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Review Article

# Recent Advances in Wafer Delivery: Chemistry, Manufacturing, and Control

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**Abstract**

Wafer drug delivery offers a promising approach to personalized medicine by enabling precise dosage adjustments, controlled release rates, and tailored drug responses. By carefully selecting the composition, wafers can optimize therapeutic outcomes for individual patients. The development of a wafer formulation involves choosing the appropriate active ingredients, excipients, and drug compounds, which directly impact stability, solubility, and release profile of the drug. This study addresses the essential components and characteristics required for formulating an optimized wafer product, alongside the critical control steps necessary for its evaluation. Additionally, the manufacturing process plays a key role in maintaining quality standards by ensuring consistent drug content, uniformity, and dissolution properties. Ultimately, thorough characterization and monitoring of wafer quality are vital to guarantee safety, efficacy, and stability. We begin by reviewing ongoing clinical trials and existing products currently available in the wafer market.

## Introduction

Wafer drug delivery is a method of administering medication through a thin, flat, and often edible wafer that contains the drug. These wafers are typically designed to dissolve or disintegrate in the mouth, allowing for the drug to be absorbed directly into the bloodstream through the oral mucosa due to requiring rapid absorption or covering the bitter taste of the drug. The lyophilized composite of polymers and plasticizers, including drugs, is commonly called a wafer The wafer rapidly disintegrates upon placement in the mouth, and the incorporated drug absorption occurs via either the transcellular or paracellular pathways.[1,2] Fast-dissolving products are oral wafers and thin films (strips). Oral wafers are further classified into flash-release wafers, mucoadhesive melt-away wafers, and mucoadhesive sustained-release wafers. These wafers can be differentiated based on their size, method of manufacture, number of layers, and site of usage factors.[3-5]

Oral thin films are developed to overcome the limitations of conventional oral and orally disintegrating dosage forms mainly due to their effect on patient compliance and successful pharmacotherapy.[6-8] The wafers are essential for improving patient compliance in cases of swallowing difficulties or needle fear. They offer several benefits, including faster disintegration, easy access to highly vascularized tissue, targeted drug release at the site of action, good mouthfeel, avoidance of first-pass metabolism, reduced side effects and gastric irritation, and lower variations in drug plasma levels. Furthermore, the buccal mucosa has lower enzymatic activity, and its tolerance for allergens or damage is remarkably high.[9]

Despite their numerous advantages, these carriers can be manufactured through highly moisturized methods, resulting in microbial contamination or degradation of sensitive active pharmaceutical ingredients (APIs). High doses of API cannot be incorporated into these products, as buccal films generally contain only 5%-30% of the API. Additionally, the handling and packaging of these carriers can be costly. There are also challenges associated with the use of bitter drugs, drugs that are unstable at oral pH, and mucosa irritants.[10,11] Like many other dosage forms, the absorption rate of wafers depends on the drug's physicochemical attributes, including its molecular

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size, and partition coefficient, being subject to enzyme-facilitated breakdown, alongside the target location of the drug inside the mouth region.[12,13]

Several lyophilized wafer formulations are particularly effective in treating acute symptoms such as migraine attacks (Table 1). For instance, rizatriptan (RZT) wafers can reduce migraine pain in 20-30 minutes, comparable to the effect of subcutaneous sumatriptan (SMT). Although the bioavailability of RZT is lower than that of subcutaneous SMT, its rapid onset of action makes it a popular choice among patients.[14] Rapid treatment is also essential in cases of prolonged seizures. Oral disintegrating tablet (ODT) for Clonazepam is as effective as rectal Diazepam, with no need for swallowing, which suits the seizure condition of complicated oral administration and reduces patient embarrassment associated with rectal administration. In another case, Loratadine wafers have improved bioavailability, resulting in several times more drug bioavailability than oral solution counterparts.[15] The ideal characteristics of an API include low-dose effectiveness, appropriate molecular weight, adequate lipid solubility, and partial unionization at the oral cavity pH.[16,17]

Clinical studies utilizing wafer delivery for prolonged-release formulations show the potential for customizing drug release profiles and maintaining consistent drug levels in the body over an extended period. This characteristic helps reduce variability in drug levels between individuals, which is crucial in clinical trials to ensure the reliability and safety of the results. Table 2 summarizes several clinical trials on wafer delivery with formulation type.

## Manufacturing methodologies

The manufacturing process of oral wafers involves three major steps: mixing, freezing, and drying. These steps must be carried out carefully to ensure the production of a stable product. For example, when dealing with encapsulated or coated particles, high-shear mixing should be avoided to prevent damage to the coating. In the laboratory, mixing is typically done using overhead mechanical stirring. However, for commercial-scale manufacturing, a larger container with temperature control and mechanically driven stirring is required. Hydrofoil or pitch blades are suitable for low-viscosity products, while planetary mixers are recommended for gelatin (GLN) formulations with higher viscosities.[18-20] Various approaches for manufacturing wafers are classified into major methods, including casting and drying, extrusion and rolling, and freeze-drying.

### *Casting and drying*

The casting and drying of oral wafers can be divided into two categories: solvent casting and semi-solid

**Table 1.** The available wafer products in the market

| API | Indication | Brand Name | Company |
|---|---|---|---|
| Metopimazine | Nausea and vomiting | Vogalene Lyoc® | Teva Santé |
| Ondansetron | | Zofran® Zydis® wafers | Aspen Global Incorporated |
| Cinnamon, vitamin C, benzocaine, and caffeine | Breath freshening *strips* | Altoid cinnamon strips, boots vitamin C strips, benzocaine films, and caffeine films | Dow chemical company |
| Listerine | | PocketPaks® | J&J |
| Piroxicam | Pain, inflammation, osteoarthritis, rheumatoid arthritis and ankylosing spondylitis | Feldene® Melt,and Proxalyoc® | Pfizer<br>Cephalon |
| Menthol, benzocaine | Pain relief for toothaches and painful gums | Orajel™ | Church & Dwight |
| Paracetamol | Pain fever | Paralyoc® | Cephalon |
| Brompheniramine maleate-phenylpropanolamine HCl | Antihistamine and decongestant | Dimetapp® ND (ODT) | Whitehall-Robins |
| Buprenorphine HCl | Opium family addiction | Espranor (Oral lyophilization) | Martindale Pharma |
| Clonazepam | Sedation, seizures, and acute panic episodes | Klonopin® (ODT) | Roche |
| Desmopressin acetate | Vasopressin-sensitive cranial diabetes insipidus And nocturnal enuresis | Noqdirna Oral lyophilisate / DDAVP Melt Oral lyophilisate / DesmoMelt Oral lyophilisate | Ferring Pharmaceuticals Ltd |
| Famotidine | Hearthburn, indigestion | Pepcidine Rapitab | Cardinal Health/Merck |
| Loratadine | Allergy | Claritin® Reditabs® | Schering |
| Loperamide | Diarrhea | Loperamide Lyoc®, and Imodium® | Teva Santé, Cardinal/J&J/ Mcneil products |
| Olanzapine | Schizophrenia | Zyprexa® Zydis® | Eli Lilly |
| Phloroglucinol | GI, biliary and urinary tract pain, ureteric colic and contraction during pregnancy | Spasfon-Lyoc® | Teva Santé |
| Risperidone | Schizophrenia | Risperdal® M-Tab® | Janssen |
| RZT benzoate | Migraine | Maxalt-MLT® | Merck |
| Selegiline | Parkinson disease | Zelapar® | Valeant/Bausch Health |
| *Chlorpheniramine and phenylpropanolamine* | Cough relief, rhinorrhea, nasal obstruction, and Itchy throat | Triaminic® | Novartis |
| Simethicone | *Gas relief* | Gas-X | |

