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Review Article

WAFERS: AN INNOVATIVE ADVANCEMENT OF ORO-DISPERSIBLE FILMS

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ABSTRACT

The formulation of oral disintegrating films has led to the development of wafers which has modified itself in the recent past years. Wafers are more advantageous over other conventional dosage forms as well as from other oral disintegrating solid dosage forms. The major difficulty in formulating wafers is the choice of drugs to be incorporated. Wafers with a low dose of active pharmaceutical ingredient (API) and with a good mouth feel are prepared for making it more patients compliant. The manufacturing procedures are quite similar to oral disintegrating film, but the composition of polymers may vary. The wafers require expensive packaging and care should be taken while handling, storage & transport. In spite of these hardships, wafers have become popular between geriatric and paediatric population because of its ease of administration and bioavailability.

Keywords: Transmucosal route, Oral films, Wafers, Fast dissolving dosage forms, Oral administration.

INTRODUCTION

In the recent few decades, prioritise has been focused for more patient-compliant dosage forms. Oral transmucosal route for drug delivery is preferred over other routes because of its versatility. The conventional pharmaceutical dosage forms are incapable of controlling the rate of drug delivery; over which novel drug delivery system maintain the drug concentration in the therapeutic range for a longer period of time. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active substances either by using novel drug delivery system or by modification of its molecular structure and physiological parameters and incorporate it in a convenient route of administration [1].

Fast-dissolving drug delivery system were first developed in the late 1970s which is an alternative to after dosage forms, for podiatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms [2].

Oral fast-dissolving dosage forms

It is a solid dosage form that disperses or disintegrates quickly in the oral cavity, resulting in solution/suspension without the need for the administration of water [3].

Advantages of oral fast dissolving dosage forms [4-5].

- It controls the release rate of the drug, thus decreases toxicity and adverse drug reaction.
- It optimizes the utilization of a smaller drug dose to produce the same therapeutic effect as a larger dose in other dosage forms.
- It releases the drug at their site of action.
- It protects the drug from first pass metabolism and improves dissolution.
- It dissolves in a short duration of time when placed in the mouth without drinking water or chewing.

Classification of fast dissolving technology [6].

- Lyophilized system
- Compressed tablet based system
- Oral thin films/strips

Oral thin films/strips

These are the most convenient and advanced form of oral solid dosage form due to the efficiency of dissolving within minutes in oral cavity when it comes in contact of saliva. It neither requires chewing nor water for administration. It gives quick absorption and instant bioavailability of drugs due to the high blood flow and permeability of oral mucosa [7].

Oral wafers/oro-dispersible wafer strips

These are paper thin polymer films of typically 2-8 cm^2 area and 20-500 µm thickness, containing typically less than 50 mg of API. They are administered directly on the tongue [8].

Classification of oral wafers [9, 10].

A. Flash release wafers

- Area–2-8 cm^2.
- Thickness–20-70 µm.
- Dissolution–60 s maximum.
- Single layered structure.
- Soluble excipients are used.
- Highly hydrophilic polymers are required.
- Drugs are dispersed in solid solution phase.
- It is applied to the upper palate of the tongue.

B. Mucoadhesive melt-away wafers

- Area–2-7 cm^2.
- Thickness–50-500 µm.
- Dissolution–1-3 min.
- Single or multi-layered structure.
- Soluble excipients are used.
- Hydrophilic polymers are required.
- Drugs are dispersed in solid solution or suspension.
- It is applied to the gingival or buccal region.

C. Mucoadhesive sustained release wafers

- Area–2-4 cm^2.
- Thickness–50-250 µm.
- Dissolution–8-10 h.
- Multi-layered structure.
- Excipients with low solubility are used.

- Non-soluble polymers are used.
- Drugs are dispersed in solid solution or suspension.
- It is applied to the gingival or oral cavity.

Positive aspects of wafers as oral fast dissolving films [11]

- Attractive dosage form with new active ingredients.
- Improvement of established products.
- Access to a new indication by means of a new absorption profile even for existing active ingredients.
- Optimization of bioavailability.
- Innovative technology for the product.
- The increase of product appeals through the innovative format.
- Exclusivity and cutting edge technology position in the market through a step forward.
- No first pass effect.
- Controlled release.
- Improved bioavailability, translates to lower doses.
- Reduction of side-effects.
- Reduced impact on the gastrointestinal tract.
- Discrete and easy application.
- Excellent compliance, especially for geriatric and paediatric patients.
- Good mouthfeel and stability.

