Mini-review

A mini-review on drug delivery through wafer technology: Formulation and manufacturing of buccal and oral lyophilizates

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HIGHLIGHTS

- This mini-review provides a thorough overview of current buccal/oral lyophilizates.
- The mini-review discusses material and process parameters using the quality by design (QbD) approach.
- This study covers trends in experimental buccal/oral formulations.
- It relates drug and dosage form limitations to aid future developments.
- It shows buccal/oral lyophilizates as safe and effective prominent drug delivery systems.

ABSTRACT

A great number of patients have difficulty swallowing or needle fear. Therefore, buccal and orodispersible dosage forms (ODFs) represent an important strategy to enhance patient compliance. Besides not requiring water intake, swallowing or needles, these dosage forms allow drug release modulation. ODFs include oral lyophilizates or wafers, which present even faster disintegration than its compressed counterparts. Lyophilization can also produce buccal wafers that adhere to mucosa for sustained drug release. Due to the subject relevance and recent research growth, this review focused on oral lyophilizate production technology, formulation features, and therapy gains. It includes Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) and discusses commercial and experimental examples. In sum, the available commercial products promote immediate drug release mainly based on biopolymeric matrices and two production technologies. Therapy gains include substitution of traditional treatments depending on parenteral administration and patient preference over classical therapies. Experimental wafers show promising advantages as controlled release and drug enhanced stability. All compiled findings encourage the development of new wafers for several diseases and drug molecules.

Introduction

American surveys have shown that 8% of patients skip doses and 4% discontinue therapy due to difficulties in swallowing tablets [1]. Another barrier for therapy efficacy relates to patient
aversion to injectable medications [2]. As buccal administration does not require swallowing nor needles, adherence to dosing regimens is likely to increase with buccal delivery. Buccal delivery provides easy access to highly vascularized tissue, avoiding first-pass metabolism and concomitant liquid intake. Furthermore, the neutral environment of the mouth allows for administration of acid-sensitive active pharmaceutical ingredients (APIs) [3]. Drugs can permeate the buccal mucosa more rapidly than they permeate the skin, but less rapidly than they permeate the intestinal wall. Absorption rates depend on drug physicochemical properties, such as molecular size, hydrophobicity, susceptibility to enzymatic degradation, and region of delivery inside the oral cavity [4,5]. Noteworthy, a buccal dosage form can release drug to the oral cavity and promote absorption throughout the gastrointestinal tract.

Buccal dosage forms include mucoadhesive tablets, films, patches, ointments, and hydrogels, each of which has limitations [4,7]. Although precision can be increased with mucoadhesive tablets, they are often uncomfortably large, limiting long-term residence and release time [6,8]. These disadvantages can be overcome with the use of films, patches, and wafers [6,9]. Buccal films are currently the preferred commercial dosage form for extended transmucosal delivery; their action depends on slow matrix erosion, high mucoadhesiveness, and adequate drug loading. However, these carriers contain enough water to favour microbial contamination or degradation of sensitive APIs [10]. Lyophilized wafers can sustain drug release as well, with the benefits of low residual moisture and increased drug loading (for low solubility drugs) [3,11]. To date, extended release wafers have been restricted to noncommercial formulations.

For rapid onset of drug action, several companies rely on orodispersible dosage forms (ODFs). These systems disintegrate rapidly in the mouth and increase therapy efficacy for disorders that require fast intervention [12]. ODFs include orally disintegrating tablets (ODTs), quick-dissolving lyophilized wafers (oral lyophilizates), and thin films [13]. According to the FDA, an ODF must be small, lightweight (up to 500 mg), and must disintegrate within 30 s [14]. Among the options, wafers present highly porous solid matrices obtained by freeze-drying of polymer gels or suspensions to an average of 3 mm thickness and 9 x 12 mm size [15,16] (Fig. 1). Owing to their potential therapeutic advantages and lack of review articles on wafer systems, this study focused on the production process, parameters, and formulation features of wafers.

