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Review Article

Wafer Technology Review: A Novel Drug Delivery System

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Received: October 25, 2021; **Published:** January 29, 2022

Abstract

A large group of population have difficulties in swallowing tablets and capsules and other traditional dosage forms and fear with injections. Therefore, the buccal and oral dispersible dosage forms were formulated. Wafer dosage form is an advancement in this with it's characteristics properties i.e. high absorption, high stability, reduced side effects due to low dose and the high bioavailability. Wafers dosage form is suitable to the patients like Paediatric, geriatrics and patients who are unable to swallow the traditional conventional dosage form. These system consist of thin film which is placed on the tongue or in buccal cavity which rapidly dissolve and disintegrates to release active ingredients, which get absorbed by mucosal tissues to give systemic or local action. Wafer gain the popularity as alternative to the fast dissolving tablets because it doesn't have fear of choking. These are formulated by using the various methods like extrusion, casting etc. The wafer is evaluated by using various evolutionary parameters like surface pH, swelling property, disintegration time, dissolution time, thickness, etc.

Keywords: *Wafer Technology; Novel Drug Delivery System; Buccal Drug Delivery*

Introduction

Administration of drugs from oral route is the prominent way for the drug delivery due to various advantage over other routes of administration, however oral administration still need drastic improvements to be made due their side effects and disadvantages. Numbers of geriatric and paediatric patients are due to fear of choking afraid to consume tablet and capsule preparation. The loopholes in tablets is their surface, size, unpleasant taste and the choking during swallowing tablets was more perceptible in paediatric and geriatric patients, as well as the patients who are travelling which may be devoid of water [1].

The priority has been focused for those dosage form which are more patient compliant. Trans mucosal route for drug delivery system is favour over the other routes of drug delivery system because of its versatility and patient compliance. The traditional drug delivery systems are non to control rate of the drug delivery, over which the New Drug delivery system keep the concentration of drug in the therapeutic window for a long time. Fast-dissolving drug delivery was first developed in the late 1970s which is an alternative to conventional dosage forms [2]. Difficulty in swallowing of capsules and tablets can be a big task for number of peoples and can lead to enormous adverse effect and patient noncompliance with particular therapy regimens. It is concluded that more than 16 million people in the United States have difficulty in swallowing, which is also called as dysphagia [3]. For these individuals, swallowing a capsule and tablets can be

challenging. A survey of adults on problem to swallow capsules and tablets suggest that those who experience difficulty swallowing tablet and capsule, less than a quarter discuss the problems with a health care professional and 4 percent have discontinued therapy due to the during swallowing.

Wafer - A novel oral dosage form

Novel thin oral films, generally-mention as wafers, thus formulating new probability for patient compliance and action profiles. Wafers are paper-thin polymer films used as transporters for pharmaceutical moieties. The novel dosage form is consume orally devoid of water or swallowing [4].

The rationale for use and development and of new drug delivery systems may require one or more of the following arguments [4]:

- Reduces the occurrence of adverse drug reactions and toxicity by maintaining the level of metabolites/drug in the systemic circulation at the site of action.
- Boost the drug distribution by using a micro drug dose in a controlled - release form to give the same pharmacological effect as in larger dose in a general dosage form.
- Control the site of release and rate of a drug that functions locally hence the drug is released where the pharmacological effect is required rather than at other sites where it may originate unwanted side effects.

Benefits [5]:

- It gives the direct entry of drug particles into the blood circulation.
- Enhancement of the bioavailability of the oral drugs that destroyed by hepatic first-pass metabolism.
- It upgrade the patient compliance with painless comfort.
- Drug absorption can be stopped if emergency exist.
- It provides nature of passive system, which restricts activation process.
- Rapid cellular recovery occur with damage or local stress.
- Withstand environmental changes like change in temperature or pH, etc.

Silent features [6]:

- Thin film with good elegancy.
- Available in various shapes and size.
- Un-obstructive.
- Amenable and Adaptable to existing packaging machinery and processing.

- Cost effective.
- Excellent mucus-adhesion.
- Fast disintegration.
- Quick dissolution.
- Rapid release.
- Do not leave any residue in oral cavity or mouth.

