



Mini-review

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



Juliana Souza Ribeiro Costa ^{a,b}, Karen de Oliveira Cruvinel ^a, Laura Oliveira-Nascimento ^{a,*}

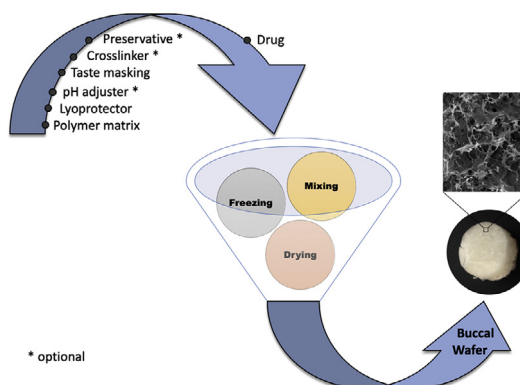
^a Faculty of Pharmaceutical Sciences, University of Campinas, Rua Candido Portinari 200, 13083-871 Campinas, São Paulo, Brazil

^b Institute of Biology, University of Campinas, Rua Monteiro Lobato 255, 13083-970 Campinas, São Paulo, Brazil

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.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 4 December 2018

Revised 25 April 2019

Accepted 26 April 2019

Available online 3 May 2019

Keywords:

Wafer

Buccal

Lyophilization

Freeze-drying

Drug delivery

Oral lyophilizates

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 matrixes 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.

© 2019 THE AUTHORS. Published by Elsevier BV on behalf of Cairo University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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

Peer review under responsibility of Cairo University.

* Corresponding author.

E-mail address: lauraon@unicamp.br (L. Oliveira-Nascimento).

<https://doi.org/10.1016/j.jare.2019.04.010>

2090-1232/© 2019 THE AUTHORS. Published by Elsevier BV on behalf of Cairo University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 [6]. For instance, ointments and hydrogels are semi-solids that lack dosage precision or adequate hardness to resist tongue removal [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 matrixes obtained by freeze-drying of polymer gels or suspensions to an average of 3 mm thickness and 9 × 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, desloratadine 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 lyophilizates. It is abundant

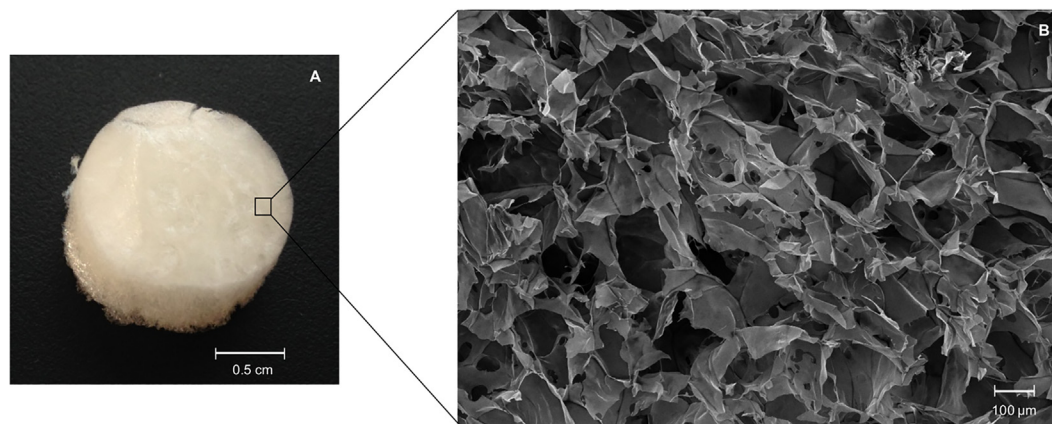


Fig. 1. An example of the macro and micro morphologies of wafers (A) Oral lyophilizate of gelatin and sodium alginate; (B) Micrograph of wafer pores obtained using a Leo 440i scanning electronic microscope (LEO Electron Microscopy/ Oxford, Cambridge, England) at 200x magnification. This Fig. was designed by the authors.