**Table 2.** Clinical trials involving wafer delivery

| Case study | Formulation type | Clinical status | NCT No. |
|---|---|---|---|
| Evaluate the efficacy and safety of the SuvaroÂ®OD tablet in patients with dyslipidemia | ODT | Phase 4 | 06153433 |
| Efficacy, safety, and acceptability of Ivermectin ODT in Preschool-aged children (PSAC) | | Phase 2 | 06184399 |
| A study of galcanezumab (LY2951742) in adult participants with episodic migraine (Rimegepant) | | Phase 4 | 05127486 |
| Safety and efficacy of BHV-3000 ODT for the acute treatment of chronic rhinosinusitis (Rimegepant) | | Phase 3 | 05248997 |
| Cannabidiol use in pain reduction and opioid use after shoulder arthroscopy | | Phase 2/3 | 04672252 |
| Cannabidiol in pain reduction for knee osteoarthritis | | | 05020028 |
| Dexmedetomidine sublingual film for the ambulatory treatment of hyperadrenergic autonomic crisis in patients with familial dysautonomia | ODF | Phase 2 | 06148311 |
| Study of bisoprolol (Nerkardou-Nerhadou International) 5 and 10 mg treatment in Egyptian patients with essential hypertension | | Phase 4 | 05880056 |
| Pharmacokinetics and safety of Dolutegravir in neonate | ODF/ODT | Phase 1/2 | 05590325 |

ODF: Oral dissolvable film; ODT: Orally disintegrating tablet.

casting methods. The dimensions of the wafer product are usually up to 3 cm × 2 cm × 3 mm. Solvent casting is used to produce fast-dissolving wafers with sizes of 3-2 × 2 $cm^2$. Briefly, following the dissolving of water-soluble polymers in an aqueous vehicle and mixing with the drug, other excipients were added. The API can be either dissolved or dispersed in emulsion or suspension forms. Then, the solution is poured into a mold to achieve the desired shape, dried, cut, and packed. The drying process can be achieved through freeze-drying, vacuum-drying, and heat-drying (Figure 1). Solvent casting offers better physical properties and uniformity of thickness compared to other methods, such as extrusion. The resulting wafers are also free from defects such as die lines. However, this method requires the use of a polymer that is soluble in a volatile solvent or water, which may limit its applicability. The method produces defects (die lines)-free wafers; however, it necessitates utilizing a polymer soluble in volatile solvents or water, potentially limiting its applicability.[21] The semi-solid method is used to produce quick-release wafers with a size range of 0.381-1.27 mm. To fabricate these wafers, plasticizers are added to the acid-insoluble polymer solution to form a gel mass, which is then molded into the desired wafer shape. The acid-insoluble polymer solution for this process can be prepared by mixing cellulose acetate phthalate or cellulose acetate butyrate with sodium or ammonium hydroxide solution in a 1:4 ratio (Figure 1).[22]

### *Hot-melt extrusion (HME)*

In HME, the active ingredient and other components, such as binders and plasticizers, are blended in a dry state, heated, and subsequently extruded. Following solvent removal, the resultant strips, which are predominantly in a solid dispersion form, are cooled and then precisely cut into the desired shape (Figure 2). The temperature in HME is usually 85-95°C, but the range is determined according to the individual production aiming towards specific characteristics for extrudate.[23,24] HME offers several advantages, such as eliminating the need for solvents, reducing the number of processing steps and unit operations, and minimizing energy consumption compared to high-shear procedures. This economical or commercially modest method also yields a more uniform dispersion of fine particles and is well-suited for poorly soluble drugs. Moreover, it has the potential to enhance the bioavailability and solubility of drugs while enabling controlled release of the active ingredient. However, a drawback of HME is the risk of thermal degradation of thermolabile APIs and the softening of binders during handling and storage.[22,25]

### *Electrostatic spray deposition (ESD)*

ESD is a very old method and has been around for more than 100 years. This method is somewhat similar to the electrospinning method, which is when the API is delivered to the collector in a liquid medium. Both powders and liquids can be used in this procedure.

The primary setting of ESD includes a feeding syringe or tube, ionizing equipment, and a heated metal plate as a collector while a source of ionization is moving the API medium. The powder and the liquid containing API should be ionized to reach and stick to the plate (Figure 3). To ionize the API phase, two strategies are approached: using an electric corona and facilitating friction, which is mostly used for powders. The corona has a voltage difference with the nozzle, resulting in an electric field in the way of the API medium, which derives the API to be ionized, accelerated, and micronized; the corona can be in the form of a gun.[26]

With a corona and liquid API medium, the process is similar to the ESM with a difference in the method of vaporizing the solvent, which is the use of heat in the case of ESD. With a corona in use the voltage difference, the distance between the nozzle and the collector, environmental factors like temperature and humidity, API medium viscosity, and the collectors' temperature affect various qualities of the final film. Powders that are used in this method should be thermoplastic, meaning the particles will deform and not form crosslinks when treated with heat. The API powder or an accompanying polymer should be thermoplastic to yield acceptable products. In