Advantage [7,8]:

- Increases life cycle of product.
- Adequate stability.
- Precision in the administered dose.
- Enhancing mouth feel effect.
- Offers devoid water therapy.
- No friability loss.
- Convenient for geriatric, paediatric and dysphasic.
- patients having difficulty in swallowing.
- Low disintegration time and high dissolution in oral cavity area.
- Fast onset of action with enhanced Pharmacological effect because it bypass hepatic first pass metabolism.
- Low dose improves the Effectiveness and safety profile of the drug and minimise side effects.
- Easy to handle in transportation and storage because portable and Flexible in nature.
- Ease of administration if patient is mentally ill, disabled, non-cooperative patients and the patients who are on devoid of liquid intake or are suffering from nausea.
- Beneficial in cases of acute pain, motion sickness, rapid allergic attack, coughing, and asthmatic attack where an quick action is desired.
- For longer time better stability, since the drug remains in solid form till it is taken.
- Dose accuracy as compared to liquid formulations.

Advantages over orodispersible tablets [8,9]

Sr. No.	Mouth dissolving Wafers	Orodispersible Tablets
01	No fear of choking	Fear of choking
02	High patient compliance	Less patient compliance
03	Small amount of drug can be incorporated	Large amount of drug can incorporated
04	Better durable then Orodispersible tablets	Less durable than mouth dissolving tablet
05	No friability loss	Sometimes occurs friability
06	Less Time consuming	More time consuming
07	Minimum damage while handling or during transportation	Risk of damage while handling or during transportation (orally fast dissolving wafers)

Table 1: *Differences in mouth dissolving wafers and orodispersible tablets.*

Limitations [10]:

- Formulations with higher amount of drug can't formulated.
- More bitter drugs are not achievable.
- Dose uniformity is major problem.
- Long term preservation is difficult.
- Special type of packaging required to optimize their stability and safety.
- Drugs Irritating to the oral mucosa cannot given by this route.

Objective of formulation of wafers:

- To improve patient comfort/compliance.
- Provide a quick action.
- Minimisation of hepatic first pass metabolism.
- To reduce side effects related to active pharmaceutical ingredients by reducing its dose.
- To improve the oral bioavailability of molecules.

Classification of oral wafer [11]:

Oral Wafers are categorised into three subclasses which are classified from each other as per below table (Table 2):

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

Parameters	Flash release wafers	Mucoadhesive sustained release	Mucoadhesive melt away wafers
Area (cm sq.)	2 - 8	2 - 4	2 - 7
Dissolution time	60 sec.	8 - 10 hrs.	Few min. Forming gel
Thickness (μm)	20-30	50 - 250	50 - 500
Structure	Film: Single layer	Multi-layer	Single/multi-layer
Site of action	Systemic or local	Systemic or local	Systemic or local
Drug phase	Solid solution	Suspension and/or solution	Solid solution or suspended drug particles
Polymers	Soluble, highly hydrophilic	Low/non soluble	Soluble, hydrophilic
Application	Tongue	Gingival (other region in oral cavity)	Gingival or buccal cavity

***Table 2**: Wafers and their characteristics [2].*

Formulation consideration [11]:

- Active pharmaceutical ingredients (1 - 30%)
- Polymers (40 - 50%)
- Plasticizers (0 - 20%)
- Sweaters (3 - 6%)
- Sialagogue (2 - 6%)
- Cooling agent
- Flavouring agent (q.s.)
- Colouring agent (q.s.)
- Aqueous surfactants (q.s.).

Active pharmaceutical ingredients [12]

Only small amount of active ingredient can be loaded in the formulated to maintain it's stability and safety. A typical formula for wafers preparation contains 1 - 30% w/w. There is no restriction to load any therapeutic agent to this drug delivery system but the drug or active content which are chemically more potent but can't be use orally because of their high first pass metabolism and non patient compliance are most preferred in this technique. There are some ideal characteristics or parameters of drug which is used in this drug delivery system which are given below. The drug used in Wafer dosage form and there concentration are mentioned in table 3.

