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A review on recent trends in oral drug delivery- lyophilized wafer technology

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Abstract
The lyophilized wafer technology is an effective and versatile drug delivery system for oromucosal application. This has been established from the extensive physicochemical and physicomechanical profiling conducted. Due to small size, little dose, thickness of buccal wafer over other dosage form is most acceptable and pleasant. Flash release oral wafer drug delivery system is an alternative approach for the tablets, capsules, and liquid oral dosage forms for pediatric and geriatric patients. The wafer system containing HPC, lactose, mannitol and glycine had the ability to disintegrate within 30 seconds. The modified wafer system, consisting of pectin cross linked with zinc ions serving as the drug reservoir, and mucoadhesive polymer combination of pectin, carmellose and gelatin, provided effective release of model drug diphenhydramine hydrochloride over approximately six hours. The semi-synthetic and synthetic natural polymer as film former in low concentration can be used for the preparation of buccal wafers and hence such dosage form are easy to handle, cost effective, fast absorbable, non- irritating and mostly preferred by patient. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. Present article overview the advancement in the oral dosage forms, application, formulation composition, method of preparation, evaluation and marketed products of oral flash release wafers.

Keywords: Lyophilized, Novel Drug Delivery, Orally disintegrating tablets (ODTs), Over the Counter Products (OTCs)

1. Introduction

Among the Novel Drug Delivery system, buccal drug delivery is the main and extensive acceptable drug delivery between the other delivery systems. Drug Delivery is often challenged to provide new technologies that offer significant clinical and financial value in addition to research and innovation niche. The innovation designs may involve modifying formulation compositions and manufacturing technologies to achieve new product performance end points.

Orally disintegrating tablets (ODTs) offer improved patient compliance as they enable oral administration without water or chewing. The US FDA defines an ODT as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [1].

The 2008 FDA guidance recommends a disintegration time of 30seconds or less based on US Pharmacopeia disintegration test method and maximum tablet weight of 500 mg. ODTs are preferred by multiple patients groups with swallowing difficulties, including geriatrics, pediatrics, dysphagic, and bed ridden. ODTs also offer potential for product line extension for first-to-market product and marketing differentiation for Over the Counter Products (OTCs).

This technology has been used for local action, rapid release of products and for direct systemic circulation in the oral cavity to release drug in rapid fashion. And also this delivery protect drug from first pass metabolism and improve the dissolution. Oral thin Wafer drug delivery systems are solid dosage forms, which dissolve in a short period of time when placed in the mouth without drinking water or chewing. These are also referred as fast dissolving Oral Wafers, wafers, buccal films/ Oral strips [2].

Wafer-an innovative oral dosage form: New oral thin films, so-called wafers, thus creating new possibilities for action profiles and patient compliance. Wafers are paper-thin polymer films used as carriers for pharmaceutical agents. The innovative dosage form is taken orally but does not require water or swallowing.

The ODT market is expected to exceed $13 billion by 2015, which is more than double its value in 2009.

The increase may be attributed to three main driving factors:

1. Increased generic competition and the need for product differentiation.
2. Expected increase in the number of prescription products switch to OTCs.
3. The 2007 introduction of the European regulation on medicinal products for pediatrics.

Tablet compression and lyophilization remain the two most popular industrial approaches to manufacture ODTs. The compressed ODT involves conventional tableting with achieved rapid disintegration using super-disintegrants in combination with lower compression forces and/or the use of water-soluble excipients. Direct compression is often the technique of choice. Some of the patented compressed ODT technologies include Flashtab, Advatab, Orasolv, Durasolv, Wowtab, and Ziplets. The lyophilized ODT employs the process of lyophilization in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. The lyophilization manufacturing process produces wafer with greater porosity, allowing for shorter disintegration times than compressed ODTs. The patented lyophilized ODT technologies include Zydis, Lyoc, and Quicksolv. Other techniques to manufacture ODTs include spray drying, molding, thin films, meltgranulation, extrusion, and sugar floss. The following article reviews the lyophilized wafer technology, specifically Lyoc. That offered the world's first ODT, ODA Lyoc (sodium saccharinate and flamenol) in 1968.

