IJLSR (2019), Vol. 5, Issue 3 **Review Article**

IJLSR INTERNATIONAL JOURNAL OF LIFE SCIENCES AND REVIEW

Received on 13 January 2019; received in revised form, 11 February 2019; accepted, 12 March 2019; published 31 March 2019

WAFER TECHNOLOGY AS A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT: The buccal cavity is considering as a door for the digestive system. It is composed of teeth, tongue, and palate. When the food enters the buccal cavity, it is moved along the pharynx and esophagus and then go onward through the stomach, small intestine, large intestine, and anal opening. When the drug is taken by the buccal delivery system, it decreases the time needed for the drug to give its action, progresses the therapeutic action of the drug and gives a better enzymatic flora for drug absorption. It provides direct entry of drug into the systemic circulation; therefore, decrease all the drawbacks of the per-oral administration of drugs as hepatic first-pass effect, pre-systemic elimination of GIT by enzymatic degradation; between different routes of drug delivery, wafers are considered the most advantageous dosage form that taken orally and gives response at once with little side effects. The buccal region is one of the most convenient and easily approachable routes for administration of the therapeutic agents to be used locally and systemically.

Keywords: Lyophilization, Theories of bio-adhesion, Wetting theory, Flash release wafers, Hot-melt extrusion, Analysis of wafers

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INTRODUCTION: Oral route is the most known and acceptable route for drug administration; in this route, the drug is placed in the mouth and swallowed. There are many advantages for oral route drug administration such as; it is convenient, portable, safe, no pain, easy to take, cheap, no need to sterilize (but must be hygienic of course), compact, multi-dose bottles, automated machines that produce tablets in large quantities and the variety of dosage forms available, fast release tablets, capsules, enteric coated, layered tablets, slow release, suspensions mixtures.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJLSR.5(3).30-41

The article can be accessed online on www.ijlsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJLSR.5(3).30-41

Drawbacks of oral route drug administration are; sometimes inefficient, high dose or low solubility drugs may suffer poor availability, only part of the dose may be absorbed. Griseofulvin was reformulated about 1970 to include the drug as a micronized powder. The recommended dose at that time was decreased by a factor of two because of the improved bioavailability [1, 2].

The oral cavity or mouth is an organ of the digestive system that is anteriorly consist of the lips, posteriorly by the oropharynx, superiorly by the hard and soft palates, and inferiorly by the tongue (anterior 2/3) and floor of the mouth, and encompassed by a buccal mucosa that lines the mouth, along with the upper and lower teeth and periodontal. The upper teeth are embedded in the maxilla, and the lower teeth are embedded in the mandible, which articulates with the temporal bones of the skull.

The part of the throat that just behind the mouth is oropharynx, where the base of the tongue is present, the soft palate, the tonsils, and the side and back wall of the throat are present. The middle part of the pharynx is oropharynx (between the nasopharynx and hypopharynx/laryngopharynx) that is located behind the oral cavity (the palate glossal arch) expansion from the uvula to the level of the hyoid bone. It opens anteriorly into the mouth through the isthmus faucium. In this site, the oropharynx is restricted by the base of the tongue (posterior 1/3) and the upper border of the epiglottic vallecula. Laterally, it is formed by the palatine tonsils, tonsillar fossa, and tonsillar pillars located between the palate glossal and palate pharyngeal arch. Superiorly, its wall contains the inferior surface of the soft palate and the uvula [3].

The mouth of human is covered with mucous membranes that save the outer cell layer of the body cavity (the epithelium) from irritation that can be done by food and harmful digestive juices while the food passes through the upper alimentary canal. The mucous membrane, along with the sub-mucosa and the serosa, is present throughout the entire alimentary tract body and is about 50% cells layers thickness. The lining epithelium of buccal mucosa is that it has a thickness of approximately 500-600 μ and surface are 50 cm. Basement membrane, lamina propria followed by the sub-mucosa is present below the epithelial layer. Lamina propria enrich with blood vessels and capillaries, which open to the internal jugular vein. Lipid analysis of buccal tissue shows the presence of phospholipids 76%, glycosphingolipids' 23% and ceramide0.72 % [4].

