International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1604-1617 www.ijprajournal.com ISSN: 2249-7781

Medicated Buccal Wafers as a Novel Approach for Drug Delivery

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Submitted: 15-05-2023 Accepted: 30-05-2023

ABSTRACT
The challenge in producing a dosage form to enhance patient appeal and compliance with a specific type of drug delivery system has increased. The dosage form is the most agreeable and pleasant form due to the wafer's thinness and small size. For paediatric and elderly patients, oral wafers act as an alternative to tablets, capsules, and liquid oral dosage forms. The buccal wafers are the most practical and appropriate dosage form in the attachment with the buccal layers. Buccal wafers can be produced from natural or semi-synthetic polymers and patients prefer them over other dosage forms because they are simple to use, affordable, fast-acting, and non-irritating. When compared to fast-dissolving tablets, it improves drug's efficacy by dissolving in the oral cavity following contact with saliva within minutes without chewing or the requirement of water for administration. This article provides an extensive review of the advantages, disadvantages, production techniques, evaluation factors and formulation of the buccal wafer.

KEYWORDS: Medicated wafer, Buccal drug delivery, Buccal mucosa, Solvent casting

I. INTRODUCTION

Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, mainly to those drugs that undergo first-pass metabolism and is used for increasing the bioavailability by reducing dosing frequency to mouth plasma peak levels, which results in minimizing the adverse effects [1].

Additionally, the buccal route offers potential routes for the absorption of hydrophilic and unstable proteins, oligonucleotides, complex, high-molecular-weight polysaccharides and conventional tiny drug molecules [2].

It is also affordable and effective in geriatric and pediatric patients. In addition, wafers have improved patient compliance due to their small size and reduced thickness, compared to lozenges and tablets [3].

Over the past ten years, the use of oral cavity membranes as the location for drug administration has increased. It is known that the therapeutic compounds which are absorbed from the oral mucosa offer the direct entry of the drug into the bloodstream, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are connected to perioral administration [4]. In terms of comfort and flexibility, wafers might be preferred to buccal tablets. Wafers will have direct contact the systemic circulation via the internal jugular vein, resulting in excellent bioavailability. Additionally, these dosage forms offer greater patient compliance, are self-administrable, and are pharmacoeconomic [4].

The delivery system consists of a postage stamp-sized thin film, which is placed on the patient's tongue or mucosal tissue, where it immediately hydrates by absorbing saliva; the film is then quickly dissolved and disintegrated to release the drug for oral mucosal absorption. This fast dissolving activity is mainly caused by the film's substantial surface area, which quickly becomes wet when exposed to the moist oral environment [5].

Much attention has been given to the idea of mucoadhesion, which entails a pharmaceutical formulation containing mucoadhesive hydrophilic polymers along with the active pharmaceutical ingredient (API) to provide site-specific drug delivery. The formulation will be "held" on a biological surface for targeted drug administration and the API release will take place nearby the site of action which leads to increasing bioavailability [6].

Anatomical and Physiological Considerations:

As the cells move in proximity to one another, the oro mucosal region acts as a lubricant and an adhesive, minimizing friction. The buccal

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cavity, lingual region, palate, and gingival region are the four areas where medications are administered. Among the four sites mentioned above, the buccal route is the one that is most usually used for medication administration. The term for the anatomic site for medicine distribution located between the cheek and gingiva is the buccal mucosa [4].

The oral mucosa is made up of an exterior layer of stratified squamous epithelium, a basement membrane, a lamina propria, and the submucosa as the innermost layer[7]. The epithelium is comparable to the rest of the body's stratified squamous epithelia which has a mitotically active basal cell layer that advances through several differentiating intermediate layers to the superficial layers, where cells shed from the epithelium's surface. The buccal mucosa epithelium is 40-50 cell layers thick, whereas the sublingual epithelium is slightly thinner. As they move from the basal to the superficial layers, epithelial cells grow larger and flatter[8].