**Therapy gains**

Wafer products are available to patients for immediate release of several APIs (Table 1). Most of these medicines showed better patient compliance, especially in acute pathologies or symptoms. For instance, acute attacks of migraine often come with nausea, which implicate in parenteral medication to avoid vomiting. With the advent of Rizatriptan wafers, pain decreases after around 20–30 min of drug administration, like standard subcutaneous sumatriptan. Although Rizatriptan is 45% bioavailable, compared to 95% of subcutaneous sumatriptan, its rapid onset of action, oral intake and similar efficacy pattern makes patients prefer the former [17,18]. To inhibit nausea and vomiting of migraine attacks and other medical conditions, fast-disintegrating antiemetics versions gained wide acceptance, including ondansetron and domperidone. Oral ondansetron was as efficacious as its intravenous administration in prevent emesis after laparoscopic cholecystectomy [19].

A prolonged seizure (over 5 min) is another condition that requires rapid chemotherapy without tablet/liquid swallowing. Among the options, oral clonazepam wafers were as efficient as rectal diazepam in stopping seizures. This data alone is meaningful because it reduces patient embarrassment related to the rectal administration [20]. As a last case for illustration, the antihistaminics, desloradatine and loratadine, have wafer and tablet versions for relief of allergy symptoms. Wafers did not decrease the time to achieve a maximum concentration in plasma (Tmax) when compared to traditional tablets; however, a 5 mg loratadine version resulted in 25% more drug bioavailability than its tablet counterpart. Since allergy symptoms include itchy throat, a fast-disintegrating dosage form can also decrease discomforts related to medicine administration [21].

Mucoadhesive wafers (without fast disintegration) were tested in few clinical trials, with no commercial representatives. Current research focuses consists of wound healing enhancement and pain management. On this matter, ketorolac/lidocaine polymeric wafers reduced pain and enhanced tissue healing in dental patients previously subjected to gingivectomy [22].

**Formulation features**

**Matrix forming polymers**

Concerning excipients, gelatin is the most used matrix-forming polymer (Table 1) of commercial oral lyophilisates. It is abundant in

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**Fig. 1.** An example of the macro and micro morphologies of wafers (A) Oral lyophilizate of gelatin and sodium alginate; (B) Micrograph of wafer pores obtained using a Leo 440i scanning electronic microscope (LEO Electron Microscopy) Oxford, Cambridge, England) at 200x magnification. This Fig. was designed by the authors.
in animals, cost-effective, biocompatible, biodegradable, and has favorable physicochemical properties (forms hydrosols and is hydrophilic, translucent, colorless, and flavorless). Gelatin forms physical crosslinks that break at body temperature [29]. This effect “melts” the dosage form, resulting in drug release. Zydus was the first gelatin-based technology available to patients. It can incorporate doses of up to 400 mg of poorly soluble drugs and 60 mg of water-soluble drugs. This technology has limitations: drug and excipient particles should be smaller than 50 μm; hot packaging increase costs; inadequate friability is a common product defect [23–28]. A few Lyoc® products use polyvinylpyrrolidone instead of xanthan gum or even no polymers at all (Table 1). Although there are many other wafer technologies on the market, we could not find commercial products using them.

Alternative experimental polysaccharides include the algal derived alginate (Fig. 2B) and chitosan (Fig. 2C). For example, combination of alginate with magnesium aluminum silicate improved the stability of nicotine used for replacement therapy [35]. Extended release versions require mucoadhesiveness, which allows for longer swelling time in the buccal cavity. Experimental wafers can also be formulated with synthetic polymers, such as thiolated chitosan, which is reported to be up to 10 times more bioadhesive than chitosan, but still biodegradable. Hydrophilic sodium carboxymethyl cellulose delivers drugs effectively through gastrointestinal mucosal tissue absorption. Sodium carboxymethyl cellulose does not require organic solvents and is usually combined with other matrix-formers, such as alginate [11,34–36].

As polymers constitute a large portion of the carrier, the following characteristics must be considered: molecular weight

### Table 1

Examples of commercial oral lyophilizes (US and EU markets).