Among the various routes of drug delivery, the oral route is the most attractive site for the delivery of drugs. The most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery is the buccal cavity. Buccal adhesive drug delivery system prolongs the residence time of the dosage form at the site of application or absorption and facilitate a close contact of the dosage form with the absorption surface and thus help to improved therapeutic performance of the drug [5]. The buccal cavity is an attractive and achievable site for systemic drug delivery as it increases the bioavailability. A phenomenon of interfacial attraction forces is an expression for bio-adhesion, in which two materials are joined together, it occurs between the surfaces of biological, subtract of the natural or synthetic polymers, which allows the polymer to join to the biological surface for an expanded period. Generally, bio-adhesion is a code that marks adhesive interactions with biological or non-biological derived substances [6].

Advantages of Buccal Route: Buccal route avoids the first pass effect and exposure of the drug to gastric and intestinal fluids, therefore, increasing their bioavailability. It also develops patient compliance by avoiding pain and the formulation can be removed if medication needs to be stopped. Also, the chance of accidental choking in the respiratory tract is minimized [7]. When compared with other routes such as transdermal, mucosal surfaces do not have a stratum corneum. Hence the main barrier to drug transport is removed and therefore provides fast onset of drug action. The buccal route is a promising route for administering drugs which have high first-pass metabolism, low dose, log P value in the range of 1.60–3.30 andsmall molecular size [8].

Limitations of Buccal Drug Delivery: There are some restrictions of buccal drug delivery system such as drugs which are unstable at buccal pH cannot be taken, drugs which have a bitter taste or unpleasant taste or a noxious odor or burn the mucosa cannot be administered by this route, drug required with small dose can only be administered, Those drugs that are absorbed by passive diffusion can only be taken by this route and eating and drinking may become limited [9].

Anatomy of the Buccal Mucosa: The oral mucosa contents are an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the submucosa as the innermost layer. The mucosa of the gingival and hard palate is keratinized as the epidermis has neutral lipids like ceramides and acylceramides which aren't permitted for water to cross. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides [10].

Buccal Absorption: Buccal absorption can cause systemic or local action by buccal mucosa.

A) Mechanism of Buccal Absorption: Buccal drug absorption occurs by passive diffusion of the non-ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species through the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membranes and the more lipophilic the drug molecule, the more readily it is absorbed. The dynamics of buccal absorption of drugs could be adequately expressed by first-order rate process. Several potential barriers to buccal drug absorption have been identified that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth [11].

B) Factors Affecting Buccal Absorption: The oral cavity is a complicated environment for drug delivery as there are many interdependent and independent factors which decrease the absorbable concentration at the site of absorption [(12).]

Membrane Factors: This includes the degree of keratinization, the surface area that is available for absorption, mucus layer of the salivary pellicle, intercellular lipids of the epithelium, basement membrane, and lamina propria. Also, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal, and enzyme content will all share in reducing the rate and amount of drug that enters the systemic circulation [13].

Environmental Factors are consisting of Saliva and Salivary Glands: Saliva is the thin film throughout the lining of buccal mucosa and is named salivary pellicle or film. The thickness of the salivary film is ranged between 0.07 to 0.10 mm. The thickness, composition, and movement of this film affect the rate of buccal absorption. Salivary glands are positioned in an epithelial or deep epithelial area of the buccal mucosa. They constantly secrete mucus on the surface of the buccal mucosa. Although mucus helps to retain mucoadhesive dosage forms, it is a potential barrier to drug penetration [14].

Movement of Buccal Tissues: Buccal region of the oral cavity gives fewer active movements. The mucoadhesive polymers are to be united to keep dosage form at the buccal region for long periods to withstand tissue movements during talking and if possible, during eating food or swallowing [15].

C) General Considerations in Formulation:

Physiological Considerations: In designing buccal dosage form, physiological factors such as a surface of buccal mucosa, limiting device size, drug load, the thickness of the mucus layer, its turn over time, the effect of saliva and other environmental factors are to be considered.

Saliva contains certain enzymes (esterases, carbohydrase's, phosphatases) that may degrade some drugs. Although saliva secretion facilitates the dissolution of the drug, involuntary swallowing of saliva also affects its bioavailability [16].

Pharmacological Considerations: Buccal drug absorption based on the partition coefficient mechanism of the drugs. The transcellular route is the way which through the lipophilic drugs is absorbed, whereas hydrophilic drugs absorb through the paracellular route. Other pharmacological factors as residence time and local concentration of the drug in the mucosa, treatment of oral diseases, the amount of drug transport across the mucosa into the blood [17].