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. The permeability of the buccal mucosa is thought to be 4–4000 times larger than that of skin [9]. Because of the unique shapes and functions of the different oral mucosa, there are significant variances in permeability between different parts of the oral cavity, as seen by the wide range in this reported value [10]. The so-called "membrane coating granules" (MCGs), which are intercellular components, are primarily responsible for the oral mucosa's permeability barrier feature. The membrane-coated granules (MCGs) migrate to the cell's apical surface, where their membranes fusion with the cell membranes causing the lipid content to be ejected into the extracellular space [11].This barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using some of very large molecular weight tracers, such as horseradish peroxides and lanthanum nitrate[8]. In general, oral mucosa permeability decreases in the sequence of sublingual more than buccal and buccal greater than palatal. The sublingual mucosa is comparatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized [12].

A mucus layer covers the surface of the epithelial layer of cells. This has a significant impact on cell-to-cell adhesion, oral lubrication, and mucoadhesion of mucoadhesive drug delivery systems. The buccal area has a smooth, relatively immobile surface that is ideal for the placement of a retentive system. Adhesion to the oral mucosa allows for not only the intimacy of contact and the possibility of improved drug absorption for buccal drug delivery but also the ability to achieve an optimal residence time at the site of administration [4].

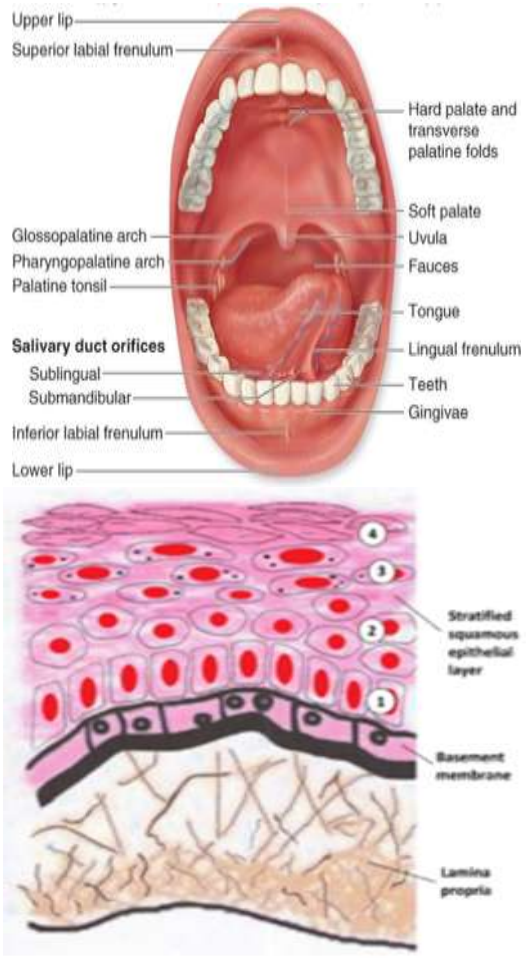

Fig. No. 01: Anatomy of oral mucosa

Advantages of Buccal drug delivery

- Bypassing the gastrointestinal tract and the hepatic portal system, improves the bioavailability of oral medications that would otherwise undergo degradation via hepatic first-pass metabolism[13].
- Better patient compliance as a result of the absence of injection-related pain [13].
- Long-term medication delivery[13]

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- Compared to the oral route, a relatively quick onset of action is possible, and the formulation can be removed if the need arises to stop the therapy [13].
- Simplified drug administration [13].
- The oral cavity's large contact surface aids in the quick and thorough absorption of drugs [13].
- Greater perfusion results in more rapid and efficient absorption [13].
- Vomiting and nausea are greatly reduced [13].
- Employed when a patient is unconscious and uncooperative [13].
- Drugs that exhibit low oral bioavailability can still be administered easily. For instance, drugs that are metabolized poorly in the alkaline or enzymatic environment of the intestine or that are unstable in the acidic environment of the stomach [13].
- When compared to other forms, modification by adding permeability enhancers and protease inhibitors to improve the delivery of high molecular weight substances such as peptides, proteins, and ionized species is simple [14].

Disadvantages of buccal drug delivery [13]

- Drugs that irritate the oral mucosa, have a harsh taste, create allergic reactions, or cause tooth discoloration cannot be manufactured.
- If the formulation contains antibacterial medicines, it impacts the natural microbes in the buccal cavity.
- This route can only be used to provide medications that are absorbed through passive diffusion.
- This route cannot be used to give drugs that are unstable at buccal pH.
- Swallowing saliva may also result in the loss of dissolved or suspended medication.
- The buccal membrane has a low permeability as compared to the sublingual membrane.