The rationale for development and use of novel drug delivery systems may include one or more of the following arguments:

1. Decrease the toxicity and occurrence of adverse drug reactions by controlling the level of drug and/or metabolites in the blood at the target sites.
2. Attractive dosage form with new active ingredients.
3. Improve drug utilization by applying a smaller drug dose in a controlled – release form to produce the same clinical effect as a larger dose in a conventional dosage form.
4. Provide greater patient convenience and better patient compliance by significantly prolonging the interval between administrations.
5. Improvement of established products.
6. Provide a uniform blood concentration and/or provide a more predictable drug delivery.
7. Optimization of bioavailability.
8. Increase patient compliance.
9. Innovative technology for product.
10. Increase of product appeal through innovative format.
11. Exclusivity and cutting edge technology position in the market through a step forward.
12. Control the rate and site of release of a drug that acts locally so that the drug is released where the activity is needed rather than at other sites where it may cause adverse reactions.
13. Access to new indications by means of a new absorption profile even for existing active ingredients.

Advantages of Wafers technology [3-5]

1. High dissolution due to a large surface area.
2. No risk of choking.
3. More patient compliance.
4. Improved bio-availability, translates to lower doses.
5. Reduction of side-effects.
6. Reduced impact on the gastro intestinal tract.
7. Better durable than Oro-dispersible tablet.
8. Low dose can only be incorporated.
9. No first – pass effect*
10. Conrolled release.
11. Discrete and easy application (no additional intake of liquids required).
12. Excellent compliance, especially in children and seniors.

Disadvantages of Wafers technology

1. The disadvantage of OTF is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip 7.
2. Expensive packaging of oral film.

Type of wafers

There are three subclasses:

1. Flash dissolved wafers
2. Melt away wafers
3. Sustained release wafers
4. Flash dispersed wafers

Open Matrix-Type Wafers and Tablets (WOWTab) [6-15]

With the introduction of the Zydis® system in the late 1970s, the concept of quick disintegrating drug delivery systems gained much attention. It was the first of this class of delivery systems to be manufactured on a large scale. It is a freeze-dried wafer made from various standard tablet adjuvants. The wafer essentially works on the principle of forming an open network containing the active ingredient. The Zydis® manufacturing process. The freeze-dried tablet disintegrates within 2-3 seconds, releasingthe active ingredient. The drug either forms dispersion or dissolves in the saliva, which is then swallowed and absorbed via the GIT.

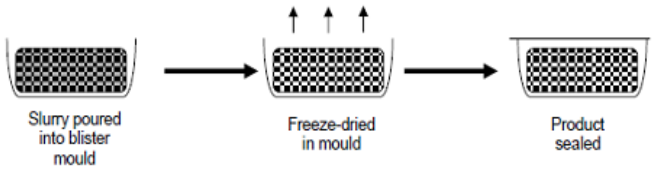

Fig 1: Production of Zydis® lyophilized wafer.

The WOW Tab® (With-Out-Water tablet) has been produce by Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan). This tablet is manufactured using conventional granulating and compression. The rapid disintegration is attributed to the blending of a low and high mold ability saccharide. The unique combination of saccharides provides sufficient mechanical strength as well as quick tablet disintegration.

Lyoc technology is an oral solid porous dosage form that immediately dissolves in the mouth without the need for water

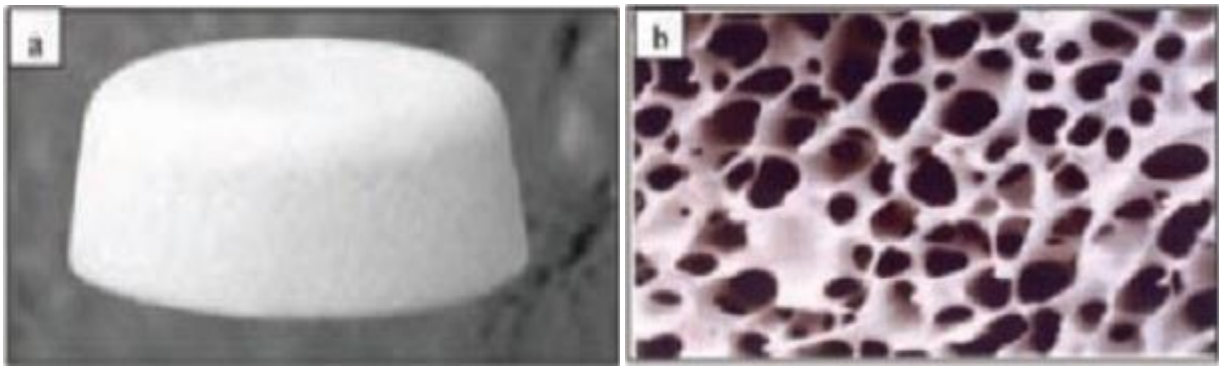

Fig 2: (a) Lyoc tablet, (b) Porous structure.