Pharmaceutical Considerations: While designing a formulation drug release, penetration through the buccal mucosa, organoleptic factors, and effects of other excipients irritation caused at the site of application are to be considered. Some additives can be incorporated to improve drug release pattern and absorption.

Mucoadhesive agents are used to maintaining an intimate and increase duration of contact of the formulation with the absorption site while penetration enhancers develop the drug penetration through the mucosa (trans-mucosal delivery) or into deepest layers of the epithelium (mucosal delivery). The enzyme inhibitors save the drug from the degradation byways of mucosal enzymes [18].

D) Theories of Bio-adhesion or Mucoadhesion: The fundamental mechanism of adhesion has been explained by different theories.

Wetting Theory: Wetting theory can be applied to liquid bio-adhesive systems and analyzes adhesive and contact behavior in the expression of a liquid or a paste to be spreader through a biological system [19].

Diffusion Theory: According to this theory, the polymer chains and the mucus are mixed to a sufficient depth to create a semi-permanent adhesive bond. The accurate depth to which the polymer chains penetrate the mucus based on the diffusion coefficient and the time needed for contact. This diffusion coefficient, in turn, relies on the worth of molecular weight between crosslinks and decreases significantly as the cross-linking density decreases [20].

Electronic Theory: According to this theory, the electronic transfer takes place upon connecting 8 of an adhesive polymer and the mucus glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layer [21].

Fracture Theory: According to Fracture theory of adhesion, it is related to the separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by,

$$G = (E\varepsilon. /L)\ ½$$

Where: E = Young's module of elasticity, ε = Fracture energy, L = Critical crack length when two surfaces are separated.

Adsorption Theory: According to this theory, after initial contact between two surfaces, the materials adhere due to surface forces acting between the atoms in the two surfaces. There are two types of chemical bonds such as primary covalent (permanent), and secondary chemical bonds (including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds) are involved in the adsorption process [22].

Wafers as New Pharmaceutical Technology: These are the paper-thin polymer films of plastic that usually 2-8 cm^2area and thickness of 20-500 microns; typically contain less than 50 mg of API. These programs are taken directly on the tongue. This is the most acceptable and advanced form of the dosage form solid mouth because of the efficiency of the solution in a matter of minutes in the oral cavity when it comes in contact with saliva. It does not require chewing and water management. It gives a fast absorption and bioavailability moment of medicines because of the high blood flow and permeability of the oral mucosa [23]. This dosage form is taken orally but does not need water for swallowing. Dissolves quickly in the mouth cavity of the active ingredient can be absorbed into the bloodstream by the oral mucosa. Avoiding liver first pass effect, thereby improving bioavailability, the active ingredient may be a solution, emulsified or dispersed in the polymer [24].

Objectives of Wafers: There are many objectives of formulating wafers such as improved patient compliance and give fast action, border the extent of first-pass hepatic metabolism, to reduce side effects related to the API by decreasing the dose, in addition to the progress the bioavailability of oral molecules. Some companies like; Labtec Pharma, Pfizer, Novartis, Del, Zydis, *etc.* are producing wafer as a dosage form [25].

The lyophilized wafer has been progressed throughout this review, which is considered an effective and versatile drug delivery system for the oral mucosal application. This has been established from the global physicochemical and physic mechanical profiling conducted. Hydroxy probyl cellulose (HPC) had the lowest gelation characteristics and was, therefore, suitable for the development of the wafer system when screening and selection of polymers are done. Suitable excipient and polymer combinations were established that allowed for the development of rapidly disintegrating and prolonged release wafer systems. The wafer system is consisting of HPC, lactose, mannitol, and glycine that could disintegrate within 60 sec. In the modified wafer system, it is consisting of pectin that makes crosslinked with zinc ions that serving as the drug reservoir, and mucoadhesive polymer which is a combination of pectin, carmellose, and gelatin, that provide effective release of model drug diphenhydramine hydrochloride through approximately six hours.

The modification of this technology is done to provide a long duration for the drug release through

a mucoadhesive system, which seems promising. It imagines that this system will be easy to be applied to many drugs need the expansion release of bioactive material. Therefore, the lyophilized wafer matrices progressed in this study is highly effective in the fast delivery of drugs by using the oral route as a site of administration [26].