Why Buccal Delivery

The oral mucosa is less sensitive than other types of mucosa because of irritation and impairment. The buccal and sublingual mucosa serve as absorption sites for transmucosal medication delivery, which has two curative objectives. Drug distribution is typically accomplished using it because of its great mucosal permeability. The buccal method is typically used when a continuous release of the active ingredient is required, as in the case of chronic illnesses [15].

The activity of the tongue interferes with the contact of the dosage form to the mucosa, which is worsened by the surface being constantly washed by saliva. The buccal process has greater potential for the placement of a control release system, which the patient also tolerates well. The buccal mucosa is flushy and has a fixed surface when compared to sublingual mucosa. These characteristics make it an appropriate site for controlled drug delivery in various chronic systemic treatments [16].

Mechanism of action of wafers

Wafers are placed on the tongue or any other oral mucosal tissue of an individual. Because of the presence of hydrophilic polymer and other excipients, they are quickly moistened by saliva; the film rapidly hydrates and dissolves to release the drug for mucosal absorption [17].

Fast-dissolving drug delivery systems were originally developed in the late 1970s as an alternative to traditional paediatric and geriatric dose forms. These systems are meant to dissolve or disintegrate rapidly in saliva, often in less than 60 seconds [18].

Fig. No. 02: Image of wafer placed on cheek

Wafer – It is an innovative oral dosage form

Wafers, or novel oral thin films, provide new options for action profiles and patient compliance. Wafers the paper-thin polymer films utilized as drug delivery systems. The novel dosage form is swallowed without water and is administered orally [19].

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Fig. No. 03: Image of wafer

Effective absorption of active ingredient

The wafer immediately dissolves in the mouth, and the oral mucosa allows the active substance to enter the bloodstream. By passing the liver's first-pass action after being absorbed by the oral mucosa, the active component increases bioavailability. The release of the active component can also be extended depending on the wafer type that was chosen. In this instance, it is swallowed and then absorbed through the digestive system [20].

Ideal features of wafers [21]

- It has to taste excellent.
- Drugs should be extremely moisture-resistant and saliva soluble.
- It should be able to penetrate the oral mucosa
- It should be having an adequate tension resistance
- It should be ionized in the oral cavity pH.
- It should be having a quick action.

Benefits of wafers [22]

- There is no need for a special industry setup.
- There is a larger surface area, which promotes rapid disintegrating and dissolution in the oral cavity as well as systemic absorption of APIs.
- There is no need for water or a spoon during administration, and chewing is not necessary.
- The dose is more accurate than with syrup.
- Reduced hepatic first-pass effect.
- Lower doses
- Minimal side effects
- Avoidance of the destructive acidic environment of the stomach
- Relatively simple termination of delivery if necessary.
- Localized and site-specific activity
- Non-invasive

Drawbacks of wafers [23]

- Unpleasant-tasting drugs must be avoided, or inert chemicals must be used for masking the taste of bitter API.
- The administration or incorporation of greater doses is restricted.
- Mucosal irritants should not be delivered in this way of delivery.
- Saliva contains a proteolytic enzyme, which must be suppressed in the case of protein-based medications using enzyme inhibitors.

Type of wafers [17]

There are three subclasses:
1. Flash release wafers
2. Mucoadhesive Melt away wafers
3. Mucoadhesive Sustained release wafers

Flash release wafers

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

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.

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.

Objectives of formulating wafers [24]

- To increase patient compliance and offer an immediate effect.
- To minimize the API's adverse effects by lowering the dose.

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- To improve the compound's oral bioavailability.

Formulation consideration [25]

Buccal films with a surface area of 1-3 cm^2 are preferred. According to estimates, a 2 cm^2 device has a daily medication delivery capacity of between 10 and 20 mg over the buccal mucosa.The form of the delivery device can also vary, although an ellipsoid shape appears to be best for buccal medication administration.

1. Drug substances (API) 5-30%
2. Wafer forming Polymer 45%
3. Plasticizer 0-20%
4. Saliva stimulating agent 2-6%
5. Surfactant Q.S.
6. Sweeteners 3-6%
7. Flavours, Colours, Fillers Q.S

Active pharmaceutical ingredients (APIs) [26]

Because the thin films need to be small enough to be placed on the tongue, active pharmaceutical components with high doses are not appropriate candidates for integration into oral thin films.