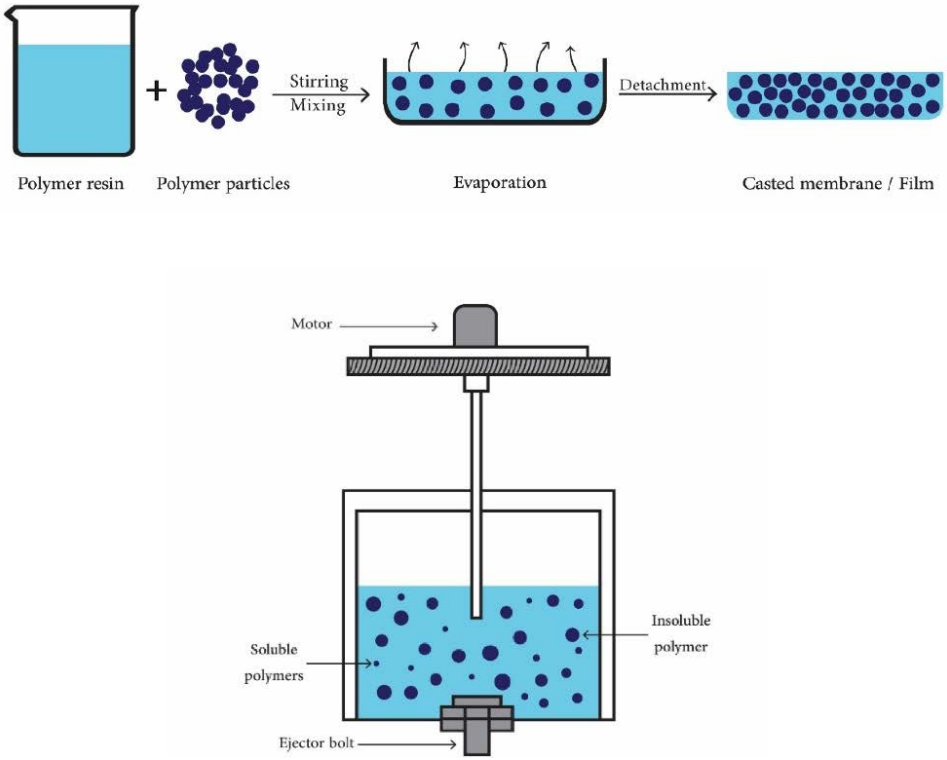


**Figure 1.** Membrane or film casting; Up) Traditional solvent casting and Down) Semi-solid approaches casting

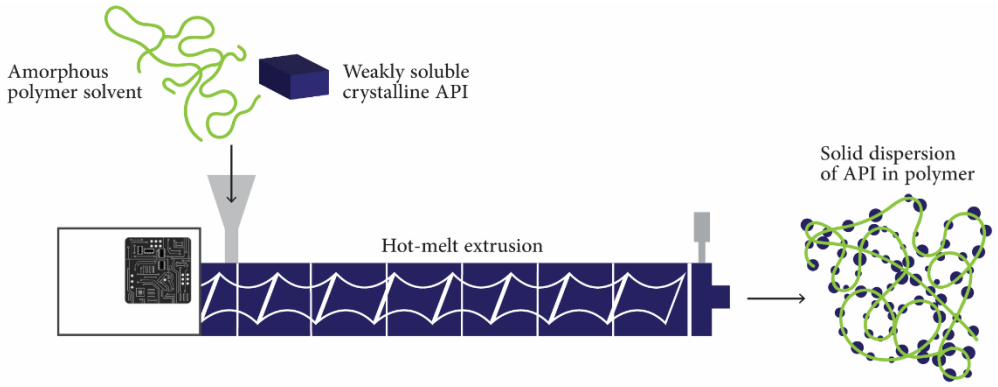


**Figure 2.** Hot-melt extrusion from amorphous and weakly soluble crystalline API to wafer formation

the case of powders, friction can be the source of ionization, which is induced by the movement of the powder and the collisions between them, but friction is not the primary ionizing source since the corona apparatus has higher efficiency amplified by an additional electric field set in the space between the nozzle and the plate. Lastly, the layer of powder is coalescence and leveled by heat, which gives a final product with homogeny thickness, which will be cooled and pealed in the end. The factors affecting the film derived from powders are particle electrical resistivity, size distribution, and shape and flow, alongside factors related to the apparatus mentioned earlier.[26]

In the ESD process, the generation of droplets occurs at the tip of a capillary tube when a sufficiently strong electric field is established between the capillary and the conductive substrate (Figure 3). This electric field must reach a critical value whereby the electrostatic forces surpass the surface tension of the coating solution. Only when this condition is met can the coating material be effectively atomized and sprayed. The interplay between the electrostatic forces and surface tension is crucial, as it determines the quality and uniformity of the deposited film. Thus, understanding this mechanism is essential for optimizing ESD techniques in various coating applications.

### *Electrospinning method*

This method was established over 100 years ago, but it has caught the attention of researchers in many areas of science in the last 20 years. As a method for producing wafers, a rapid release is favored for the final product. This method can result in a burst release because of the API deposition on the surface product; however, this method can also obtain a controlled release.

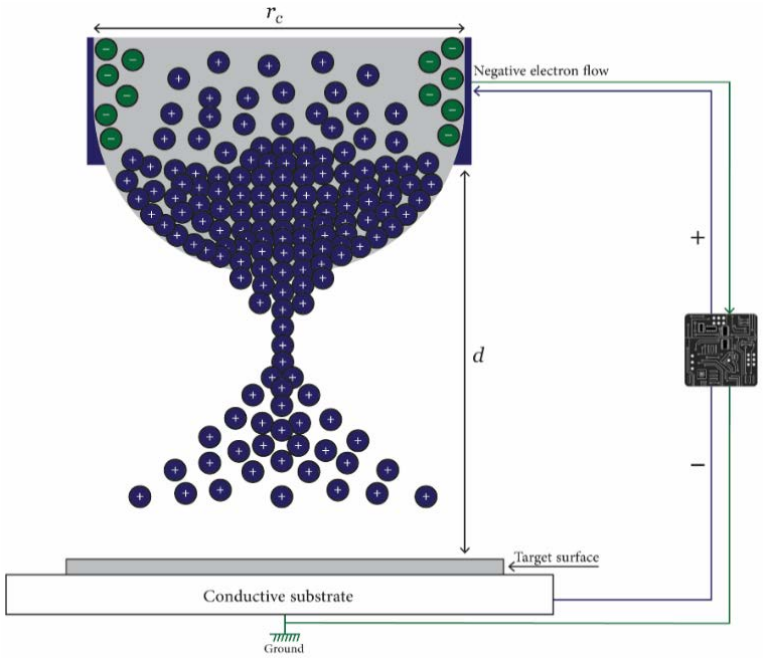


**Figure 3.** Representative overview of the ESD process

The formulation is generally formed by shooting a string of dissolved polymer onto a receiver surface and the solvent vaporizing in the meantime, resulting in a highly porous fiber ranging from nanometers to millimeters in diameter. Shooting of the initial mix is achieved through the voltage difference between the initial mix and the collector surface, which can be amplified with an auxiliary electrode attached to the tip of the syringe.

Emulsions with APIs in the dispersed phase can be used as the initial mix, resulting in a controlled release of the API. The properties of the fibers depend on many factors, such as the initial mix, conductivity, the distance between the feeder and collector, solvent vapor pressure, viscosity, and environmental factors such as humidity and temperature. Lastly, chemical and physical modifications can be made to the collector according to the conditions of the different components included in the process.[27-29]

Figure 4 illustrates the electrospinning configuration is characterized by the alignment of the syringe needle positioned directly above the collection substrate. The vertical arrangement facilitates a consistent gravitational influence on the polymer solution, promoting stability during the electrospinning process. Additionally, this setup often yields a more uniform fiber morphology due to the direct downward trajectory of the fibers, minimizing the occurrence of drift or irregular deposition.