Advantages of Wafers: Positive aspects of wafers as oral fast dissolving films can be approved be many things such as attractive dosage form that has novel active ingredients, improve establishing product ,access to a new indication by definition a new absorption even for the active ingredients found, increase the bioavailability, innovative technology for the product, increasing of product seems through the creative format, cutting edge technology position through a step forward in the market, no first-pass metabolism, controlled release, develop the bioavailability, decrease side effects, reduced impact on the gastrointestinal tract, intermittent and easy application, improve compliance, especially for the elderly and children to patients and feels good mouth and stability [27].

Disadvantages of Wafers: There are drawbacks of wafers as high dose aren`t united, but concentration level of active ingredients may be progressed up to 50% per dose weight, packaging needed is very high costs, extreme bitter medicine is not feasible, concerns about handling during manufacturing, drugs that are unstable at pH through the mouth cannot be included. And medications that irritate the mucous membrane cannot be taken [28].

Composition of Wafers: The drug can be inserted up to a single dose of 15mg. It has been reporting on considerations such as the drafting of the important factors that affect the mechanical properties of the wafer, such as changing the temperature of the glass transition temperature drop[29].

Drug: There are different categories of drugs can be formulated as oral wafers. Whatever including Antiulcer (such as omeprazole), antiasthmatics (salbutamol sulfate), antitussives, expectorants, antihistamines, NSAID'S (such as paracetamol, meloxicam). Wafers have ideal characteristics for drugs that will be selected. The low-dose drug, be a good taste of the medicine, have a smaller and moderate molecular weight, good stability and water solubility as well as saliva, unionizes partly in the pH in the oral cavity, the capability to permeate oral mucosal tissue [30].

Water Soluble Polymers: The use of polymers that are soluble in water as makers of wafers has attracted the use of chip wafers in the forming of polymers soluble films great interest in medical applications and nutrition. Polymers are soluble in water to achieve rapid disintegration; good mouth feels and mechanical properties [28].

Plasticizers: It has been reported as a drafting consideration are serious factors that affect the mechanical properties of the wafer. Mechanical properties such as tensile strength and elongation have also been progressed through the addition of plastic materials. The difference in concentration may affect these properties. Plastic materials usually used are glycerol, phthalates bilateral butyl glycol and polyethylene, *etc.* [30]

Penetration Enhancers: It is essential needed penetration enhancers also when the drug has to get to the systemic circulation for the exercise of their work. These should be non-irritating and have an effect inverted: epithelium expected a recovery of the barrier properties after they have been drug absorption. And it includes the most known categories of breakthrough enhancer's buccal fatty acids, surfactants, and among these bile salts, azone, and alcohol.

Increasing the fluidity of lipid bilayer membrane; increased retention of the drug at mucosal surface others octisalate, padimate, menthol acting on the components at tight junctions; increasing the fluidity of lipid bilayer membrane [28].

Surfactants: Wafer is getting dissolved within seconds and shot active agent immediately because of surfactants that used like solubilizing, wetting or dispersing agent. Some of the usually used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, and tweens [31].

Flavor: You can join any flavor, such as intense mint, sour fruit flavors or flavors of sweet desserts. Flavoring agents recognize changes flavors from one individual to another based on the race and liking. It was noted that age has an important role in fancy taste. Flavoring agents may be chosen

from synthetic flavor oils, resins pacifier, extract derived from different parts of plants such as leaves, fruits, and flowers. Flavors can be used alone or in a group. Peppermint oil, cinnamon oil, peppermint oil, and nutmeg are examples of oils vanilla flavor while, cocoa, coffee and chocolate [32].

Color: A full range of colors available, including FD & C colors and the EU colors, natural colors and custom colors Pantone Matching.

Saliva Stimulating Agents: Saliva stimulating agents rise the rate of secretion of saliva, which helps to decay faster than the chips (Multiply - 2.6% w / w). Examples of citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid, and flavoring agents: they may be chosen from the artificial. Flavor oils, oleoresins, from parts of the plant. Citric acid and malic acid and lactic acid, and ascorbic acid and tartaric acid are a few examples of the salivary stimulant, citric acid, which is the most preferred among them [28].