S. No.	Active ingredients	Therapeutic activity	Dose (in mg)
1	Cetirizine	H1 antagonist	5.0 - 10.0 mg
2	Ketoprofen	Analgesia inducer	12.5 mg
3	Nicotine	Anti smoking	1.0 - 15.0 mg
4	Omeprazole	Anti Ulcers	10.0 - 20.0 mg
5	Famotidine	Antacids	10.0 mg
6	Zolmitriptan	Anti migraine	2.5 mg
7	Azatadine maleate	Anti histamine	1.0 mg
8	Acrivastine	Anti allergic	8.0 mg
9	Phenylephrine hydrochloride Dicyclomine	Muscle relaxant	10.0 mg

***Table 3:** List of drug which can be loaded in wafer dosage form.*

Ideal parameters of the drug for wafer dosage form [13]:

- The drug should be effective in small dose.
- The drug should not have unpleasant odour and taste.
- The drug should have permeable to oral mucosal tissues.
- The drug should be ionised at p^H 6.2 - 7.6.
- The drug should have better solubility and dissolution.
- For Environmental Stimuli drug have less sensitivity.

Film forming polymers [14,15]

Film forming polymer is important characters used in wafer technology. The capacity of film formation is strictly depends on the amount and type and of polymer used. There are some ideal characteristic of polymer used in oral wafer dosage form are given below.

The table 4 contains the examples of polymer which are commonly used.

S. No.	Polymer
1	Starch
2	Xanthan
3	Gelatine
4	Poly ethylene oxide
5	Pullulan
6	Hydroxy propyl cellulose
7	Methyl cellulose A-3, A-6 and A-15

Table 4*: List of polymer used for wafer dosage form.*

Ideal parameters of the polymer for wafer dosage form [16,17]:

- The polymer should free from toxicity and non irritant.
- The polymer should in water soluble.
- The polymer must have higher shelf life.
- The polymer should have low molecular weight.
- The polymer should have better film forming capacity.

- The drug must be free from all type of impurities.
- It should be colour less and taste less.

Plasticizers [18]

These are the chemical agents which affect the mechanical properties of the Wafers, such as tensile strength and elongation of the wafers can be enhanced by adding the plasticizers. mechanical Properties of wafer depends up on amount and type of plasticizer used. Examples: glycerol, PEG and dibutylphthalate, etc.

Sweaters

Sweaters have become the Unique part of the pharmaceutical products and food products as well as intended to be dissolved or disintegrated in the Mouth cavity. 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.

S. No.	Sweaters
1	Eosin red
2	Mannitol
3	Saccharin
4	Sucrose
5	Sorbitol
6	Aspartame
7	Cyclamate

Table 5: *List of sweeteners used for wafer dosage form.*

Sialagogue [18,19]

Sialagogue are the chemical substance which are also known as saliva secretion enhancer. As name indicates these agents increase the activity of salivary glands and increase saliva secretion which supports in fast dissolution and disintegration of the oral wafer dosage form. They indirectly helps in the process of dissolution and disintegration. lactic acid, Citric acid, ascorbic acid, malic acid, and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

Colouring agents [9]

Pigments like titanium dioxide or FDC approved colouring agents are loaded (not more the concentration of 1 percent; w/w) in formulation when some of the ingredients or drugs are present in insoluble or suspension form.

Surfactants

Surfactants are the chemical agents which are used to decrease surface tension and to increase the wettability of the film. Generally non-ionic surfactants are used such as polyoxyethylene sorbitol fatty acid esters (Tween) and polyoxyethylene alkyl ethers.

S. No.	Surfactants
1	Tweens
2	Benzalkonium Chloride
3	Spans
4	SLS
5	Poloxamer 407

Table 6: *List of surfactants used for wafer dosage form.*

Method of formulation of wafer [32,33,37]:

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling.