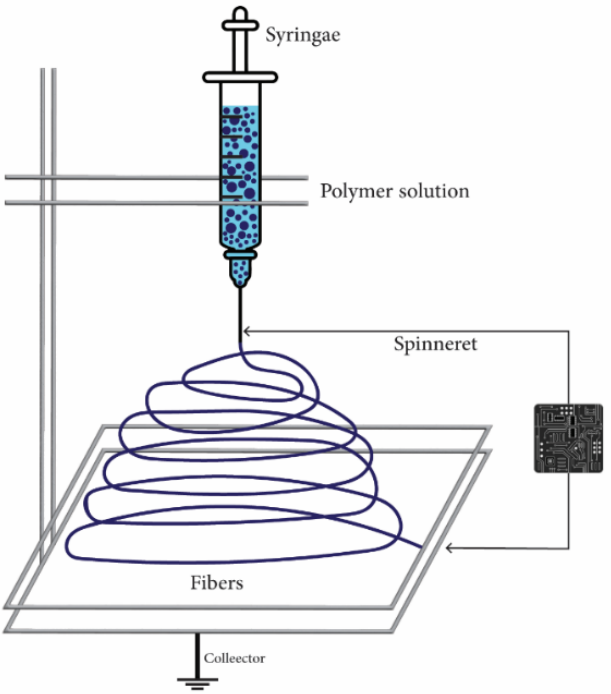


**Figure 4.** The vertical setup of the electrospinning apparatus

### *Poorly soluble APIs*

Among the main obstacles to drug discovery and formulation is API's insufficient water-solubility, especially in wafers, due to the low drug load. Nanostructured APIs are shown to yield exceptionally high drug loads such as Doxil®. There are several ways to incorporate poorly soluble drugs in ODFs. Steiner et al., studied five strategies for amorphous solid dispersion, or ADS, by utilizing solubility-enhancing agents like glycerin and a water/ethanol mixture, resulting in the solubilization of API molecules in the ODF up to a certain ratio.[30]

The following strategy is to load the API in lipid nanodispersions where tristearin is used as a solid lipid for the preparation of a nanosuspension, and medium-chain triglyceride (MCT) is the liquid lipid used for the nanoemulsion; these nanodispersions are then embedded in the polymer mixture and eventually cast into films. Another formulation is prepared by milling the API in

a specific media containing SDS as a surfactant, which results in a nanosuspension that is mixed with the polymer mixture and cast into films.

A micro-suspension was prepared as well by adding the API straight to the film-forming mixture. The APIs studied in the article were fenofibrate (FFB) as a lipophilic molecule and naproxen (NPX) as a more hydrophilic molecule in comparison, which are both poorly soluble in water. The results indicated that the ASD formulation had the best disintegration time while containing only 2% FFB due to its lipophilic nature compared to 8% for NPX.

However, according to FFB lipophilicity, this API had better results when formulated as lipid nanodispersions. Generally, the embedding of lipid nanodispersions reduced the tensile strength, and the use of nanoparticles (NPs) prolonged the disintegration time. In another study, herpetrione nanosuspensions were embedded in the film mixture and cast into films, which showed improved bioavailability and dissolution profiles.[31]

### *3D printing*

3D printing is a beneficial technique for manufacturing wafers because the process takes less time, resulting in films with better mechanical properties due to the precision and control over the printed material. There are several methods for 3D printing, including the fused deposition method (FDM), hot melt extrusion or HME printing, and print-fill, which can perform the printing with thermoplastic polymers such as PVA, PLGA, and PVP. Personal medicine has been under the spotlight as a field of use for 3D printing methods, especially FDM, because of the attainable customization of API dose and the ability to produce release-modified formulations. The ability to print personalized films alongside the possible modifications of the final product with 3D printing leads to higher efficacy of medications, fewer adverse effects, and better outcomes in general. Also, non-conventional shapes are achievable through 3D printing, which can improve the release kinetics and elevate the level of compliance with pediatric medication by printing in appealing shapes. FDM as the most case study, is based on heating filaments loaded with API and excipients to alter the resulting film properties, such as nozzle diameter, platform temperature, feeding speed, extruding speed, and most importantly, filament melting properties. FDM produces films with excellent mechanical properties and low prices for the method, but it's limited to the degradation of heat-sensitive API and excipients alongside difficult scale-up.[32]

During freeze-drying or cryodesiccation, a polymer mixture containing a polymer and a bulking agent is prepared and pipetted into pre-oiled cylinder cavities. The mixture is then frozen at -60 ºC for 2 hours in a freeze-dryer. The drying phase is continued for 24 hours under 25 m-torr pressure. In specific freezing processes, nitrogen tunnels are necessary because most industrial freeze-driers cannot reach temperatures below -40 ºC. This method produces porous wafers with an extended shelf life, as lyophilization eliminates the solvent at low temperatures. An additional benefit is the enhanced stability of thermolabile APIs. However, it's important to note that lyophilized products are expensive and sensitive to humidity and higher temperatures. This method is typically suitable for low-dose medications; higher dosages may lead to longer disintegration due to decreased tablet porosity.

Nevertheless, it is feasible to efficiently include 400 mg of low-solubility drugs in these formulations.[33,34] This technique exhibits partial incompatibility with drugs of higher solubility. Highly soluble drugs may form eutectic mixtures that are challenging to freeze-dry, limiting their applicability to quantities as much as 60 mg.[17,35] Current technology used to manufacture wafer production based on lyophilization approaches for wafer production is summarized in Table 3.

In the rolling method, active ingredients, such as active agents, are initially dissolved in an aqueous solvent utilizing a high-shear processor. The resulting solution or suspension is subsequently rolled and dried on a multi-roller apparatus and then eventually cut into the desired sizes or shapes.[22]

## Wafer components

### *Polymers*

As main components in a wafer formulation, the polymers make up different proportions of the product weight based on the polymer type and desired characteristics. The wafers must be durable for handling and transportation; therefore, polymers must be used alone or in combination to achieve the desired properties. As an illustration, sodium carboxymethyl cellulose (SCMS) is commonly used in a mixture with other matrix-forming ingredients, one of which is alginate. The amalgamation of alginate with magnesium aluminum silicate has demonstrated enhanced stability in formulations containing nicotine, which is utilized for replacement therapy.[40] The desirable characteristics of wafer-forming polymers include being non-toxic, non-irritating, providing a pleasant mouthfeel, offering good wetting properties, and ensuring extended shelf-life.

Optimizing the polymer quantity is crucial to prevent gel formation and ease the product's removal from the mold. Polymer gelation can lead to delayed disintegration and, consequently, the release of active substances. For hydroxypropyl cellulose (HPC), the recommended concentration typically falls within 1-10 % (w/v). Other polymers commonly utilized in wafer formulations include methylcellulose, pullulan, GLN, acacia, and tragacanth.[41-44] Molecular weight, chain flexibility, and hydrogen bond formation capacity are key players affecting adhesiveness in wafer formulations. Chain flexibility influences polymer diffusion through the mucosal surface, while stronger hydrogen bonding enhances adhesion to the mucosal surface. The release pattern is determined by