Sweetening Agents: Sweeteners have become a significant part of the food products, as well as pharmaceutical products, to be broken up or soluble in the mouth cavity. Sweetness plays an important role in proving wafers compliance in several children. Natural sweeteners, artificial sweeteners, are playing a vital role in progressing the palatability of dissolving formulations through the mouth. Conventional source of the sweetener is sucrose (which is derived from cane or beets in the form of a liquid state or dry), dextrose, fructose, glucose, liquid glucose and maltose [29].

Taste Masking Agents: Taste masking substances taste bitter or objectionable drug is extremely important for any form of oral doses. There are different methods to conceal the bitter taste of pharmaceutical dosage forms a quick solution, the polymer coating to the solution of the drug or suspension applied to the substrate, and the coated particles or active drug entities directly [31].

Mechanism of Action of Wafers: Wafers are placed on the tongue of the patient or any kind of oral mucosal tissues. The moist immediately through saliva because of a hydrophilic polymer and other excipients; film hydrates fast and dissolves to emission the drug for absorption membranes [32].

Classification of Oral Wafers: Anatomic and physiological considerations: there are four sites within the buccal cavity have been used for drug administration. The four regions have different permeability, which has a role in the absorption of drugs through the oral mucosa. As seen in the four key areas are the buccal cavity, the lingual area, the palate, and gingival region. The most usually used sites for drug insertion of the four mentioned above are the sublingual and buccal route. Using the sublingual route, the medicament is placed under the tongue, usually in the form of a fast dissolving tablet. The anatomic site for drug insertion between the cheek and gingival is known as the buccal mucosa. The oral mucosa is consisting of three layers. The first layer is the stratified squamous epithelium; which located underneath this layer lays the basement membrane. The basement membrane overlies the lamina propria and submucosa [33].

The four classifications of wafers are:

1. Flash release wafers.
2. Mucoadhesive melt-away wafers.
3. Mucoadhesive sustained release wafers.
4. Flash dispersed wafers.

Flash Release Wafers: Flash release wafers have very rapid action (60) s maximum, the thickness is 20-70 µm, the area is 2-8 cm^2, single-layered structure, and soluble excipients are used, highly hydrophilic polymers are required. The wafers are dispersed in solid solution phase; in addition to it is applied to the upper palate of the tongue.

Muco-adhesive Melt Away Wafers: Muco-adhesive melt-away wafers have area 2-7 cm^2, thickness–50-500 µm. Dissolution time (1-3) min, single or multi-layered structure, soluble excipients are used, need for hydrophilic polymers. Drugs are dispersed in solid, solution or suspension. Also, it is applied to the gingival or buccal region.

Muco-adhesive Sustained Release Wafers: Muco-adhesive sustained release wafers have area 2-4 cm^2, thickness 50-250 µm, dissolution time needed (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, and it is applied to the gingival or oral cavity [32].

Manufacturing Methodologies of Wafer: Methods for preparing wafers that are rapidly dissolving are classified to:

A. Casting and drying method: It is divided to (a) casting solvent (b) semi-solid casting.

B. Extrusion method: It can be done by; (a) hot melts extrusion (b) solid dispersion extrusion.

C. Freeze dried wafers method.

D. Rolling method.

Solvent Casting Method: This method works for the manufacture of fast dissolving chips from size 3×2 cm^2 and 2×2 cm^2. Dissolved polymers are soluble in water and water car. It dissolves the drug along with other excipients in a suitable solvent, and is mixed and stirred alike. And cast in the end on a Petri dish or plate is consists of glass, plastic or Teflon and dried. The use of certain types of equipment in production is on a large scale, as well as reels used for pouring the solution on the inactive base. It is trapped air space clearance. The last step is drying the wafer and removing the solvent and helps to get the final product. Weaver is dried and then cutting, stripping and be done packaging [33].

Solvent casting methods have some Advantages that make that the most known used route. This advantage is reduced of costs; self-medication is possible, acceptable, painless [34], uniformity better than the thickness of clarity and better extrusion, wafers have a beautiful luster, and freedom from defects such as lines die and more flexibility and physical properties better.