Drawbacks of wafers

- High dose cannot be incorporated, but concentration level of active ingredients can be improved up to 50% per dose weight.
- Expensive packaging is required.
- Excessive bitter drugs are not feasible.
- Handling concerns during manufacturing.
- Drugs which are unstable at oral pH cannot be incorporated.
- Drugs which irritate mucosa cannot be administered.

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 [10].

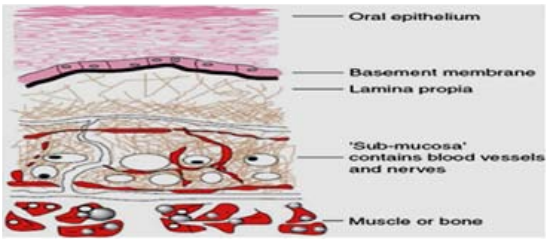

Fig. 1: mucosal region of mouth

Anatomical and physiochemical of oral mucosal cavity [11-16]

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the sub-mucosa as the innermost layer.

The buccal mucosal site offers a smooth, immobile surface with vascular perfusion, in contrast to the sublingual mucosal site, which lacks an immobile mucosal surface. 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.

Drug absorption from the buccal cavity can take place either by the transcellular route (intercellular route) or para-cellular pathway. The oral mucosa is in general intermediate between that of the epidermis and intestinal mucosa in terms of permeability. The wafer quickly dissolves in the oral cavity and the active moiety absorbs via oral mucosa into the blood stream.

Objective of formulating wafers

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

Some companies like Labtec Pharma, Pfizer, Novartis, Del, Zydis, etc are producing wafer as a dosage form [4].

Formulation of wafers [18-20]

A. Drug or active pharmaceutical ingredient

Generally, 5-30% of API can be incorporated in the buccal film. Water soluble APIs are present in the dissolved state in the buccal film/solid solution form. Micro ionized API will improve the texture of the film and also for better dissolution and uniformity in the buccal film [21].

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

- Drug should have pleasant taste.
- Incorporated drug should have low dose.
- Possess smaller and moderate molecular weight.
- Good stability and solubility in water as well as saliva.
- Partially unionizes at the pH of the oral cavity.
- Ability to permeate oral mucosal tissues.
- BCS class-I drugs are used.

Various methods for improving the palatability of the formulation [5]

Simplest method

It includes the blending of bitter drugs with pleasant taste drugs, called as obscuration technique.

Barrier method

To mask bitter taste by complexation, polymeric coating, micronisationetc

B. Wafer forming polymers

The polymers form the majority of formulation i.e. they are used 45% (w/w), alone or in combination to obtain the desired properties. The wafer should be tough enough so that there won't be any damage while handling or during transportation used in alone or in combination to improve hydrophilicity [23, 24]. Some examples of polymers are methyl cellulose, pullulan, gelatin, gum acacia, tragacanth, etc.

Ideal properties of the wafer forming polymers: [25, 26].

- Non-toxic, non-irritant 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 the property.

C. Plasticizers

Plasticizers used should be compatible with the polymer and also with the type of solvent employed. It is added up to 20% (w/w) of the formulation. It improves the flexibility of the strip and reduces the brittleness. It reduces the glass transition temperature of the polymer used in the range of 40-60 degree Celsius for the non-aqueous solvent system and below 75 °C for the aqueous system [28]. However, inappropriate use of plasticizers may lead to cracking, splitting and peeling of wafers. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug [29]. The commonly used plasticizers are glycerol, dibutyl phthalate, polyethylene glycols, etc.

D. Saliva stimulating agent

The saliva stimulating agents are the excipients that increase the saliva production rate, aids in the faster disintegration of the wafer when used in a concentration of 2-6% (w/w). The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at the equal time under the same condition. The stimulant action of sweeteners depends on the sweetness value. Sweeteners used as saliva stimulating agents are fructose, xylose, maltose, lactose and glucose. Certain flavouring agents are also used like peppermint, cinnamon, nutmeg, vanilla, cocoa, coffee, chocolate, apple, cherry, etc [30-33].

E. Surfactant

It acts as solubilizing, wetting and dispersing agents in the formulation so that the wafer gets dissolved within seconds and release active agent quickly. Some of the commonly used surfactants are sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, etc [34].