Solvent casting

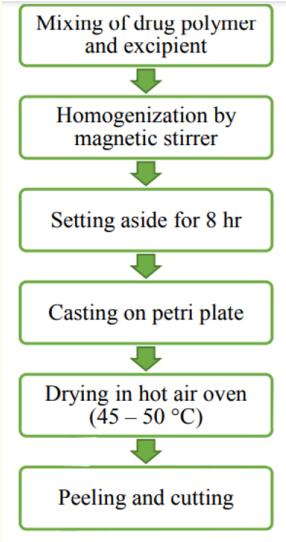

Figure A

Semisolid casting

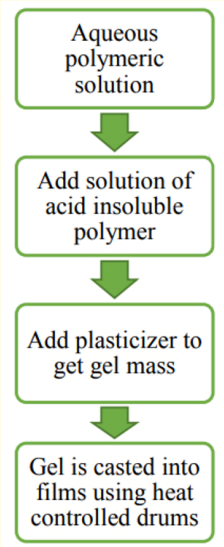

Figure B

Hot melt extrusion

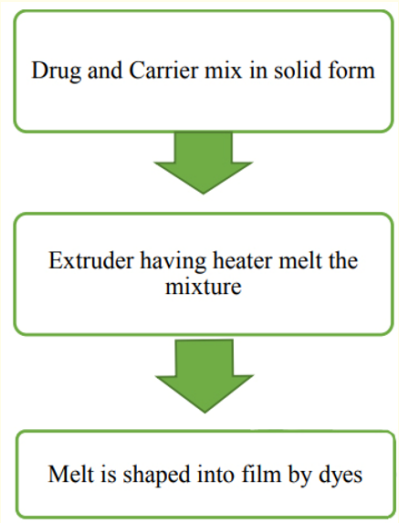

Figure C

Solid dispersion extrusion

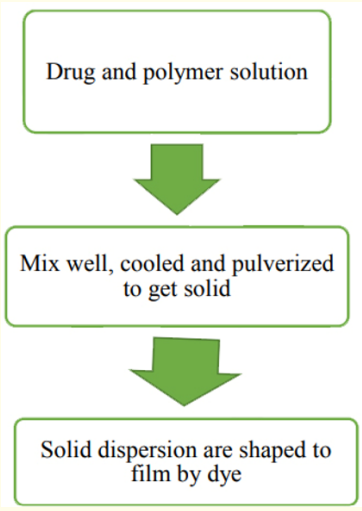

Figure D

Rolling

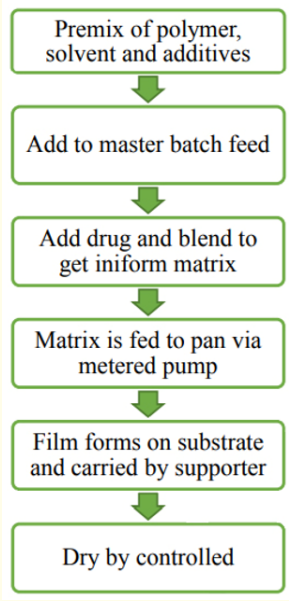

Figure E

Procedure: The process of formation of oral wafers has occurs a few steps, as shown in figure 1. The most censorious steps for stability are mixing, freezing and drying. Because many patent technologies perform some variations of the presented backbone, Production at laboratory level permits blending in magnetically stirred beakers [22] with the help of overhead mechanical stirring [21]. Although, industrial level production needed a temperature-controlled tank with mechanical agitation. The mixing depends on mainly rheological properties of the formed mixture. The compound having Low viscosity can be mixed well by pitch blades or hydrofoil. When encapsulated or coated particles are used high shear mixer may disrupt the coating and it should be avoided [23]. The resultant viscosity will depend on the particles present. And consequential sedimentation rate, and additionally disintegrating and mechanical performances. For formulations containing gelatine, patents describe the use of planetary mixers with high viscosities and low shear rate [24], but some documents does not give equipment details.