**Table 3.** Current technology used to manufacture wafer production

| Techniques | Advantages | Disadvantages | Example products | Ref. |
|---|---|---|---|---|
| Zydis® | • The initial fast-dissolving freeze-drying method using GLN<br>• Easy to handle<br>• Thick tablet with fast disintegration (less than 10 s)<br>• Dosage up to 400 mg for poorly soluble and 60 mg for water-soluble drugs | • The requirement for drug and excipient particles to be under 50 µm poses inadequate friability and high production costs<br>• The final product's high sensitivity to humidity necessitates specialized packaging methods due to its fragility | Claritin® Reditab®, Feldene® Melt, Maxalt-MLT®, Pepcid® RPD, Zofran ODT®, Zyprexa® | 36,37 |
| NanoCrystal™ | • Avoiding manufacturing operations associated with powder content<br>• Suitable for highly potent or hazardous drugs<br>• Available with non-hygroscopic material<br>• Up to 200 mg of drug content per tablet<br>• Physiochemically stable for conventional packaging<br>• Safer production due to less aerosolization | This technology is developed for NPs (smaller than 2 µm), API should be dispersible in colloidal form. | - | 37 |
| Quicksolv® | • Uses GLN as a matrix<br>• Less friable products<br>• Facilitated packaging<br>• Very fast disintegration rate<br>• Uniform porosity in the final product<br>• API can enter emulsion and suspension (process) form | • Relies on more excipients<br>• Required second solvent*<br>• Amino as excipients may lead to drug instability<br>• Gas bubbles are blown into the curated product for solvent evaporation, which is costly considering the use of inert and pure gasses | Dimetapp® ND disintegrating oral tablet | 37,38 |
| Lyoc® | • Relies on xanthan gum or PVP as the matrix polymer<br>• Forms coherent and stable products<br>• Feasible for poorly soluble drugs<br>• Well potential to form suspended NPs in the oral cavity once disintegrated<br>• Improved bioavailability of poorly soluble drugs<br>• The apparent yield stress is higher than GLN-based products<br>• Less friable wafers<br>• Facilitated storage/packaging<br>• Molding can be performed using the heat method and solvent method, which provides variability of APIs that can be formulated under this technology. | • Requires many un-dissolved inert fillers to maintain homogeneity<br>• Poor mechanical resistance,<br>• A high concentration of fillers is needed to increase the tablet homogeneity, which increases the disintegration time as well. | Loperamide Lyoc®, Vogalene Lyoc®, Paralyoc®, Proxalyoc®, Spasfon-Lyoc® | 37 |
| Wafertab™ | • Incorporates APIs into an ingestible filmstrip<br>• Flavor and taste are masked<br>• Can be prepared in different shapes and sizes<br>• Produces stable products by dosing and integrating APIs into the body of a pre-manufactured XGel™ film<br>• Bonding multiple films with different activities | XGel™ films are necessary | - | 39 |
| XGel™ | • Economical products due to continuous production<br>• Good potential to undergo taste masking, coloring, layering, and enteric coating<br>• Suitable to encapsulate all orally administered formulations, religious and vegetarian restrictions<br>• Good solubility regardless of water temperature | - | PocketPaks®, Gas-X, Orajel™ | 39 |
| Soluleaves™ | • Possible indication for tussis or viral rhinitis, pain-relief pharmacotherapy, micro/macronutrient deficiency formulation<br>• Possible adjustments made to the formulation to attain mucosal cohesiveness and obtain a release rate of 15 min | - | - | 39 |
| Foamburst™ | • A special variant of Soluleaves™ can form films resembling a honeycomb<br>• The potential for rapid dissolution offers a unique mouthfeel experience<br>• Desired for the confectionary and food industry to deliver flavors | - | - | 39 |

*The two solvents should be miscible and limited to low-dose drugs, which is immiscible in the second solvent.

matrix pore size, polymer ionization, interconnections within the matrix, and the erosion or swelling behavior of the polymeric chain lengths and types.[45] Polymorphism is another factor affecting the final product disintegration time regarding both API and the final product with the polymers present. Generally, amorphous forms are the goal of manufacturing due to stable and reproducible results that result in the content uniformity of the final product.[46]

Carrageenan, a naturally occurring sulfated marine polysaccharide derived from red seaweed, comes in various forms that differ in sulfate content (kappa, iota, and lambda). Moreover, it is frequently employed as a thickening agent regarding proven safety. Its sweet taste can mask the unpleasant flavors of drugs, eliminating the need for additional flavoring.[47] Chitosan (CTS), a crustacean-derived polymer, and SCMS are alternative polysaccharides. CTS is among the extensively studied

biodegradable natural polymers, known for its capacity to enhance mucoadhesion and drug delivery.[48] Some saccharides, such as mannitol, xylitol, and trehalose, can enhance hardness, particularly when added to a GLN-based medium. Therefore, an optimal concentration should be implemented for efficient lyophilized disintegrating.[49] Alginate formulations are noted for being mechanically resilient and for their disintegration time. In contrast, products containing xanthan gum disperse slowly compared to GLN formulations.[50,51]

### *Thiolated chitosan and gelatin*

Thiolated CTS, as higher bio-adhesiveness CTS, creates disulfide bonds with mucus glycoproteins, masking thiol groups and notably improving mucoadhesion. Therefore, cationic CTS could be a promising choice for prolonged-release wafer formulations with strong mucoadhesive properties, improved permeation, and the ability to inhibit peptidase and efflux pump proteins.[52,53] GLN is a common matrix-forming polymer in oral wafers, the physico-chemical crosslinks can break at body temperature which can be used for thermosensitive drug release. Chemical crosslinks are established with crosslinking agents like carbodiimides. GLN could prepare extended-release wafers when combined with CTS.[54,55]

### *Plasticizers and surfactants*

Plasticizers are low-molecular-weight molecules added to wafer formulations to improve the physicochemical properties of the final product, like elongation, tensile strength, and porosity. Lipophilic or hydrophilic plasticizer, which differs in size, molecular weight, and polarity, contributes to a maximum of 20% (w/w) in the formulated mixture, but there are higher percentages of plasticizers and their effects on the unique formulations. The changes observed in a formulation after enriching it with plasticizers are because of the new bonds formed between the plasticizer and other excipients and the API, which are believed to be predominantly hydrogen bonds. The addition of plasticizers to thin film wafers reduces the brittleness and glass transition temperature of the polymer in use by 40-60 °C in non-aqueous formulations and 75 °C in aqueous formulations. For example, to study gellan gum films, glycerol was used in different concentrations to plasticize the formulation, and results showed improvement in tensile strength of less than 50% (w/w). However, for adequate drug delivery, Fluconazole needs glycerol concentrations over 70% (w/w) for effectiveness, but this high concentration reduces the film's mucoadhesive properties by disrupting the bonds between the polymer and mucosa. Inappropriate plasticizers or concentrations other than the optimized number, significantly lower, may make the film stiffer and less rubbery, which is the opposite of the favorable income. Several plasticizers can influence the API's rate of absorption as well since different plasticizers alter the final film water vapor permeability; for example, glycerine, a small, polar, and hydrophilic plasticizer leads to higher permeability, whereas lipophilic plasticizers decrease the permeability. Common plasticizers are glycerol, dibutyl phthalate, triethyl citrate, propylene glycol, glycerin, and polyethylene glycol. The perfect plasticizer should be adequate, stable, and suitable with the polymer and the solution medium in use.[56-59]