F. Sweetening agents

Sweeteners play an important role in improving compliance wafers in the paediatric population. Natural sweeteners and artificial sweeteners play an important role in improving the palatability of oral dissolving formulations. The uses of natural sweeteners are restricted in people with diabetics and thus artificial sweeteners are used. The classical source of sweetness is sucrose which is derived from cane or beet in the form of liquid or dry state; dextrose, fructose, glucose and maltose are also used. Saccharin, cyclamate and aspartame are the first generations of artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. All of the artificial sweeteners have toxic and carcinogenic effects, so natural sweeteners like rebiana is used [35].

G. Flavouring agents

Perception of flavours changes according to individual's ethnicity and liking. The acceptance of the oral disintegrating or dissolving formulation by an individual, by and large, depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which tastes for at least about 10 min. Flavours can be used alone or in combination. The amount of flavour needed to mask the taste depends on the flavour type and its strength. Flavouring agents can be selected from synthetic flavour oils, oleo resins and extract derived from various plants. Various flavour oils added are peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg, etc [36].

H. Colouring agents

Pigments or FD&C approved colouring agents are incorporated like titanium dioxide. EU colours, natural colour and custom pantone-matched colour are also used [37].

I. Cooling agent

Cooling agents are added to give mouth-feel effect and to enhance the flavour like WS3, WS23, Utracoll-II can be used [38].

J. Thickening agent

It improves the viscosity and consistency of dispersion or solution before casting of wafers. Agents like gum, carrageenan and cellulosic derivatives in the concentration of 5% (w/w) are used as thickening agents [9].

K. Penetration enhancers

These are required for a drug to reach the systemic circulation to exert its action. These must be non-irritant. The most common classes of buccal penetration enhancers include fatty acid, bile salt, azone, alcohols, chitosan and its derivatives [39-41].

L. Taste masking agents

Examples of taste masking agents are sorbitol, mannitol, xyliol, dextrose, etc [42]. The various approaches for taste masking of bitter drugs:

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

Manufacturing methodologies of wafer

Various approaches to manufacturing of rapid dissolving wafers are classified as follows: [43].

A. Casting and drying—(a) solvent casting (b) semi-solid casting

B. Extrusion—(a) hot-melt extrusion (b) solid dispersion extrusion

C. Freeze dried wafers

D. Rolling method

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 a suitable solvent, and both are mixed and stirred. It is finally casted on petridish 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 [44-45].

Advantages

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

Disadvantages

- The polymer used must be soluble in volatile solvent or water.
- The stable solution with a reasonable minimum solid content and viscosity should be formed.
- Multiple casting techniques may be selected on the basis of the fluid rheology, desired applied mass and required dosage uniformity.
- Formation of a homogeneous and release from the casting support must be possible.

Semi-solid casting method

This technique is employed to manufacture flash release wafers of size 0.015-0.05 inch. A solution of water soluble wafer forming polymer is prepared. Then the solution is further added to acid insoluble polymer solution i.e. either cellulose acetate phthalate or cellulose acetate butyrate in sodium or ammonium hydroxide solution in the ratio 1:4. Then plasticizers are added to obtain a gel mass which is casted to wafers using heat controlled drums [46].

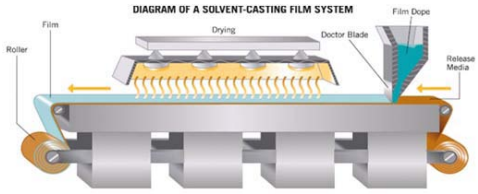

Fig. 2: Solvent casting system

Solid dispersion extrusion

The immiscible components are extruded with drug, and then solid dispersions are prepared. Solid dispersions are shaped in wafers by use of dies [47].

Advantages

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

Hot-melt extrusion

The active moiety and other ingredients are mixed in 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 sixe. The high temperature used in this process may degrade thermolabile APIs [48-50].

Advantages

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Good dispersion mechanism & bioavailability for poorly soluble drugs.
- More uniform dispersion of the fine particles because of less intense mixing and agitation.
- Less energy compared with high shear methods.
- Cost effective process with less processed time and unit operations.

Disadvantages

- Thermal degradation due to high temperature.
- Lower melting point binder risks a situation where melting/softening of the binder occurs during handling and storage of agglomerates.
- Higher melting point binders require high melting temperature and can contribute to volatility problems especially for heat labile materials.
- Flow properties of the polymers are essential to processing.