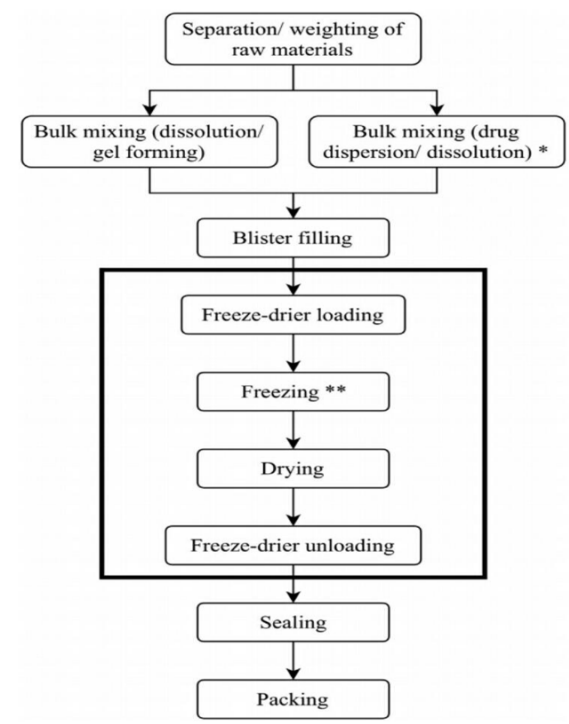

Figure 1: *Flowchart of the production process.*

Gels are dried by freeze-drying, in which water is evaporated from the frozen matrix by sublimation associated with vacuum. This technique has number of advantages, such as improved stability of heat sensitive active pharmaceutical ingredients [25] and formed products with high porosity which permits successive gain in loading capacity per weight [25]. The whole process can occur in a freeze-drier. A industrial freeze-driers do not cool below 40^0C, ultra-freezers or nitrogen tunnels can require for specific freezing procedure. Freezing shapes wafers determines the surface topology and porosity. Because of, target temperature, rate, and intermediate thermal procedure are entered as settings in advance. Fast rates produced tiny particles and higher crystals, which dry slowly, that results in increase in drying time. However slow freezing rate results in large crystals, thermal treatments (annealing) can cause homogeneity and reduced it's drying rates [26]. Recently, in pharmaceutical freeze-drying processes refers to nucleation control of ice crystals on freezing process. Because nucleation occurs in a broad ranges of temperature, its occurrence produce batch heterogeneity and prolonged process.

Therefore, inducing simultaneous nucleation can increase product homogeneity and significantly reduce process time and cost [27]. The technologies with scalability to induced nucleation are depressurization, ice fog and temperature quench freezing [28].

After freezing, the product is put under vacuum. Removal of solvent occurs in two steps: primary or free solvent removal and secondary drying or bound solvent removal. The former should initiates below the collapse temperature (Tc) of the formation of satisfy structural integrity and adequate residual moisture. However bio-polymers used in wafers have high collapse temperature, drugs commonly have lower collapse temperature values. Primary drying is time-consuming because sublimation occurs in higher amounts at lower temperatures unlike bound solvent. Higher initiating temperature results in lower drying time and cost [29]. As such, when collapse temperature is close to or lower than 40C, re-formulation occurs. Quicksolve patent claims to facilitate drying by using another solvent, which is miscible with water and lower vapour pressure and don't dissolve the other components. Although, the patent of the technology does not limit freeze-drying is the only method possible; it is unclear which is mixture of claims were tested and result in optimal formation [30]. Regarding packaging, the oral lyophilized fragility requires specific blisters that resist humidity and physical stress [31]. Special packaging is not required for modified released forms due to enhanced mechanical strength, but they still requires to resist water entry.

Quality control tests

- Organoleptic evaluation
- Thickness
- Dry test/tack test
- Tensile strength
- Percent elongation
- Swelling properties
- Transparency
- Taste evaluation
- Assay/content uniformity
- Disintegration time
- *In-vitro* dissolution test
- Stability testing.

Organoleptic evaluation

Colour should be attractive and good patient compliance [34]. Psychophysical analysis of the product, special controlled human taste panels are used. *Invitro* methods by using taste sensors, designed apparatus and drug release by modified pharmacopoeia methods are used for this purpose. These *invitro* taste evolution apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.

Thickness

The thickness of oral wafers can be measured by Micro-meter screw gauge at various strategic locations. This is important to ascertain uniformity in thickness of Wafer as this is directly related to the accuracy of dose in the wafer form [36].