Surfactants are used to enhance solubilization, wetting, and dispersing of films, and reduce the risk of API crystallization or insufficient local drug solubility. Surfactants can also be used as penetration enhancers as studied for buccal drug delivery. The improvement in the dispersion is achieved by either forming micelles or lowering surface tension between the solvent and solute. Sodium lauryl sulfate, benzalkonium chloride, and benzethonium chloride are widely used surfactants.[60] Another wafer surfactant is Poloxamer407, a block copolymer encompassing polyethylene glycol and propylene oxide, which is a non-ionic surfactant capable of enhancing drug solubility.[61]

### *Saliva stimulating, sweetening, and thickening agents*

Saliva stimulation can be achieved through various methods like electric stimulation of the nerves, parasympathetic APIs, and mucosal stimulants. However, in wafer formulations, saliva stimulating agents are employed at 2-6% (w/w) to increase the saliva secretion rate, leading to enhanced disintegration, wetting, API dissolution, and overall bioavailability profile. The stimulation of salivation is measured by comparing the amount of resting flow and stimulated flow at a time point under the same controlled conditions which can be up to 5 mL/min. For this purpose, weak acids with small molecular weight, such as malic acid, tartaric acid, and ascorbic acid, are added to the formulation to mildly irritate the mucosa and result in a response to saliva secretion. Moreover, sweeteners like fructose, sucrose, and polyols like xylitol, sorbitol, and erythritol can stimulate saliva secretion, which in the case of polyols is also beneficial for dental health.[62]

Sweetening agents are essential for the enhancement of patient compliance with wafer formulations, especially in pediatric drug administration. The unpleasant taste of a wafer is significant due to the full disintegration of the formulation within seconds and inside the oral cavity. The use of nature-acquired sweetening agents is limited for diabetic patients.; artificial sweeteners are developed to this end alongside newer plant-based sweeteners like stevia powder, which is a disintegrant agent; the classic sweetener is sucrose, which is extracted from natural resources. Dextrose, fructose, glucose, and maltose are other examples. Saccharin, cyclamate, aspartame, acesulfame-K, sucralose, alitame, and neotame fall under the artificial sweeteners category.[63]

Thickening agents like gums and cellulosic derivatives improve the rheology and uniformity of a dispersion or solution before the casting stage of wafer formulations

also they are used to assess the primary mix solutions in the 3D printing method for a better final product with improved flexibility, mechanical strength, and content uniformity. However, there is a specific limit for using thickening agents; adding more after reaching a certain concentration will not affect the dispersion but will increase the dissolution time.[64,65]

### *Flavoring, and coloring agents*

The initial flavor tasted in the first few seconds determines the acceptance of the formulation. Flavors could be synthetic oils, oleoresins, or plant extracts that are used alone or in combination. Their amount depends on the type and strength of the taste or smell that needs to be masked. Peppermint, cinnamon, spearmint, and nutmeg oils are some examples. The flavor chosen for the formulation strongly depends on the target patients for example, a geriatric patient's liking of flavors is different than that of a pediatric patient; Additionally, cultural differences should also be taken into account.[66]

Pigments or food, drug, and cosmetic (FD&C) approved colorants like titanium dioxide, natural colors, and cooling agents (like WS3, WS23, and Utracoll-II) are incorporated in the formulations to enhance the flavor profile and patient compliance.[67,68]

### *Penetration enhancers and crosslinkers*

The buccal penetration enhancers, including fatty acids, bile salts, Azone®, alcohols, CTS, and its derivatives, are incorporated to ensure API delivery to the systemic circulation for physiological and further therapeutic effects. These compounds must be non-irritant. In the case of CTS, which is a sufficient option as discussed before, the enhancement is achieved through thiolating the polymer, which helps the surface of the formulation form sulfide bonds to the mucus. This mechanism has also been employed to prolong NP residence time by altering the surfactants sticking out on the nanoparticle active surface.[69] Other excipients used in wafer formulation are listed in Table 2. Crosslinkers are usually used to form a bond between two different polymers. The choice of a proper crosslinker depends on the polymer used for the formulation. For example, alginate crosslinking with pectin occurs at neutral pH. This is done using calcium carbonate and gluconic-delta-lactone, which gives the final formulation proper physical properties such as tensile strength without opposing a high risk of API degradation.[70] Moreover, CTS is crosslinked to polyvinylpyrrolidone (PVP) or polyvinyl alcohol (PVA) by either glutaraldehyde or sodium tripolyphosphate, which is of an ionic nature.[71]

## Quality control of the wafer characterization

### *Physicochemical studies*

#### *Dissolution, content uniformity, and stability testing*

Dissolution testing consists of API dissolution per time under the surface between the solid API and the medium in liquid form, and solvent concentration (37 °C and 50 rpm). This test is performed by using the standard basket/paddle apparatus described in any of the pharmacopeias. The medium is selected for sink conditions and the highest dose of API.[72] For the particular API, the standard assay method is described in the renowned pharmacopeias. The limit of content uniformity is determined from 85%-115%. Finally, to evaluate short-term stability, according to the International Council for Harmonisation (ICH) guidelines, wafers need to be packaged inside an air-tight aluminum container at 25 °C under normal humidity conditions (50%-60%), and another group of wafers are kept at accelerated conditions (40 °C and 75% humidity), and both were monitored for any changes.[72]

### *Morphological and mechanical studies*

Scanning electron microscopy (SEM) aids in studying the top and bottom surfaces of the film product; it is also useful in determining the distribution of the drug.[73] To study any interactions among formulation components, a Fourier transform infrared spectroscopy (FT-IR) of the wafer and pure compounds could be obtained. Additionally, an X-ray diffractometer (XRD) could be implemented for aiming to examine morphologic characteristics (amorphous or crystalline) of the pure drug, polymer, and wafers.[74]

Hardness includes the formulation's resilience against becoming deformed and its intrinsic interest in recovering the original shape once put through stress. A texture analyzer (TA) measures the mechanical attributes under pressure, disintegration time, and mucoadhesive properties of the wafers.[10,61,75] For this, the product thickness should be measured beforehand.[75]

### *Mucoadhesion studies*

The mucoadhesion strength is equal to the peak force needed for removing the test film from the model simulating buccal mucosa.[76] To this end, a GLN with 6.67% (w/v) concentration, which represents the buccal mucosal structure, should be poured into Petri-dishes, and then placed in a standard refrigerator for 6-8 hours or one night's time to solidify. To mimic the buccal mucosa more precisely, PBS or simulated saliva should be spread over the surface of the GLN.[10] Then wafers, attached to an adhesive probe, are lowered to contact the model mucosa surface with a force of 1 N and detached after 60 seconds. To measure adhesion, the area under the force-distance graph and the total displacement of the wafers before full separation are measured.[77,78]

### *Thickness, tack, and tensile strength assessment*

The assessment of thickness includes methods such as digital or manual calipers, micrometers (ideal for thin materials), and optical methods. Additionally, X-ray or ultrasonic testing is used for thicker or multilayered materials. Notably, the latter two approaches are non-destructive.[79] To define uniformity in the thickness of the

film, the thickness is measured by a micrometer screw gauge at least at five different locations. Determining this is crucial because the precision of the delivered dose is influenced by the changes in thickness.[77] Tack strength is the quality of being able to grab other materials that have been pressed to the surface of the formulation.[80] Tensile strength refers to the highest stress tolerated by the formulation before its breaking.[81]

The tack testing method includes loop tack, quick stick, peel, shear, and probe tack tests to accurately assess the tack properties of polymer materials.[82-84] The loop tack method measures adhesive strength by pressing a loop against a substrate and pulling it away. The quick stick test evaluates immediate stickiness with a rapid force application. The peel test examines adhesion by peeling the material from a substrate, while the shear test assesses the resistance of an adhesive bond under shear forces. The probe tack test provides a quantitative measurement of the tack of pressure-sensitive adhesives.