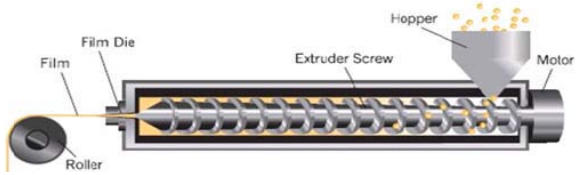

Fig. 3: Extrusion method

Freeze-dried wafers

A polymer of concentration 1% (w/w) and lactose as a bulking agent of concentration 6% (w/w) was added to deionized water and mixed for 45 min. 1.5 ml of the various polymer solutions was pipetted out into the cylinder cavities pre-oiled with mineral oil. The formulation was subjected to a freeze-phase in a freeze-dryer at-60ºC for 2h & the dying phase was executed at a pressure of 25 m-tor for 24 h. Wafers were stored in glass jars with 2g of desiccant sachets [51].

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 [52].

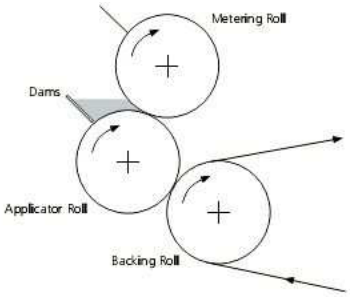

Fig. 4: Rolling method

Evaluation of wafers [53, 54]

Organoleptic evaluation

This is an essential step in case of most oral formulation due to more residence time in the oral cavity. The product should possess the desired features of sweetness and flavour which is acceptable to a large mass of the population. Experiments using electronic tongue measurement have also been reported to distinguish between sweetness levels in taste masking formulation. *In-vitro* methods of utilising taste sensors are being used for this purpose [55, 56].

Morphological studies

The scanning electron microscopy (SEM) study refers the differences between upper and lower side of the films. It also helps in the determination of the distribution of API. Near-Infrared chemical imaging (NIR-CI) study helps in determining the difference between drug distributions in drug loaded films and recrystallization [57].

Mechanical properties

Mechanical properties of wafers are evaluated using TA. XT2 texture analyser equipment equipped with a 5 kg load cell. Wafers are held between two clamps positioned between 3 cm. During measurements, the strips were pulled at rate of 2 mm/s. The force and elongation were measured when wafer breaks [58].

The following mechanical properties are measured:

a. Thickness: The thickness of the film can be measured by micrometre screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film [59].

b. Dryness/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 [60].

c. Tensile strength: It is the maximum stress applied to the point at which the wafers sample breaks [61].

$$\text{Tensile strength} = \frac{\text{loadatfailurex}\ \ 100}{\text{waferthicknessxwaferwidth}}$$

d. Percent elongation: When stress is applied, wafer sample stretches and this is referred to as strain [62].

$$\text{Percent elongation} = \frac{\text{Increseinlengthofwaferx} \quad 100}{\text{initiallengthofwafer}}$$

e. Tear resistance: the maximum stress or force that is generally found near the onset of tearing (2inch/mm) required to tear the film of 51 mm is recorded as tear resistance value in N or pound-force [63].

f. Folding endurance: It is determined by repeated folding of the wafer at the same place till it breaks [64].

g. Young's modulus: It is the measure of the stiffness of wafers. Hard and brittle wafers demonstrate a high tensile strength and Young's Modulus with small elongation.

$$\text{Young's modulus} = \frac{\text{slopex } 100}{\text{filmthicknessxcross} \quad -\text{headspace}}$$

h. Stickiness determination: It is evaluated by texture method usually for measurement of the tack of pressure sensitive adhesives.

i. Swelling properties: Wafer swelling study is conducted using stimulated saliva solution. The wafer sample is weighed and placed in a stainless steel wire mesh. The mesh containing wafer sample is submerged into 15 ml medium in a plastic container. Increase in the weight of the wafers determined at pre-determined time interval until a constant weight is observed [65].

Degree of swelling = $(w_t - w_o)/w_o$

W_t= weight of wafer at time t

W_o= weight of wafer at time t

j. Contact angle measurement: Time-dependent contact angle is measured by an optical contact angle meter. The contact angle measured by different methods like the tangential method, height-width ratio, circle fitting and sessile drop fitting [66].

k. Transparency: The transparency of the wafers can be determined using a UV Spectrophotometer by cutting the wafers into rectangles and placing them on the internal side of the spectrophotometer cell. The transparency is determined at 600 nm [53, 54].