<table>
<thead>
<tr>
<th>Drug (strength)</th>
<th>Indication</th>
<th>Trade name</th>
<th>Company</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brompheniramine maleate – phenylephrine hydrochloride</td>
<td>Antihistamine, Decongestant</td>
<td>Dimetapp® Quick Dissolve</td>
<td>Whitehall-Robins</td>
<td>Aspartame, FDCA Blue No. 2, FDCA Red No. 40, flavors, gelatin, glycine, mannitol</td>
</tr>
<tr>
<td>Buprenorphine hydrochloride (2, 8 mg)</td>
<td>Opioid drug dependence</td>
<td>Esprano</td>
<td>Martindale Pharma</td>
<td>Gelatin, mannitol, aspartame, mint flavour, citric acid</td>
</tr>
<tr>
<td>Clonazepam (0.125, 0.25, 0.5, 1, and 2 mg</td>
<td>Sedation, seizures, panic attacks</td>
<td>Klonopin® wafer</td>
<td>Roche</td>
<td>Gelatin, mannitol, methylparaben sodium, propylparaben sodium and xanthan gum</td>
</tr>
<tr>
<td>Desmopressin acetate (25, 50, 60, 120, and 240 μg)</td>
<td>Vasopressin-sensitive cranial diabetes insipidus, nocturnal enuresis</td>
<td>Noqdirma</td>
<td>Ferring Pharmaceuticals Ltd</td>
<td>Gelatin, mannitol, citric acid</td>
</tr>
<tr>
<td>Famotidine (20, 40 mg)</td>
<td>Heartburn, Indigestion</td>
<td>Pepcidine Rapib</td>
<td>Cardinal/Merck</td>
<td>Aspartame, mint flavor, gelatin, mannitol, red ferric oxide and xanthan gum</td>
</tr>
<tr>
<td>Loratidine (5, 10 mg)</td>
<td>Allergy</td>
<td>Claritin® Reditabs®</td>
<td>Schering</td>
<td>Citric acid, gelatin, mannitol, mint flavor</td>
</tr>
<tr>
<td>Loperamide (2 mg)</td>
<td>Diarrhea</td>
<td>Loperamide Lyoc®</td>
<td>Teva Santé</td>
<td>Aspartame, sorbitol, polysorbate 60, xanthan gum, sodium hydrogen phosphate, dextran 70, lactose monohydrate, raspberry flavor powder: ethyl acetate, isoamyl acetate, limonene, benzoic acid aldehyde, benzyl acetate, beta ionone, vanillin, propylene glycol, maltodextrin, vegetable gum</td>
</tr>
<tr>
<td>Loperamide (2 mg)</td>
<td>Diarrhea</td>
<td>Imodium®</td>
<td>Cardinal/J&amp;B</td>
<td>Gelatin, mannitol, aspartame, menthol flavour, sodium bicarbonate</td>
</tr>
<tr>
<td>Metopimazine (7.5 mg)</td>
<td>Nausea and vomiting</td>
<td>Vogalene Lyoc®</td>
<td>Teva Santé</td>
<td>Xanthan gum, aspartame, sodium docusate, dextran 70, mannitol</td>
</tr>
<tr>
<td>Ondansetron (4, 8 mg)</td>
<td>Nausea and vomiting</td>
<td>Zofran ODT®</td>
<td>Eli Lilly</td>
<td>Aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavor</td>
</tr>
<tr>
<td>Olanzapine (5, 10, 15, and 20 mg)</td>
<td>Schizophrenia</td>
<td>Zyprex® Zydus®</td>
<td>Gelatin, mannitol, aspartame, sodium methyl paraben, sodium propyl paraben</td>
<td></td>
</tr>
<tr>
<td>Piracetam (20 mg)</td>
<td>Pain, inflammation</td>
<td>Nightly®</td>
<td>Cardinal/Pfizer</td>
<td>Aspartame, gelatin, mannitol, citric acid</td>
</tr>
<tr>
<td>Piracetam (10, 20 mg)</td>
<td>Pain, inflammation</td>
<td>ParacetaMelt®</td>
<td>Cephalon</td>
<td>Capsule: Aspartame, polyvynyl 60, xanthan gum, dextran 70, orange flavouring, mono hydrous lactose</td>
</tr>
<tr>
<td>Phloroglucinol (80 and 160 mg)</td>
<td>Osteoarthrosis, rheumatoid arthritis, ankylosing spondylitis</td>
<td>Spasfon-Lyoc®</td>
<td>Teva Santé</td>
<td>Xanthan gum, aspartame, sodium and xanthan gum</td>
</tr>
<tr>
<td>Risperidone (2, 4 mg)</td>
<td>Schizophrenia</td>
<td>Risperdal®/M-Tab®</td>
<td>Janssen</td>
<td>Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbonic, sodium hydroxide, aspartame, red ferric oxide, peppermint oil</td>
</tr>
<tr>
<td>Rizatriptan benzoate (3, 10 mg)</td>
<td>Migraine</td>
<td>Maxalt-MLT®</td>
<td>Merck</td>
<td>Gelatin, mannitol, glycine, aspartame, peppermint flavor</td>
</tr>
<tr>
<td>Selegiline (1.25 mg)</td>
<td>Parkinson's disease</td>
<td>Zelapar®</td>
<td>Cardinal/Elan</td>
<td>Gelatin, mannitol, glycine, aspartame, citric acid, yellow iron oxide, grapefruit flavor</td>
</tr>
</tbody>
</table>