Tensile strength

Tensile strength is the amount of stress applied to a point at which the wafers breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as in the equation below [45]:

Tensile strength= (Load at failure/wafer thickness) x 100.

Disintegration time [35]

The disintegration time limit for orally disintegrating Tabletsis30 s or less that described in CDER guidance can be applied to fast dissolving oral strips. However, no official guidance is now available for oral fast disintegrating wafers, this may be used as a qualitative guideline for quality control test or at development stage. According to Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time is 5 - 30s [18].

Dryness test/tack test

Tack is the tendency with which the wafer attached to an accessory (a paper piece) that has been pressed into contact with the wafer [41].

Swelling property

Wafer swelling analysis is conducted by using imitated saliva solution. The oral Wafer sample is weighed and set in a stainless steel wire mesh. The mesh containing Wafer sample is submerged into 15 ml solution in a plastic container. Increase in the weight of the Wafer is determined at determined time interval until a constant weight is observed [43]. The degree of swelling is calculated using formula:

$\alpha = (wt-wo)/wo$

Wt is weight of Wafer at time t, and Wo is a weight of wafer at time zero.

Surface pH

pH determined by placing the wafers on the surface of 1.5% w/v agar gel followed by placing pH paper ranges between pH 1 - 11 on wafer. The change in the colour of pH paper was observed and report [38,44].

Stability test

A piece of oral wafer preparation was stored in an Aluminium package. Wafers are stored at 40ºC and 75% Relative Humidity for not more than 3 months and these are evaluated for their drug content, physical appearance and *in-vitro* dispersion time at specified intervals of time [40].

Assay/content uniformity

Content uniformity is determined by using any standard assay method described for the particular Active Pharmaceutical Ingredients in any of the standard pharmacopoeia. Content uniformity is determined by estimating the active content in individual strip. Limit of content uniformity is 85 - 115 percent [35].

Dissolution test

Dissolution testing can be carried out using the standard basket or paddle apparatus described in all pharmacopoeias. The dissolution medium will essentially be selected on the basis of sink conditions and larger dose of the active pharmaceutical ingredients [39]. Number of time the dissolution test can be difficult to perform because of the tendency of wafers to float on the dissolution medium when the paddle apparatus is employed.

Packaging

Numbers of packaging materials are use for packaging of the oral fast dissolving wafers or films but mostly Aluminium pouch are used for packaging of oral fast dissolving wafers. Another packing system, Core-Peel®, is developed by Amcor Flexibles and popular in the field of packaging of fast disintegrating oral films [42].

Selected characteristics packaging material:

- 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 are not capable to change product's taste or odour.

Conclusion

wafers can provide rapid or sustained delivery of Active Pharmaceutical Ingredients for local or systemic effects. As it is revolutionary and an innovative dosage forms for all age groups, specifically paediatric, geriatric patients and patients with difficulties swallowing tablets, capsules and other traditional dosage forms because of is compatibility and the good mouth feel. The advantage of wafers located in the process, as the absence of compression and heating stresses and also protect particles from deformation and aggregation. Wafers are formulates as a improvement in oral fast dissolving films with it's special characteristics of the high absorption, high stability and the high bioavailability. This review concludes that Flash release oral Wafer is most admissible and accurate oral dosage form which reduced side effects due to low concentration, bypass the hepatic system and show more therapeutic response. The marketed products of the wafers are still less but there are so many more to come in the market.

Acknowledgement

Firstly, I am grateful to Allah for the good health and well-being that were necessary to complete this project. I always have a pillar of strength in Him. I gratefully acknowledge my deep gratitude to the Dr. Sameer Shaikh Shakur, Principal, Durgamata Institute of pharmacy, Dharmapuri, Parbhani and I would like to express my sincere gratitude to my supervisors Shri krishna Harkal, Department of Pharmaceutical Analysis, Durgamata Institute of pharmacy Dharmapuri, Parbhani for providing advice and helpful discussions for this dissertation. My Completion of this project could not have been accomplished without the support of my parents. Thanks a lot.

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Volume 6 Issue 2 February 2022
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