The tensile testing of wafer polymers is performed using a universal testing machine (UTM) that applies a controlled uniaxial tensile load to the sample, enabling accurate measurement of mechanical properties. Key parameters, including tensile strength, yield strength, elongation at break, and modulus of elasticity, are evaluated during the test. These parameters are determined by plotting a stress-strain curve, which helps analyze and interpret the mechanical behavior of the material under stress.[85,86]

### *Elastic modulus and swelling evaluation*

The stiffness of wafers is determined by Young's modulus which indicates elastic modulus. It is equal to the ratio of applied stress over the strain in the region of elastic deformation. Hard and brittle wafers possess slight Young's Modulus while their tensile strength is high.[87,88] A swelling study is performed to examine the water absorption profile using PBS or stimulated saliva solution at 37 °C. For this purpose, the sample weight is recorded at specific time points until it shows no further change.[33,77,89]

### *Contact angle measurement*

By measuring contact angle, wetting behavior, and disintegration time, the dissolution of the oral film could be anticipated. Measuring the contact angle for time is performed with an optical contact angle meter; a drop of water which has gone through distillation two times, is sited upon the upper side of the wafer. Then for angle determination, images of water droplets are recorded and analyzed within 10s via a digital camera and image software. It is worth mentioning that, contact angle could also be measured by the tangential method, height-width ratio, circle fitting, and sessile drop fitting.[73] The tangential method involves drawing a tangent line at the point of droplet contact with the surface and measuring the angle between this line and the surface. The height-width ratio method calculates the contact angle based on the geometric dimensions of the droplet, specifically the ratio of its height to its width. The circle fitting method involves fitting a circle to the droplet's profile to derive the contact angle from its geometry. Finally, the sessile drop fitting method employs mathematical models, such as the Young-Laplace equation, to analyze the entire droplet shape, incorporating the effects of gravity and surface tension. Together, these methods provide valuable insights into liquid-solid interactions critical for various applications.[90,91]

### *Transparency and taste analysis*

To evaluate the wafer product's see-through quality a sample from the final product is prepared by slicing it into a rectangular shape and it is then put inside the UV-vis spectrophotometer chamber.[92] The efficiency of taste masking is examined through *in-vivo* and *in-vitro* methods. Assessing the flavor test with *in-vivo* methods appears to be challenging in pediatric healthcare due to possibly drastic differences between children's and adults' understanding of flavors. Several scholars have proposed diverse approaches to evaluate the effectiveness of taste masking in the finished product. Pein et al. and Gittings et al. thoroughly examined these methods in their reviews.[93]

The majority of *in-vivo* studies are conducted on a group of 4-30 healthy adult individuals. They are asked to report their instant perception of taste following the proper administration of the product in the oral cavity; the result is recorded again after 3-4 minutes. To maintain the integrity of the test, it is necessary to assess the bitterness value, defined as the lowest detectable drug concentration by a human subject. The flavor is evaluated by a number between 1 and 5; every examination must be performed 3 times with 15 min in between each assessment.[94] Additionally, as these products should provide the satisfaction of a large scale of population, their sweetness and flavor should be assessed delicately. Therefore, electronic tongue and taste sensors are developed to assess *in-vitro* sweetness levels in the formulation.[73,95,96]

### *Taste masking*

An unpleasant taste will decrease patient compliance. Taste masking by adding sweeteners or adjusting the pH is a common and straightforward technique for removing bitterness or improving undesirable taste.[37] When bitter taste cannot be improved by these methods, physically isolating the fine drug particulates by encapsulation could be implemented. This will prevent the API from reaching the taste receptors. Coating techniques require careful consideration since they can negatively impact bioavailability and affect local drug delivery. For example, according to Kondo et al., coating the drug particles in the acetaminophen ODTs impacts the dissolution profile.[97] MicroMask™ technology is a way to mask the taste; in this method mixing waxy lipids or protein substances with the API decreases the physical closeness between the drug and the taste receptors.[38] Another method for covering unpleasant taste in formulations is the encapsulation or

coating of API particulates with polymers or lipids while maintaining the release and absorption ability of the drug.

## *In-vitro studies*

The studies are conducted to determine drug dissolution, release profile, and cytotoxicity of drug-loaded wafer formulation *in-vitro*.

### *In vitro drug release*

*In-vitro* release of wafers containing API could be evaluated using a Franz-diffusion cell apparatus or USP apparatus.[73] In this setting, two kinds of solution medium are introduced to the receiving container [(0.01M PBS solution (pH 6.8 ± 0.1) and SS (pH 6.8 ± 0.1)]. Donor and acceptor chambers are tightly enclosed to avoid leakage, then they are placed in a water bath and magnetically stirred (37 °C, 200 rpm). Formulations are accurately weighed, and positioned on a mesh in the space separating the two phases, then on specific time points, the product is wetted by the solution on one side, samples are withdrawn, filtered, and analyzed using HPLC or UV/Vis spectroscopy. The cumulative percentage of drug release is then calculated and plotted against time.[98] For drug release from wafer formulations, some considerations need to be taken. The API delivery through formulations made from polymers like sodium carboxymethylcellulose (NaCMC) usually comprises the intake of delivery site water through the formulation by the polymeric structure and subsequently forming a gel coat as a result of swelling. The viscous resistance of this layer to drug diffusion controls the release properties.[99] In the case of a solubilized API, diffusion across the swelled layer is shown to be relative to the radical of time in a linear manner. For products displaying swelling behavior, erosion should be noted as another process of drug release. The best mathematical representation of this bi-factorial mechanism is the Peppas transport equation which can be utilized to predict the first 60% of the release.[100,101]

### *Cell viability assay*

To assess the toxic effect of formulations such as dressing and wafers, an MTT assay is conducted. For this reason, proper cells should be grown in a culture and supported as explained in the ATCC recommendations.[77] UV radiation is implemented for sterilizing the test samples for 6-8 hours or one night utilizing an air-filtered bench. Then the processed formulations are submerged in 2.5 mL of full nutrient medium and put inside an incubator at 37 °C in a $CO_2$ (5%) for 24 hours. Then the samples are extracted through filtration with a 0.2 µm cut-off. Afterward, the media is removed, then 100 µL of each sample extract is transferred to the wells. This process is performed in three sets of wells for each sample. The plates are put in the incubator at 37 °C for a maximum of 72 hours.

At certain points of time (24, 48, and 72 hours), 10 µL of MTT reagent is introduced to every well, including the blank which contains only the medium. The plates are placed in the incubator for at least 4 hours, or to the point that an insoluble purple substance is detected using an inverted microscope.