D. Taste evaluation: Taste acceptance 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 time and bitterness level was determined [67].

E. Assay/content uniformity: This is determined by any standard assay method described for the particular API in any of standard pharmacopoeia. The limit of content uniformity is 85-115%

F. Disintegration time: The disintegration time limit of 30 sec or less for strips of 5-30g by disintegrating test apparatus can be applied. Although there are no specifications in pharmacopoeias [68].

G. *In-vitro* dissolution & residence time: Dissolution testing is performed by using standard basket/paddle apparatus. The medium will essentially be selected as per sink conditions and highest dose of API [69].

H. Stability testing: A piece of wafer preparation was stored in an aluminium package at 25 ºC with 50-60% humidity (normal condition) and another wafer at 40 ºC with 75% humidity (accelerated conditions) and both are observed [69].

I. In-vivo evaluation: An animal study can be conducted using Hamster Cheek Pouch Model, which is not performed now-a-days [70].

Established parameters of formulation variables

A. The concentration of HPC: Lower and upper limits were determined to be 1% (w/v) and 10% (w/v) respectively. The upper limit of 10% (w/v) was set because wafers of higher polymer concentration were difficult to remove from the mould.

B. The concentration of diluent: The concentration of diluent would affect both the solubility and textural properties of the matrices. Lower and upper limits are 1% (w/v) and 5% (w/v) respectively.

C. Type of mould: Polystyrene moulds trays proved to be the most successful with minimum deformation of the final product as those moulds could be easily split down the middle to release the wafer.

D. Type of lubricant: Mineral oil produced the greatest ease of removal of the product as compared to the other lubricants analysed, impairing minimal hydrophobicity and having no effect on the taste of the final product as opposed to other substances such as maize oil.

E. Freeze-drying parameters: The melting and discoloration of the matrices occur on storage. This is attributed to moisture present within the products, indicating that the freeze drying process needed to be conducted for a longer period.

F. Gelation of matrices: The characteristics for matrix formation require assessment of forms on the basis of selection of a suitable polymer. Gelation of polymer would delay the disintegration and ultimately release of active substances [71].

Packaging of oral wafers [72, 73]

Selected characteristics of packaging materials

- 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 impact to the products taste and odour.

a. Single pouch: It is used for quick dissolve soluble films with high barrier properties. The pouch is transparent. The foil lamination has zero transmission of both gas and moisture essentially.

b. Blister card with multiple units: The blister container consists of two components: the blister, which is formed a cavity that holds the product and the lid stock which seals the blister.

c. Polyvinyl chloride: The most commonly used blister material is PVC. This material, which provides a nominal or zero barriers to moisture, is used when the product does not require effective moisture production.

d. Barrier film: They provide moisture protection, materials such as polycholo-triflurothylene and polypropylene is used.

Future prospects, challenges and marketing status [74-75].

The drug delivery sector of fast dissolve products has grown rapidly from sales in 2001 of about $850 million to 2005 were estimated sales were around $1.4 billion (IMS Data). The modification of this technology to provide a prolonged release mucoadhesive system seems promising. It is envisaged that this system will be appreciated to many drugs requiring the extended release of bioactive material. Therefore, the lyophilised wafer matrices developed in this study are highly effective in the rapid delivery of drugs, using the oral route as a site of administration.

The market of these types of product is in excess of $15 billion worldwide. Currently, worldwide sales of drugs that incorporate a fast dissolve technology are more than 40%. The growth is fuelled by patient demand and industry estimated show that approximately 88% of patients prefer taking medications that is incorporated in a fast dissolving dosage form as 40% of them faces difficulties in swallowing traditional tablets.

CONCLUSION

In the recent trend of obtaining more palatable dosage form, wafers as an orodispersible film have made its own place & met the expectation of the rising demand. Wafers are formulated as advancement to the oral fast dissolving films with its special properties of high absorption and high bioavailability. It is popular among people of all ages but particularly among the geriatric and paediatric population because of is compatibility and good mouth feel. The marketed products of wafers are still less but there are many more to come in the recent years.

CONFLICTS OF INTERESTS

Declare none

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