Ideal characteristics of APIs to be incorporated into wafers [19].

1. The drug should have good taste.
2. The drug that is incorporated should have a small dose.
3. Contains a low to moderate molecular weight.
4. Excellent water and saliva stability and solubility.
5. Unionizes partially at the pH of the oral cavity.

Wafer forming polymers [27]

Water-soluble polymers are employed as film formers because they provide the films with fast disintegration, a pleasing mouth feel and durability. Polymers can be employed alone or in conjunction with other materials to provide desirable film qualities such as hydrophilicity, flexibility, mouth feel, and solubility. The rate of polymer disintegration reduces as the molecular weight of polymer film bases increases.

Polymers used in oral thin films should be [28]:

- It must be non-toxic and non-irritant
- It must be hydrophilic
- It must have excellent film-forming ability
- The polymer must be good at wetting and spreading.
- Polymer should be broadly available and reasonably priced.
- Polymers should have a small molecular weight.
- It should have a sufficient shelf life.
- The polymer must have no taste or color.
- It must not cause secondary infections in the oral mucosa and must have adequate peel, shear, and tensile strengths.

Currently, both natural and synthetic polymers are used as film-forming agents.

Natural polymers- Starch, Pectin, Gelatin, Sodium alginate, Maltodextrin, Pullulan, Xantan, Polymerized rosin, Gum acacia.

Synthetic polymers- Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Polyethylene oxide, Hydroxy propyl cellulose, Polyvinyl pyrollidone, Poly vinyl alcohol, Hydroxy ethyl cellulose, Kollicoat[29].

Backing membrane [13]

The backing membrane is essential for the adherence of bioadhesive devices to the mucus membrane. The backing membrane materials should be inert and resistant to the drug and penetration enhancer. The use of an impermeable membrane on buccal bioadhesive patches avoids drug loss and improves patient compliance.

Plasticizer

Plasticizer is an essential component of the wafer formulation. It aids in the improvement of the strip's flexibility and decreases its brittleness. Plasticizer significantly improves strip properties by lowering the polymer's glass transition temperature [30].

This polymer exaggerates the mechanical properties of the film.

The accumulation of plasticizers improves mechanical properties such as tensile strength and film elongation [31].

Some of the most commonly used plasticizer excipients are glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin, and castor oil. Inappropriate plasticizer use may lead to blooming, film cracking, splitting, and peeling of the wafer [32].

Penetration enhancer

The primary barrier in preventing many drugs from forming plaques on the cheeks is membrane penetration. The oral cavity's epithelium

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acts as a highly effective barrier towards drug absorption. Mucous membranes are known as penetration enhancers [33]. When an API must enter the systemic circulation via the buccal mucosal pathway to exert its activity, permeation enhancers are also necessary [34].

Drug release is enhanced by penetration enhancers. They also make it simpler for drugs to enter living tissues through systemic administration. The following explains the way penetration enhancers work: Mucus rheology changes, Increases the double-layer lipid membrane's fluidity, Affects components in close contact, the enzymatic barrier has to be broken, Boost the drug's thermodynamic activity [33].

There are many chemicals that can increase penetration, including surfactants (like Tween), fatty acids (like oleic acid), terpenes (like eucalyptus), solvents (like ethanol), and fatty acids. Others include bile salts, azone, chitosan and its derivatives, as well as polymers having the ability to increase mucoadhesion and penetration[35].

Surfactant [36]

Surfactants can be used in a number of ways, such as a solubilizing agent, an emulsifying agent, and a dispersion agent. In general, nonionic surfactants are recommended. Tweens, Sodium Lauryl Sulphate, Cremophor, and Polaxomer are some of the frequently used surfactants.

Stabilizing and thickening agents [3]

The addition of stabilizing and thickening agents is necessary to increase the viscosity and consistency of the film preparation dispersion or solution prior to casting. Stabilizing and thickening agents include natural gums such as xanthan gum, locust bean gum, carrageenan, and cellulosic derivatives. They can be employed at concentrations of up to 5%w/w.

Saliva-stimulating agents

The use of saliva-stimulating substances is intended to boost the rate of saliva production, which will aid in the more rapidly disintegration of the rapid-dissolving strip formulations. In general, acids employed in food preparation can be used as salivary stimulants [37].

Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are a few of examples. These agents are employed alone or in combinations ranging from 2 to 6%w/w of the wafer's weight [38].

Sweetening agent

Sweetening compounds are required in mouth-dissolving formulations to improve product palatability. Natural and artificial sweeteners are two forms of sweeteners that can be used alone or as part of a blend in concentrations ranging from 3-6% w/w [39].

Natural sweeteners include fructose, glucose, honey, mannitol, sorbitol, liquorice, and glycerol sucrose, but artificial sweeteners can be both nutritive and non-nutritive.

Artificial sweeteners include nutrients such as maltose, fructose, and glucose, as well as polyols such as mannitol, sorbitol, maltitol, erythriol, and xylitol. Sucralose, saccharine, neotame, and aspartame are examples of non-nutritive sweeteners; trehalose and tagatose are examples of novel sweeteners [23].

Flavoring agents

Flavoring agents can be chosen from synthetic flavor oils, oleo resins, and extracts produced from various plant components such as leaves, fruits, and flowers. Flavors can be used singly or in combination [40].Flavor oils include peppermint oil, cinnamon oil, spearmint oil, and nutmeg oil, while fruity flavors include vanilla, cocoa, coffee, chocolate, and citrus. Fruit essences include apple, raspberry, cherry, and pineapple [37]. The amount of flavor required to completely mask the taste is determined by the flavor type and strength [40].

Coloring agents [22]

A wide variety of colors, including FD and C colors, EU colors, natural colors, and customized Pantone-matched colors, are also available, along with pigments like titanium dioxide.

Manufacturing methods [41]

Various methods for producing oral wafers are classified

I. Conventional Method

a. Casting Method
- Solvent casting
- Semi-solid casting

b. Extrusion Method
- Hot melt
- Solid Dispersion

c. Rolling Method

II. Non- conventional Method

a. Inkjet Printing
- Continuous Inkjet Printing (CIP)

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- Drop on Demand Printing (DoD)

b. Flexographic Printing

I. Conventional Method

Solvent Casting method [42]

The solvent casting method is now the most favored manufacturing approach for the production of oral thin films. In this method of preparation, both the water-soluble polymer and the plasticizer are dissolved in distilled water [43]. The above solvent mixture was left overnight, then triturated until uniformly distributed, at which point glycerine was added to create a gel. To prevent air bubbles from becoming entrapped inside the patch or film, the entire gel was exposed to vacuum desiccators to remove bubbles. The gel was then poured into glass molds lined with aluminum foil, which allowed gel casting for 24 hours. After the films become dry, they are cut, stripped, and packaged. Films of appropriate size and shape can be cut. The widely available sizes are 3 x 2 cm^2 and 2 x 2 cm^2 [44].

The solvent casting method involves the steps which are described below [45],

Step 1: Preparation of casting solution
Step 2: Deaeration of the casting solution
Step3: Transferring the deaerated casting solution into the mold
Step 4: Drying the solution
Step 5: Cutting of dried film into proper dimensions
Step 6: Packaging of formed films

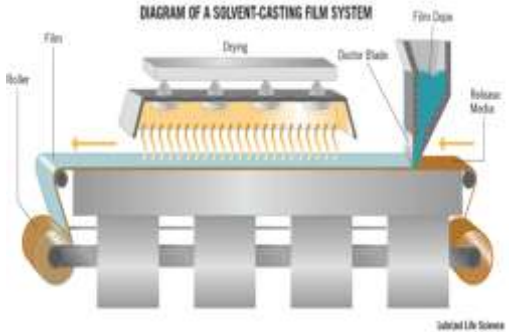

Fig. No.04: Solvent caster

Advantages [17]

- Better thickness uniformity and clarity than extrusion.
- Wafer has fine shine and is free of defects such as die lines.
- Wafers are more flexible and have better physical qualities.

Disadvantages [17]

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with an acceptable minimum solid content and viscosity must be generated.
- Depending on the fluid rheology, desired applied mass, and dose homogeneity, multiple casting procedures may be used.
- Homogeneous formation and release from the casting support must be achievable.