The technology is suitable for a variety of actives with different physicochemical properties and can be tailored to incorporate drug particles with different functional coatings, including taste-masked, extendedrelease, and modified-release coating. There are currently seven commercialized ODT products utilizing Lyoc technology, including Spasfon-lyoc (phloroglucinol), Para-lyoc (paracetamol), Proxa-lyoc (piroxicam), and Loperamide-lyoc (loperamide).

Lyoc utilizes a unique manufacturing process based on an innovative nonpolluting, nonpolluting, environment-friendly, freezedrying technology that yields high purity and safe products as it operates in the absence of organic solvents. The typical Lyoc manufacturing steps include:

Preparation of a suspension, solution, or emulsion containing active ingredients.

Distribution of this liquid homogenous preparation in preformed blisters.

Very low temperature freezing (preferably below -40Â°C). At this stage, the active molecules are immobilized; their properties remainunaltered as the rate of chemical reactions is nearly nil at this low temperature.

Sublimation or water elimination: this is typically carried out at low temperature and low pressure. Under particular conditions, the ice is directly converted into the vapor phase.

The finished product is a porous solid capable of very rapid disintegration. The active ingredients remain in a dispersed state within the mass.

Sealing the blister with top foil.

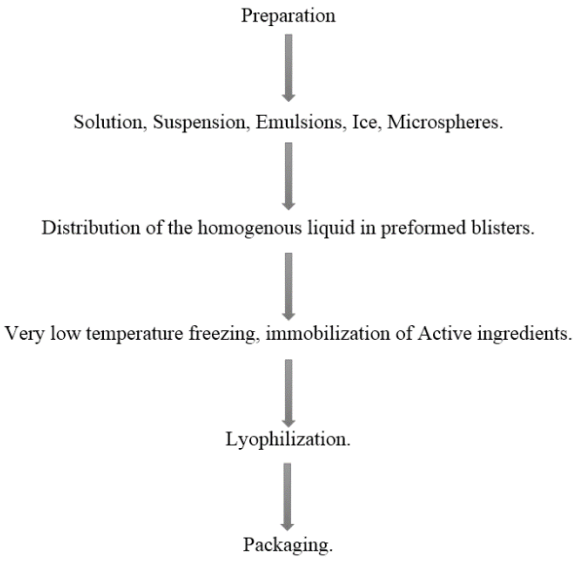

Fig 3: Flow chart of method of preparation of Lyoc tablet.

Formulation consideration/ Details

1. Active pharmaceutical ingredient: 5 -30%
2. Wafer forming polymers: 45%
3. Plasticizer: 0 -20%
4. Sweetening agent: 3 -6%
5. Saliva stimulating agent: 2 -6%
6. Flavoring agent: Q.S
7. Coloring agent: Q.S

Analysis/Evaluation of Wafers

Evaluation of Fast Dissolving Wafers [16]

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

1) Organoleptic evaluation

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

2) Mechanical properties

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

a) Thickness

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

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 wafer as given in the equation below:

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

d) Percent Elongation

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

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

e) Tear Resistance

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

f) Folding Endurance

Folding endurance is determined by repeated folding of the

strip at the same place till the strip breaks. The number of times the Wafer is folded without breaking is computed as the folding endurance value.

3) Swelling property

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

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

W_t is weight of Wafer at time t, and W_o is weight of Wafer at time zero.

4) Transparency

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

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

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

5) Taste evaluation

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

6) Assay/ Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.

7) Disintegration Time

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

8) *In-vitro* Dissolution Test: Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times dissolution test can be difficult due to tendency of the strips to float on the dissolution medium where paddle system is used.

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

List of marketed wafers

Product	Manufacturer
Altoid cinnamon strips, Boots vitamin c strips, Benzocaine films, Caffeine films	Dow chemical company
Theraflu Thin Strips Long Acting Cough	Novartis
Sudafed(Phenylephrine)	Wolterskluwer health, Inc.
Gas-X(Simethicon), Triaminic	Novartis
Suppress Cough Strips	InnoZen
Little Colds Sore Throat Strips	Prestige Brands

Future prospects

Historically, drug delivery has taken the form of injection, infusion, ingestion, and inhalation, with additional variations of each category. These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These can offer several biopharmaceutical advantages such as improved efficiency ov er conventional dosage forms.

These products usually degrade rapidly in the stomach. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors. The challenge for both drug and drug delivery companies is to deliver both existing and emerging drug technologies in a manner that improves the benefits to the patients, healthcare workers and the healthcare system. Areas that are being targeted for improvements through device development includes improved efficiency, minimized side effects, continuous dosing (sustained release), reduced pain from administration, increased ease of use, better compliance, contribution of healthcare workers decreased, improved safety for healthcare workers.

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