However, the solvent casting method has many advantages there are also some disadvantages like, they have shorter expiry time, not convenient as it needs careful measurements, polymers used must be soluble in volatile solvents or water, concerns raised regarding the dissolution profile, must be the formation of a stable solution with a solid content reasonable minimum and viscosity, you can choose multiple casting based on the fluid rheology techniques, needed applied mass necessary uniformity and dosage in addition to must be the forming of a homogeneous and the emission of the casting support possible.

Semi-Solid Casting Method: This technique is carried out to manufacture flash release wafers of size 0.015-0.05 inch. A solution of water-soluble wafer forming the polymer is prepared. Then the solution is further added to the 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 cast to wafers using heat-controlled drums [35].

Solid Dispersion Extrusion: Emanate miscible with the drug ingredients, and then prepared a solid disperse forming solid dispersions in chips by the use of plants [36]. The advantages are fewer processing steps and more accurate uniform dispersion of the particles due to severe mixing and agitation.

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 eliminated. The strips are further cooled and cut to the desired six. The high temperature used in this process may degrade thermolabile APIs [37].

Excipients for Hot-Melt Extrusion:

Carriers: Thermoplastic polymers are good for hot -melt extrusion [38]. Drug-polymer compatibility, polymer stability, drug release kinetics, and route of administration are taken into account when choosing a polymer as a carrier for hot-melt extrusion [38, 39]. A chosen polymer has to be compatible with the drug and thermally stable along the processing time. A required release profile is usually obtained by a good selection of the polymer. The route of insertion has to match with properties of selected polymer.

Plasticizers: Plasticizers are incorporated into polymers to principally reduce Tg and brittleness, adjust the mechanical properties, and improve the flexibility and workability of polymer [40, 41, 42]. In general, plasticizers seem to be small molecular liquids; due to the benefits of plasticizers on polymers, they have been widely utilized in the process of hot-melt extrusion to promote the processability of polymers [43, 44] and lower the extrusion temperatures [45, 46, 47]. For thermal labile

drugs or ingredient such as peptides and proteins [48], the decrease of processing temperatures by a plasticizer allows them to be fabricated using hot-melt extrusion. The processing temperatures above Tg are principally required to soften polymeric carriers enough to flow through a hot-melt extruder [49]. Therefore, the decrease of melt viscosities and Tg with the addition of a plasticizer results in the reduction of extrusion temperatures.

Another Excipient: Another excipient can be incorporated into a dosage form prepared by hot-melt extrusion. They aim to be a processing aid and a release modifier. A processing aid excipient is generally used to help hot-melt extrusion to process easily and efficiently. It has no or a little impact on properties of end drug products. Glyceryl monostearate was investigated as a thermal lubricant. The addition of glyceryl monostearate and the drug helped facilitates the thermal process. The decrease in the melt viscosity and the drag flow were observed without a change in Tg of the polymer [50, 51]. Hot- melt extrusion not needed to use solvents or water. Other Advantages are fewer processing steps, compressibility characteristics of the API may not be of importance, dispersion mechanism and bioavailability suitable for poorly soluble drugs, more accurate uniform dispersion of the particles due to less intense mixing and agitation, finally less energy compared with high shear roads.

Disadvantages of hot- melt extrusion is thermal deterioration due to high temperature, low-risk status documented melting point where melt / soften the binder during the handling and storage of the blocks happen, folders melting point higher high temperature melting require, and can contribute to the volatility of problems, especially for materials heat labile, finally Flow properties of polymers are necessary to address.

Rolling Method: It is any solution or suspension of the medication contains a carrier returned. The solvent is mainly water or a mixture of water and alcohol. The dried chip on reels and cut into desired shapes and sizes. Other components, including active elements dissolved in a small part of the aqueous solvent using a high shear processor. Hydrocolloids dissolved water soluble in water to form a homogeneous viscous solution [52].

Freeze Drying Method (Lyophilization): Freeze drying or lyophilization is a technique that is used to dry a solution to produce a solid product. This method gives the means to dry heat-sensitive drugs or specimens at low temperatures due to decreasing of the decomposition or deactivation of such products. Because of large surface area, a freeze-dried product is capable of absorbing solvent (typically) upon its reconstitution. This is useful for solubilizing freeze-dried vaccines and antibodies during reconstitution for injections [53].