Semi-solid casting method

In the semi-solid casting procedure, a solution of a film-forming polymer that is water soluble is first made. A solution of an acid-insoluble polymer (such as cellulose acetate phthalate or cellulose acetate butyrate), produced in ammonium or sodium hydroxide, is added to the resultant solution. After that, the proper quantity of plasticizer is added to create a gel mass [46]. Finally, using heat-controlled drums, the gel mass is cast into the films or ribbons. The thickness of the film is between 0.015 - 0.05 inches. The ratio of film-forming polymer to acid-insoluble polymer should be 1:4 [47].

Hot melt extrusion method [48]

Hot melt extrusion is a process that involves extruding a mixture of drugs, polymers, and excipients at high temperatures to generate a homogeneous mass that is then cast to make smooth films. Although this is a solvent-free technique, the processing of thermo labile compounds is a considerable drawback due to the use of high temperatures during extrusion.

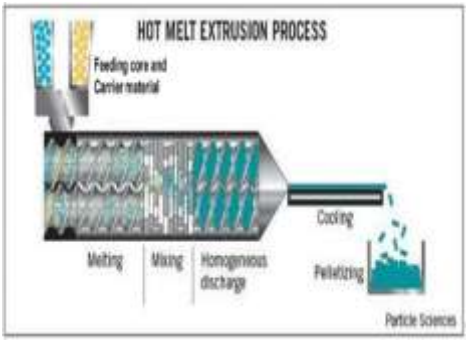

Fig. No. 05: Hot melt extruder

Advantages [17]

- There is no need to use a solvent or water.
- A reduction in the number of processing steps.
- The API's compressibility qualities may be unimportant.

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- Improved dispersion and bioavailability for poorly soluble medicines.
- More consistent fine particle dispersion due to less vigorous mixing and agitation.
- Uses less energy than high-shear processes.
- A cost-effective procedure that requires minimal processing time and unit operations.

Disadvantages [17]

- Thermal deterioration as a result of high temperatures.
- A lower melting point binder increases the possibility of melting/softening of the binder during the handling and storage of agglomerates.
- Higher melting point binders need a high melting temperature, which might contribute to volatility issues, particularly in heat-labile materials.
- Polymer flow characteristics are critical for processing.

Solid dispersion extrusion method

The term "solid dispersions" refers to the dispersion of one or more active substances in a chemically inactive carrier in the presence of amorphous hydrophilic polymers in a solid state [39].

1. In this technique, one or more active chemicals are transported in a solid state in an inert carrier in the presence of amorphous hydrophilic polymers.
2. To form a solution, API is dissolved in a suitable solvent.
3. Without removing the liquid solvent, the solution is added to the melt of a suitable polymer (PEG) at temperatures below 70°C.
4. Finally, solid dispersion is formed into films using dies [50].

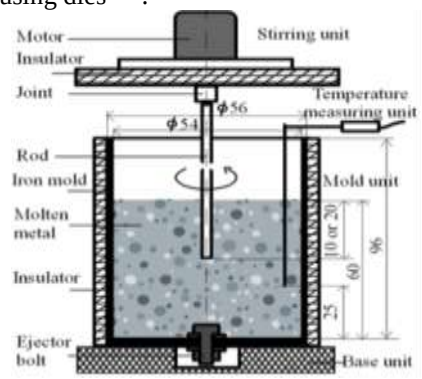

Fig. No. 06: Solid dispersion extruder

Advantages [17]

- Fewer steps of processing.
- Because of the vigorous mixing and agitation, fine particles are dispersed more uniformly.

Rolling Method

Water and water-alcohol mixtures are the principal solvents employed in this approach. The active component and other ingredients are dissolved in a tiny amount of aqueous solvent using a high-shear processor [32]. Hydrocolloids that are water-soluble are dissolved in water to create a homogeneous, viscous solution. The drug-containing solution or suspension is then rolled onto a carrier. The finished film is then cut into the required shapes and sizes [51].

II. Non- conventional method [52]

The development of 3D printing technology as a platform for producing pharmaceutical products has acquired great momentum in recent years. The following benefits over traditional techniques of production exist due to the adoption of these technologies for the fabrication of wafers:

i. Accuracy in drug loading, particularly when using potent drugs that are given in tiny doses.
ii. Compatibility with many API types, including proteins, peptides, and those that are not extremely water-soluble.
iii. The OTF's homogeneity, which is difficult to produce using traditional approaches.
iv. Cost-cutting results from effective recycling and less waste.