Data collected from company sites and Refs. [23–28].
(adhesiveness increases above 100,000 Da), chain flexibility (related to polymer diffusion through the mucosal surface), hydrogen bond formation capacity (greater hydrogen bonding augments interactions with the mucosal surface), and hydration capacity (favors increased contact with the barrier surface) [3,4]. Accordingly, natural cationic chitosan allows for extensive mucoadhesion, and provides permeation enhancement and inhibition of peptidases [5,37]. The performance of chitosan makes it an excellent candidate for use in prolonged release wafers, which is supported by at least 45 papers (PubMed search, October 25, 2018) and over 40 patents (Orbit software search, October 25, 2018). Gelatin can be used to prepare extended release wafers when combined with other excipients, including chitosan, which can enhance its mechanical properties and mucoadhesiveness [38,39].

Matrix pore size, interconnections, and erosion/swelling of the polymeric chain determine drug-matrix interactions and release rates. Crosslinkers in wafers are mainly ionic in nature and include divalent cations (such as CaCl2 for use with alginate) or polyanions (such as sodium tripolyphosphate, TPP, for use with chitosan) [40]. Alginate crosslinking occurs at physiological pH and room temperature, which are desired properties for biological applications and drug stability. In turn, chitosan crosslinks with TPP under mild acidic conditions, which limits labile drugs incorporation in the gel phase. Chemical crosslinking changes the polymer network and increases resistance to disintegration, which is why orodispersible forms do not include this additive [41].

Other excipients

Freeze-dried formulations have low water content, and do not support microbial growth, precluding the need for inclusion of these additives. However, some formulations (e.g., Zydis technology) use these additives to inhibit microbial growth during manufacturing [42]. Oral lyophilizates generally contain taste-masking agents, lyoprotectors, and pH adjusters. Sweeteners mask unpleasant taste and are essential for patient compliance. Yet, most of these compounds have multifunctional roles. Xylitol has the added benefit of antimicrobial action. Mannitol prevents structural collapse during freeze-drying (lyoprotector), enhances mechanical properties, accelerates disintegration, and facilitates removal of

![Fig. 2. Structural features of natural matrix polysaccharides. (A) Molecular structure of xanthan gum, (B) molecular structure of sodium alginate and (C) molecular structure of chitosan.](image-url)
wafers from molds [43,44]. Another way to deal with unpalatable particles is by coating or encapsulation, as exemplified by the amberlite ion exchange resin in risperidone formulations [45].

Taste-masking can have the added benefit of drug solubility enhancement, as observed with cyclodextrin (CD)-drug complexation. CDs are soluble cyclic sugars that accommodate hydrophobic drugs/moieties inside their lipophilic cavities. CDs enhance permeation [46,47] and are approved by the FDA for oral use. As most wafer-based polymers are hydrophilic, drug solubility affects not only dissolution and bioavailability but also drug incorporation/homogeneity. CD-econazole complexes increased drug solubility by 66-fold, which allowed for solubilization in pectin/carboxymethylcellulose gels prior to wafer freeze-drying [48]. Although we did not find any other wafers that included this kind of complexation, many buccal films use this complexation technique to enhance solubility. The addition of CD to a polyethylene oxide buccal film increased the release of triamcinolone acetonide in the presence of mucin from 7% to 47% [49].