Lyophilization includes three separate, unique, and interdependent stages, with each step being critical to the final quality of the product. These comprise freezing the formulation and reduction of the solvent (usually water) content by sublimation (primary drying process). This is followed by desorption (secondary drying process) to a residual solvent level that will no longer support biological activity or chemical reactions [54]. At industrial scale, the freezing stage is usually carried out by use of a freeze-drying machine through the material should be cooled below its eutectic point in advance using a freezer or liquid nitrogen. At temperatures lower than the eutectic point, the possibility of solid and liquid material coexisting will be reduced, which is desirable. The length of the freezing cycle can be altered as a consequence of the following:

- Freezing and annealing procedures encourage crystallization while maximizing the size of the crystals and reducing drying rates.

- The length of the freezing procedure is affected by the thickness of the sample, which leads to water vapor molecules experiencing resistance while escaping from the dried portion of the gel. Therefore, reducing the thickness of the starting material (*e.g.,* gels) reduces the resistance to vapor flow; hence, the drying process is faster [55].

Freeze Drying Cycle:

i) Freezing or Freeze-Annealing: The freezing cycle can be performed either by freezing sample continuously at a certain temperature while the drying process is on-going or freezing coupled with annealing. During freezing and annealing, the liquid sample is cooled until pure crystalline ice forms from part of the liquid and the residue of the

sample is freeze, concentrated into a glassy state which possesses high viscosity and prevents further crystallization [55].

ii) Primary Drying: During the primary drying step, the majority of the sample's water content present in the form of ice crystals is removed which require specific pressure (vacuum) conditions in the freeze dryer instrument. Sublimation is the basic mechanism of water removal from the substrate (*e.g.,* gels) during freeze-drying and occurs by the escape of free ice crystals through the frozen gel during the primary drying step.

Primary drying or sublimation is a time-consuming process, taking place at cooler temperatures and completed safely below the substrate's critical temperature (eutectic point of the formulation). It also requires heat energy to initiate the sublimation process. To obtain the maximum drying yield during the primary drying, several parameters should be considered.

Evaluation of Wafers:

Organoleptic Evaluation: This is a necessary step in the case of most of the drafting of the mouth due to more residence time in the oral cavity. It should have the required product features of sweetness and flavor that are acceptable to a large mass of the population. As it has been reported experiments using measuring tongue-mail to distinguish between levels of sweetness in the taste masking formulation. In the laboratory and used methods use sensors taste for this purpose [56].

Morphological Studies: A study scanning electron microscope (SEM) differences between the top side and bottom of the film. It also helps in determining the distribution of API. Near-infrared chemical, imaging helps [57] studies in determining the difference between the drug distributions in films drug load and crystallization [40].

Mechanical Properties: The evaluation of the mechanical properties of chips is done by using the TA equipment XT2 texture analyzer equipped with a 5 kg load cell. Held between the chips and put it between 3 cm clamps.

During the measurements, the strips were pulled at a rate of 2 mm/sec. It was measured strength and elongation at chip intervals [58].

Analysis of Wafers:

Weight Uniformity: Weight uniformity was used to measure the reproducibility of the wafer production process. Wafers individually are weighed, and standard deviations are calculated. All experimentation was carried out in triplicate. The reproducibility of the production way was performed by the low standard deviations (SD) calculated from the mass for each of the various polymer systems.

The results obtained from the various polymer wafer systems are shown. Mean weight of wafers formulated (N=3) [59]. The standard deviation of the samples is shown to be low, but slightly increased values were observed for polymers such as pectin and PEO. This may be referring to the high viscosity of the initial solution, and therefore, greater variability in the production process.

Gelation of Matrices: The main aim of this study was to form a rapidly dissolving wafer system. Thus, the matrix formation characteristics needed assessment and formed the basis for the selection of a suitable polymer. Gelation of the dosage form can make the disintegration and ultimately the release of active substance late. A novel method was developed to assess the matrix forming profiles of the wafers. Wafers are weighed before being put in a Petri dish (diameter 85mm, depth 10 mm) containing 20 ml of simulated saliva (pH 7.1). The Petri dish was agitated for 30 sec on a Vortex-Genie 2 on the lowest setting. The contents of the Petri dish were sieved across a stainless-steel mesh (pore size 1mm).

Then determine the mass of the remaining residue on balance and then use it to calculate the rate of matrix formation. The simulated saliva solution contains 2.38g Na_2HPO_4, 0.19g KH_2PO_4, and 8g NaCl in 1000 ml of deionized water [61].

