjected to mass variation study by individually weighing randomly selected patches. The average of 5 observations of each batch was calculated. Same done for each batch.

Appearance, Size and Shape

The formulated wafers were checked for their appearance, shape and thickness. The thickness of the wafer was determined at two different places using a digimatic micrometer

and mean value was calculated (Sushmitha *et al.*, 2014).

Folding endurance

To estimate the mechanical properties of a wafer. It is measured by repeatedly folding a wafer at the same point until it breaks. Folding endurance value is number of times the wafer is folded without breaking. Higher folding endurance value depicts the more mechanical strength of a wafer. As mechanical strength is governed by plasticizer concentration so it is clearly evident that plasticizer concentration also indirectly affects folding endurance value.

Drug content uniformity/Assay

Wafer dissolved in simulated saliva (100 ml pH 6.8) by homogenization for 30 min continue shaking. Content uniformity estimating the API content in individual wafer. Limit: 85-115% (Lim *et al.*, 2013).

Disintegration time

Disintegrating time is defined as the time (seconds) at which a wafer breaks when brought in contact with water or saliva. Typical disintegration time for wafer is 5-30 seconds (Reddy *et al.*, 2017).

Dissolution time

The cumulative drug release and the cumulative percentage of the drug is calculated. Invitro drug dissolution is performed by using USP paddle type apparatus. The studies were carried out at 37°C of stirring speed 75 rpm in 900 ml phosphate buffer (pH 6.8). 5 ml of the samples withdrawn at the predetermined time intervals of 2, 4, 6, 8, 10 min and they are replaced within the same volume of buffer. The samples were collected and the concentrations were determined at the

appropriate wavelength by using UV-visible spectrophotometer (Thakur *et al.*, 2012).

% Moisture Uptake

% Moisture Uptake Formulation was exposed to an atmosphere of 84% RH at 28°C for three days using a saturated solution of NaCl. After three days the wafer was removed, weighed and percentage moisture absorbed was calculated. Average percentage moisture absorption of each wafer was calculated.

Stability studies

The purpose of the stability testing is to provide evidence on how the quality of the drug substance or the drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and the light, enabling the recommended storage condition, retest periods and the shelf life. The stability studies were carried out as per the International Conference of harmonization (ICH) Guidelines. The Stability studies were carried out at 40° C / 75% RH for 3 months. The optimized wafer formulations were packed in amber colored bottles, which were tightly plugged with cotton and capped. They are stored at 40°C / 75% RH for 3 months and these are evaluated for their physical appearance, drug content and in-vitro dispersion time at specified intervals of time (Mehravaran *et al.*, 2022).

Diffusion study

Before the diffusion study, drug assay and uniformity of OME within the wafer was determined. This is measured by weighing wafer accurately 5mg and hydrated in 8 mL of drug dissolution media. This hydrated wafer was stirred at the 37± 0.5°C until it completely gets dissolved. The concentration

of OME was analyzed by using UV Spectrophotometry.

CONCLUSION

Migraine remains a prevalent and disabling neurological disorder that demands prompt and effective therapeutic intervention. Conventional oral formulations often fail to provide rapid relief due to delayed gastrointestinal absorption and challenges in administration during migraine-associated nausea or vomiting. Fast-dissolving oral wafers (FDOWs) have emerged as a promising alternative, offering rapid onset of action, improved bioavailability, and enhanced patient convenience.

These wafer systems, composed of biocompatible polymers and suitable excipients, disintegrate within seconds upon contact with saliva, releasing the active pharmaceutical ingredient either for oromucosal absorption or systemic delivery. The technology is particularly advantageous for pediatric, geriatric, and dysphagic populations, and for drugs that undergo extensive first-pass metabolism. Various manufacturing techniques such as solvent casting, hot-melt extrusion, rolling, and freeze-drying have made it possible to design wafers with optimal mechanical strength, taste, and dissolution properties.

With continued advancements in polymer science, nanotechnology, and formulation design, fast-dissolving oral wafers hold immense potential for revolutionizing acute migraine therapy. They not only ensure rapid symptom relief but also significantly enhance patient compliance and therapeutic outcomes. Future research should focus on the development of newer polymers, incorporation of novel anti-migraine agents,

and large-scale clinical evaluations to fully establish their role in modern migraine management.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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