Additional formulation techniques can be used to increase solubility, such as pH modifiers, emulsions, amorphization, co-solvents, solid dispersions, and nanotechnology [50,51]. Curcumin was solubilized in solid lipid nanoparticles prior to dispersion in freeze-dried wafers (“sponges”) of polycarbophil. In vivo studies (with 5 adult volunteers) showed a buccal residence time of 1.5 h and sustained release over 14–15 h. However, studies demonstrating permeation or bioavailability were not performed, as the formulation was designed for local treatment of precancerous oral lesions [52]. Finally, another formulation strategy for sustained release is the use of beads. Beads offer a particulate matrix to sustain release and diminish burst effects (initial rapid release). Chitosan lactate beads loaded with tizanidine prevent burst release from chitosan lactate buccal wafers. An in vivo pharmacokinetics study (with six male volunteers) showed a considerable increase in $T_{\text{max}}$ and an increase in the bioavailability of tizanidine (2.27 folds) compared to those of the immediate release product Sirdalud® [53].

Production process

The process to obtain oral wafers has a few steps, as shown in Fig. 3. The most critical steps for stability are mixing, freezing and drying. Since many patent technologies perform slight variations of the presented backbone, we discuss some of the particularities along this topic.

Production at laboratory scale allows mixing in magnetically stirred beakers [54] with overhead mechanical stirring [32]. However, industrial production requires a temperature-controlled tank and mechanical agitation. The impeller geometry for mixing depends mainly on the rheological properties of the resultant mixture. Low viscosity products can be mixed well by hydrofoil or pitch blades. When working with encapsulated or coated particles, a high shear mixer may disrupt the coating and should be avoided [55]. The target viscosity will depend on the presence of particles and consequent sedimentation rate, as well as disintegrating and mechanical performances. For gelatin-based formulations, patents describe planetary mixers (higher viscosities, low shear) [56,57], but most documents do not provide equipment details.

Gels are dried by lyophilization (or freeze-drying), in which water is removed from the frozen matrix by vacuum sublimation. This technique has many advantages, such as improved stability of thermolabile APIs [58] and final products with high porosity (which allows subsequent gain in loading capacity per weight) [58]. The entire process can occur inside a freeze-drier. As most industrial freeze-driers do not cool below –40 °C, nitrogen tunnels or ultra-freezers can be required for specific freezing processes.

Freezing shapes wafers and determines the porosity and surface topology. Therefore, target temperature, rate, and intermediate thermal procedures are entered as settings in advance. Fast rates produce smaller particles and more crystals, which dry slower, resulting in increased drying time. Although slow freezing results in larger crystals, thermal treatments (such as annealing) could result in homogeneity and reduced drying rates [59]. A recent innovation in pharmaceutical freeze-drying processes refers to nucleation control of ice crystals upon freezing. Because nucleation occurs in a wide range of temperature, its occurrence provokes batch heterogeneity and prolonged process. Therefore, inducing simultaneous nucleation can increase product homogeneity and significantly reduce process time/cost [60]. The technologies with proven scalability to induced nucleation are depressurization, ice fog and temperature quench freezing [61].

After freezing, the product is placed under deep vacuum. Solvent removal occurs in two steps: primary (free solvent removal) and secondary drying (bound solvent removal). The former should start below the collapse temperature (Tc) of the formulation to assure structural integrity and adequate residual moisture. Although biopolymers used in wafers have high Tcs, drugs generally have lower Tc values. Primary drying is time-consuming
because bulk water sublimates in larger amounts and at lower temperatures unlike bound solvent. Higher starting temperature results in shorter drying time and lower cost [63]. As such, when Tc is close to or lower than −40 °C, reformulation often occurs. Quicksol® patent claims to facilitate drying using a second solvent, which must be miscible with water, present a lower vapor pressure and do not dissolve the other components. However, the patent of the technology does not limit freeze-drying as the only method possible; it is unclear which combinations of claims were really tested and result in optimal formulations [64]. Concerning packaging, the oral lyophilizate fragility demands specific blisters that resist physical stress and humidity [23]. Special packaging is not necessary for modified released forms due to enhanced mechanical strength, but they still need to resist water entrance.