Inkjet Printing

Inkjet printing is a computer printing procedure that converts digital pictures created on the computer into three-dimensional objects by pushing droplets of ink onto chosen surfaces. Inkjet Printing may be separated into two major groups when it comes to pharmaceutical applications.

i. CIP (Continuous Inkjet Printing)
ii. DoD (Drop on Demand Printing) [52]

In the CIP technique, the drops are created by a transducer or a droplet-loading device that emits a steady stream of droplets. To achieve the desired charge, the droplets are then directed towards an electrically charged element. The formed droplets then touch the substrate to produce the final 3D product [53].

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When voltages are applied in DoD printing, droplets are created in numerous nozzles due to a change in the structure of a piezo-electric substance in the ink chamber that produces a pressure wave in the ink [52].

Flexographic printing technique

Flexographic printing technology is based on the contact printing principle. This printer is made up of a fountain roller that transports the ink, which contains API in suspension or solution form, to an Anilox Roller. This roller accurately determines the volume of ink required for a consistent thickness to the plate cylinder, which contains a polymeric strip. By applying pressure, ink is applied to the polymeric strip [41]. However, due to the need for organic solvent (in a higher ratio) for drug solubilization and the inherent risk of precipitation and activity loss, flexographic printing is difficult to use in the pharmaceutical industry [54]. Moreover, it must be ensured that the employment of these methods does not alter the therapeutic or physicochemical features of the loaded medication [41].

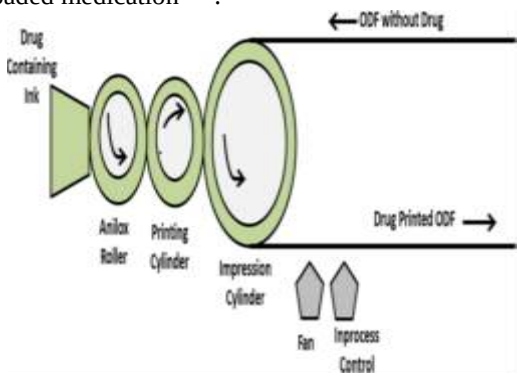

Fig. No. 07: Flexographic printer

Evaluation parameters of wafers

Organoleptic evaluation [17]

Due to the longer residence time in the oral cavity, this step is crucial in the majority of oral formulations. The product must possess the desired characteristics of sweetness and flavor that are acceptable to a large portion of the population. The ability to differentiate between different sweetness levels in taste-masking formulations has also been demonstrated in experiments using electronic tongue measurement. To achieve this, taste sensors are being used in in vitro methods.

Morphological studies

Electron microscopy can be used to investigate the surface characteristics of film between different excipients and drug scanning [55]. Additionally, it aids in figuring out how the API is distributed. A study using near-infrared chemical imaging (NIR-CI) may help in distinguishing between recrystallization and drug distributions in drug-loaded films [56].

Wafer thickness

The thickness of the wafer should be determined using a micrometer screw gauge or Verniercalipers[55]. Wafers should be measured at five different locations, including the center and four corners, and the mean thickness calculated. The experiment has to be conducted on six strips of each formulation, with the maximum variation in wafer thickness being less than 5% and the mean S.D. calculated. The maximum wafer thickness is less than 5% [57].

Weight variation [58]

By weighing each wafer separately, wafers that were chosen at random were used in the mass variation study of the wafer. Each batch's average of five observations was calculated. These assessments were made for each batch.

Surface pH study

Examining the pH of the film is essential because the surface pH of a wafer may damage the oral mucosa. The pH of the wafer's surface needs to be around 7 or neutral [43]. For this, a combined glass electrode was employed. The patches were kept in contact with 1 ml of distilled water (pH 6.6± 0.2) for 15 minutes at room temperature to allow them to swell. The pH was measured by placing an electrode in contact with the patch's surface and letting it to equilibrate for 1 minute [59].

Tensile Strength

The highest stress at which a film will break is known as the tensile strength. This test determines the mechanical strength of films [60]. The following equation was used to determine the load responsible for the film's deformation and rupture [61]:

$$\text{Tensile strength} = \frac{\text{Weight placed on pan the along with clip (kg)}}{\text{Width of the film (cm)}} \times \text{Thickness of the film (cm)}$$

- Unit Kg/cm²
- Multiply Kg/cm² by 0.098 (acceleration due to gravity) to get N/mm².