Determination Limits for Formulation Variables: Determinations of lower and upper limits are done using trial and error methods. Wafers of different polymer and diluents concentrations (up to 30% w/v of each) were carried out and inspected visually. Polymers such as sodium alginate, pectin, and PEO will be made to form a gel-like substance when hydrated and agitated rather than undergo disintegration.

Sodium alginate introduces the highest amount of residue, possibly because of its low water solubility. In contrast, the highly hydrophilic polymers such as HPC were completely disintegrated within 30 sec into small particles which were capable of crossing through the pores on the sieve. The mass of intact material after sieving of the various dissolved wafers tests are done to the mass of intact material after sieving of the various dissolved wafers. Depending on the results obtained, HPC was set as the most suitable polymer for the wafer system, as there is no residue was produced after 60 sec of hydration and agitation in simulated saliva. This may be assigned to the fact that HPC is highly soluble in polar solvents, so it undergoes disintegration rapidly without forming a gel residue, making sure of rapid matrix disintegration [62].

Development of the Manufacturing Process: To establish the suitability of mold in terms of ease of the system removal, well plates, blister packs, and disposable polystyrene trays were estimated. To get rid of problems of wafers sticking to the mold, different lubricant systems were considered. Magnesium stearate, span 60, maize oil, and mineral oil were determined for their anti-adhesive properties. It was also necessary to determine suitable timeframes for the lyophilization process [59].

Established Parameters of Formulation Variables 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 as wafers of higher polymer concentrations were hard to take off from the mould. Some wafers have been produced with polymer concentrations below 5%w/v collapsed. Less than 1% w/v of HPC was not good for the formation of the wafer matrix [55].

The concentration of Diluents: The concentration of the diluents affects both the solubility and textural properties of the matrices. Both lower and upper limits were determined to be 1% w/v and 5% w/v respectively. Concentrations of lactose higher than 5% w/v caused the wafer to be powdery and be fragile [33].

Type of Molds: The main problem that was encountered was the elimination of the wafers from the molds with no disrupting the delicate structure. The most successful and known mold is Polystyrene trays which have minimal deformation of the final product as these molds can be easily split down the middle to release the wafer.

Type of Lubricant: As we mentioned above, the wafers extracted from the mold was seriously problematic. Mineral oil introduces the greatest ease of elimination of the product when compared to the other lubricants analyzed, imparting minimal hydrophobicity and having no effect on the taste of the final product not like other substances such as maize oil [54].

Freeze-Drying Parameters: The wafers are prepared to be dry after a time of 24 h, but their melting and discoloration of its material take place on storage. This was attributed to moisture that exists within the products, indicating that the freeze-drying process needed to be conducted for a more period. In future processes, this will be increased to 48 h [33].

CONCLUSION: Buccal drug delivery has very high patient acceptance when we compare it with other routes of drug administration. It has a fast onset of action than another oral route, also it helps to avoid the pain associated with injections. Buccal drug delivery provides more quick and effective absorption way. Side effects of the oral route will be avoided as nausea and vomiting. The good point is that the drug reaches the blood rapidly in cases of the unconscious, less co-operative patients, and in emergency cases. Oral administration is a route of administration where a substance is taken through the mouth Wafers are a new drug delivery system for the oral delivery of the drugs. They are a very thin layer that makes the drug to dissolve rapidly in the mouth. These dosage forms are taken orally but not swallowed as they dissolve rapidly in the oral cavity and reach the bloodstream then the active ingredient is released with no change in the drug concentration. Wafers are divided into 3 types: flash release wafers, mucoadhesive melt away wafers and mucoadhesive sustained release wafers. That dosage form has many advantages as the drug will not be affected with first pass effect or PH of the stomach, so it reaches the blood vessels without a change in its concentration. The worse part of that dosage form is the expensive costs of packaging.

ACKNOWLEDGEMENT: Thanks to October University for Modern Science and Arts, MSA University.

CONFLICT OF INTEREST: Nil

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How to cite this article:
Mostafa DA: Wafer technology as a novel drug delivery system. Int J Life Sci & Rev 2019; 5(3): 30-41. doi: 10.13040/IJPSR.0975-8232.IJLSR.5(3).30-41.