Quality attributes and related process/material parameters

International drug-related agencies recommend the Quality by Design (QbD) approach to assure product quality. Quality, safety, and efficacy must define pharmaceutical product attributes for the intended dose, administration route, and patient profile (Quality Target Product Profile). Then, the identified Critical Quality Attributes (CQA) are correlated with Critical Material Attributes (CMA) and Critical Process Parameters (CPP). Risk analysis and experimental designs help define ranges and actions for CPP/CMA that produce desired results for the CQAs (design space) [65]. CQAs include physical, chemical, biological, or microbiological properties that may impact product quality depending on its range/limit/distribution. Thus, direct or indirect quality control are required. Identification of CPPs relies on a set of tools. Scientific literature and team experience support first conclusions, whereas risk management aids final decisions and further actions [66]. For oral lyophilizes, Table 2 shows the common CQAs and the most relevant operation units associated with these CQAs [67].

Table 2

<table>
<thead>
<tr>
<th>Critical Quality Attributes</th>
<th>Operation unit</th>
<th>Analytical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance (macrostructure)</td>
<td>Primary drying</td>
<td>Visual analysis¹</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td>Transference/mixture</td>
<td>Microbial limits</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>Mixture</td>
<td>Assay² (10 units)</td>
</tr>
<tr>
<td>API concentration</td>
<td>Mixture</td>
<td>Assay</td>
</tr>
<tr>
<td>Drug release profile</td>
<td>Freezing</td>
<td>USP Dissolution methods³</td>
</tr>
<tr>
<td>Oral residence time</td>
<td>Secondary drying</td>
<td>Mucoadhesiveness/USP Disintegration methods⁴</td>
</tr>
<tr>
<td>Residual moisture</td>
<td>Secondary drying</td>
<td>Karl Fischer/Thermogravimetry</td>
</tr>
<tr>
<td>Mechanical resistance</td>
<td>Secondary drying</td>
<td>Texture profile</td>
</tr>
</tbody>
</table>

Highlighted attributes are those that differ between orodispersible and extended release wafers. Obs: Drug Identification is a CQA that cannot be changed by process; therefore, it does not appear in the table.

¹ Color, presence of collapse, shape, dimensions.
² Assay is drug specific and performed as described in compendiums. Common analyses include HPLC, UV–vis, infrared.
³ For wafers loaded with nanoparticles, this assay can be performed in Franz cells or dialysis bags.
⁴ FDA recommendation. Other methods that provide results equivalent to the USP method can be used to determine disintegration time.
⁵ Extended release versions.

Conclusions and future perspectives

Freeze-dried wafers can provide immediate or sustained delivery of APIs for local or systemic action. These wafers allow for ease of administration, protection against mechanical removal, and high drug loading. Although production of freeze-dried wafers requires few, inexpensive excipients that are widely available commercially, freeze drying is a high-cost and long process. Therefore, wafers are generally reserved for drugs susceptible to degradation/crystallization during manufacturing by other methods, or for market product differentiation. Gelatin and xanthan gum are the most commonly used polymers in commercial products and sodium alginate is the most commonly used natural polymer for experimental formulations. Production of wafers requires few steps, mainly mixing and freeze-drying. The wafers are shaped in the freezing step, which is crucial for process cost and time. In addition to process parameters, several material attributes are critical, such as thermal transitions, crystallinity, and hygroscopicity.

Mucoadhesive buccal wafers are typically designed for sustained release and consist of coated APIs and particulate carriers. As this trend is consistent in ODTs and buccal films [75], wafers will probably follow them. The advantage of wafers lies in the process, as the absence of compression and heating stresses protect particles from deformation and aggregation. Development of experimental wafers is increasing within the framework of QbD, a trend based on recent guidelines from regulatory agencies. While few articles detail development of wafers, these studies provide a framework for rational improvements and optimal formula prediction. These studies also highlight the relevance of new excipients, such as chitosan lactate, to augment formulation efficacy. Nevertheless, in vivo experiments have been scarce, and should increase
in frequency in the future. Overall, buccal wafers are good candidates as dosage forms for commercial drugs, similar to their fast-disintegrating counterparts. Increasing scientific evidence will help sustained release buccal wafers reach clinical trials, allowing for verification of their performance in humans.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects

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References

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