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1604-1617 www.ijprajournal.com ISSN: 2249-7781

Folding endurance

Three wafers of each formulation are cut to the required size with a sharp blade. Folding endurance is measured by repeatedly folding the film in the same spot until it breaks [62]. The value of folding endurance is determined by the number of times the film can be folded at the same location without breaking [63].

Swelling index [62]

After the measurement of the original film weight and diameter, the samples are permitted to swell on the surface of an agar plate in an incubator with a temperature of 37º± 0.2º C. At different time intervals (1-5 h), the weight of the films (n=3) is determined. The following equation is used to calculate the percent swelling:

$$\textbf{Percent swelling}[\%S] = \frac{Xt - Xo}{Xo} \times 100$$

Where, Xt= The weight of the swollen film after time t,

Xo= The initial film weight at zero time [64].

Percent elongation [65]

When the film ruptures, enough force is applied to exceed the elastic limit and the percent elongation is measured.

Percentage elongation can be obtained by following equation [66].

$$\textbf{Elongation at break (\%)} = \frac{\text{Increase in length at breaking point (mm)}}{\text{Original length (mm)}} \times 100$$

Dryness / Tack test

Tack is the strength with which the film sticks to any piece of paper that is pressed into contact with the strip, whereas dryness is the property that determines the solvent or water content that exists in the film [67]. It has been determined that there are eight distinct stages in the drying process for films: set-to-touch, dust-free, tack-free, dry-to-touch, dry hard, dry-through, dry-to-recoat, and dry print-free [68]. These properties can now be determined with many different instruments. At the lab scale, it can be accomplished by pressing the thumb against the film [68].

Moisture Uptake [69]

The wafer's moisture uptake was determined by exposing it to a temperature of 40 °C and 75% relative humidity for one week. The percentage increase in weight was used to calculate the wafer's moisture uptake.

$$\textbf{\% moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity [70]

The strip was placed in a 100 ml volumetric flask with 100 ml of phosphate buffer pH 6.8 and allowed to dissolve for 24 hours at room temperature with the stirrer kept at 37 °C for 3 hours. The filtered solution had been diluted and subjected to a triplicate UV-VIS spectrophotometer analysis to determine the average drug content.

In vitro diffusion studies

Franz diffusion cell assembly was used to conduct an in vitro diffusion study. It has two compartments: a donor compartment that contains wafers and a receptor chamber that contains a PBS solution with a pH of 6.8. Prior to this, a dialysis membrane (molecular size 12000–14000) was soaked for 24 hours. To prevent interference with the process, a dialysis membrane was placed in contact with a receptor compartment that had been filled with PBS. It was carefully checked that there were no air bubbles between the membrane and the PBS liquid surface. Using a magnetic stirrer, the temperature was maintained at 37± 0.5 °C at 50 rpm [61]. At intervals of 15 min, 30 min, 45 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, and 24hr about 0.5 ml of the sample was taken out from the receptor chamber side tube and equilibrated with a new or fresh dissolution medium to maintain sink condition. A suitable dilution procedure was followed, and the results were examined spectroscopically using UV-visible spectroscopy [71].

In vitro Dissolution test

The dissolution test is often performed using the Pharmacopoeia recommended dissolution assembly [68]. The medium chosen is determined by the sink conditions and the maximum drug dose. Basket assembly is often used because, in the case of paddle apparatus, the wafer can float in the medium, causing problems during testing. Dissolution tests were carried out in triplicate [23].

Disintegration test[72]

A film was placed in the petri dish to determine the disintegration time. The distilled water was poured over the film, and the time until it disintegrated was recorded.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1604-1617 www.ijprajournal.com ISSN: 2249-7781

Stability test

Stability is measured by keeping the wafer in a stability chamber for 12 months under controlled conditions of 25°C/60% RH and 40°C/75% RH according to the ICH recommendation [73].

The films are evaluated for drug content, disintegration time, and physical appearance at predetermined time intervals [66].

II. CONCLUSION

Wafers as an orodispersible film have made their own position in the recent trend to achieve more palatable dosage forms, and have fulfilled the expanding demand. Wafers are designed as an enhancement to oral quick dissolving films due to their excellent absorption and bioavailability. It is popular among individuals of all ages, but especially among the elderly and children, due to its compatibility and pleasant taste.

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