Following media removal, 100 µL of DMSO is dispensed into each well, including the control wells. The plates are returned to the incubator for 30 minutes, then the absorbance is measured using a microplate reader.

## *Sterilization and packaging*

The gamma-irradiation test is done to sterilize the product and to investigate any rheological changes in the wafer formulation.[102,103] Gamma irradiation significantly impacts the modification and enhancement of properties in various polymeric systems, including individual polymers, polymer blends, composites, and nanocomposites. Unlike chemical processes, gamma radiation offers several advantages, such as eliminating the need for additives, applicability across a wide temperature range, and effective control of grafting and crosslinking. In addition to crosslinking and grafting, gamma irradiation can also be utilized for functionalization and sterilization. Gamma irradiation can significantly influence the rheological properties of polymers by altering their molecular structure and interactions.[104,105]

Wafer fragility and the presence of hydrophilic excipients in their formulations necessitate specific packaging to resist physical stress and humidity and to preserve product integrity. Modified blisters are unnecessary for modified-release formulations because of their greater physical robustness, however, the necessity of resistance against humidity remains.[41,106] A variety of packaging options exist for wafers, but they must all be individually packaged. The most common packaging is an aluminum pouch that holds the product securely. This pouch consists of two layers: a transparent side for product visibility and a thin aluminum cover that provides an airtight and moisture-resistant seal. This combination is both effective and cost-efficient.

The other packaging is a blister sheet, including two main parts: the cavity, which holds the product, and the lid stock or an aluminum foil, which seals the cavity. The cover should be selected according to the isolation level needed for the formulation to stay intact. The blister is usually made out of synthetic polymers. Blisters made of polyvinyl chloride provide nominal or zero barriers to moisture. For highly sensitive product barrier films such as Polychlorotrifluoroethylene (PCTFE) film, Polypropylene is used.

The packaging materials must be FDA-approved, non-toxic, non-reactive, and not affect the product's taste or odor. There are also some packaging considerations related to the production technology. Particularly, Zydis® tablets need to be packaged with specific materials such as PVC and aluminum. FlashDose® tablets are immediately transferred to a package with wells. OraSolv® tablets necessitate individualized packaging (PackSolv®), which includes a dome-shaped blister designed to restrict the

tablet's vertical movement within the blister cavity.[107]

### *Controlling release profile*

Techniques such as solid dispersions and methods like nanotechnology can increase solubility and control release profile besides taste masking. For example, the bitter taste of pyridostigmine bromide could be masked by solid dispersions using Eudragit® EPO.[108] Cyclodextrin is an FDA-approved soluble cyclic sugar that enhances bioavailability by accommodating hydrophobic drugs inside its lipophilic cavity. This compound is used to cover the bitter taste of meloxicam and diltiazem.[109,110] Curcumin solubilization in solid lipid NPs before dispersion in freeze-dried wafers of polycarbophil has enhanced its buccal residence time and sustained its release for more than 14-15 h in local treatment of oral precancerous lesions.[111] Using beads also offers a particulate matrix for sustained release; CTS lactate beads loaded with tizanidine prevented a rapid drug discharge and increased the bioavailability of tizanidine (2.27 folds) compared to the other immediate-release products like Sirdalud.[112]

The demand for wafers as a dosage form has risen due to their convenience and rapid dissolution in the mouth, leading to quicker absorption and action, especially beneficial for those who struggle with swallowing. Flavored wafers enhance palatability and patient compliance. Their versatility allows for the formulation of multiple active ingredients to meet various therapeutic needs, aligning with trends toward convenient supplements. Overall, their portability, improved bioavailability, and ability to bypass first-pass metabolism make them an attractive option for both consumers and manufacturers.[113-116]

The increasing demand for wafer dosage forms underscores their effectiveness and rapid delivery capabilities, as these formulations offer a unique combination of convenience and precise drug release profiles.[117] Wafers are designed for quick disintegration and dissolution, which leads to faster absorption and onset of action, making them particularly appealing for patients seeking immediate relief or effective management of symptoms. Additionally, their ability to provide sustained release without the need for frequent dosing helps maintain consistent therapeutic levels, improving patient adherence and satisfaction. This dual advantage of rapid and prolonged therapeutic effects is driving healthcare providers to adopt wafer dosage forms more frequently, reflecting their growing acceptance and recognition as a valuable option in modern pharmaceutical therapy.[118-120]

Prolonged-release wafers offer significant benefits to both patients and researchers in the pharmaceutical field by enhancing drug delivery and therapeutic efficacy.[121] For patients, these wafers improve adherence to treatment by reducing dosing frequency, ensuring stable drug levels in the bloodstream, and minimizing side effects associated with peak concentrations, thus promoting convenience and comfort in managing chronic conditions. For researchers, they provide opportunities to explore novel formulations and drug combinations, facilitate detailed studies of pharmacokinetics, and enable the collection of robust clinical data, paving the way for innovations in personalized medicine and expanding therapeutic applications across various medical fields.[122-124]

## Conclusion

Monitoring wafer quality is essential for ensuring safety, efficacy, and stability in various applications, particularly for drug delivery in pharmaceutics.[125,126] Regulation of controlled release, formulation complexity, sufficient encapsulation, and scaling up are the most common factors that affect wafer efficacy. Safety involves the rigorous inspection of wafers to detect defects such as cracks, contamination, inconsistencies, and biocompatibility which can pose significant safety risks and lead to regulatory hurdles. Finally, biodegradability provides critical insights into the materials' stability and durability. Additionally, comprehensive quality assessments foster confidence in product integrity and compliance with regulatory standards.[124,127-129]

Wafer production techniques have evolved significantly to better meet patients' needs through advancements in the development of formulation and manufacturing technologies.[130] Innovations such as thin-film technology and nano-encapsulation have improved drug bioavailability and absorption while enhancing patient compliance with palatable, rapidly dissolving wafers. Continuous manufacturing processes have increased production efficiency and consistency, while 3D printing allows for personalized dosage forms tailored to individual needs. Enhanced quality control measures ensure safety and regulatory compliance, while the integration of smart technologies addresses specific therapeutic requirements.[131-133] Additionally, a focus on sustainable practices and patient-centric designs has made medications more accessible, convenient, and eco-friendly, ultimately improving treatment adherence and health outcomes.

Wafers have been designed to be highly palatable dosage forms that enhance oral fast-dissolving films, resulting in high absorption and bioavailability properties. This makes them particularly popular among geriatric and pediatric populations. By modifying the wafer CMC, prolonged-release formulations have been developed to cater to a wider range of patients' needs. The increasing demand for these dosage forms can be attributed to their high effectiveness and rapid delivery. The oral route of administration is preferred due to its lower enzymatic activity and a high tolerance for allergens or damage.

In clinical trials, the production of prolonged-release wafers can lead to improved patient compliance, consistent drug levels, reduced variability, convenience, and the ability to tailor drug release profiles. These factors are essential for conducting successful and reliable clinical studies. Overall, the development and utilization of

prolonged-release wafers hold significant promise in the field of pharmaceuticals, offering numerous benefits for both patients and researchers alike.


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