Table 1
Examples of commercial oral lyophilizates (US and EU markets).

Drug (strength)	Indication	Trade name	Company	Excipients
Brompheniramine maleate – phenylpropanolamine HCl (1 mg–6.25 mg)	Antihistamine, Decongestant	Dimetapp® Quick Dissolve	Whitehall-Robins	Aspartame, FDCA Blue No. 2, FDCA Red No. 40, flavors, gelatin, glycine, mannitol
Buprenorphine hydrochloride (2, 8 mg)	Opioid drug dependence	Espranor Oral lyophilisate	Martindale Pharma	Gelatin, mannitol, aspartame, mint flavour, citric acid
Clonazepam (0.125, 0.25, 0.5, 1, and 2 mg)	Sedation, seizures, panic attacks	Klonopin® wafer	Roche	Gelatin, mannitol, methylparaben sodium, propylparaben sodium and xanthan gum
Desmopressin acetate (25, 50, 60, 120, and 240 µg)	Vasopressin-sensitive cranial diabetes insipidus, nocturnal enuresis	Noqdirna Oral lyophilisate/DDAVP Melt Oral lyophilisate/ DesmoMelt Oral lyophilisate	Ferring Pharmaceuticals Ltd	Gelatin, mannitol, citric acid
Famotidine (20, 40 mg)	Hearthburn, Indigestion	Pepcidine Rapitab	Cardinal/Merck	Aspartame, mint flavor, gelatin, mannitol, red ferric oxide and xanthan gum
Loratadine (5, 10 mg)	Allergy	Claritin® Reditabs®	Schering	Citric acid, gelatin, mannitol, mint flavor
Loperamide (2 mg)	Diarrhea	Loperamide Lyoc®	Teva Santé	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
Loperamide (2 mg)	Diarrhea	Imodium®	Cardinal/J&J	Gelatin, mannitol, aspartame, mentol flavour, sodium bicarbonate
Metopimazine (7.5 mg)	Nausea and vomiting	Vogalene Lyoc®	Teva Santé	Xanthan gum, aspartame, sodium docusate, dextran 70, mannitol
Ondansetron (4, 8 mg)	Nausea and vomiting	Zofran ODT®	GlaxoSmith Kline	Aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, strawberry flavor
Olanzapine (5, 10, 15, and 20 mg)	Schizophrenia	Zyprexa® Zydis®	Eli Lilly	Gelatin, mannitol, aspartame, sodium methyl paraben, sodium propyl paraben
Piroxicam (20 mg)	Pain, inflammation	Feldene® Melt	Cardinal/Pfizer	Gelatin, mannitol, aspartame, citric acid
Paracetamol (500 mg)	Pain fever	Paralyoc®	Cephalon	Aspartame, polysorbate 60, xanthan gum, dextran 70, orange flavouring, mono hydrous lactose
Piroxicam (10, 20 mg)	Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis	Proxalyc®	Cephalon	Aspartame, mannitol, povidone K30
Phloroglucinol (80 and 160 mg)	Gastro-intestinal and biliary tract pain, renal colic, contraction during pregnancy	Spasfon-Lyoc®	Teva Santé	Dextran 70, mannitol (common), and for lyophilisate 160 mg: sucralose, macrogol 15-hydroxystearate.
Risperidone (2, 4 mg)	Schizophrenia	Risperdal®/M-Tab®	Janssen	Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, peppermint oil
Rizatriptan benzoate (5, 10 mg)	Migraine	Maxalt-MLT®	Merck	Gelatin, mannitol, glycine, aspartame, peppermint flavor
Selegiline (1.25 mg)	Parkinson's	Zelapar®	Cardinal/Elan	Gelatin, mannitol, glycine, aspartame, citric acid, yellow iron oxide, grapefruit flavor

Data collected from company sites and Refs. [23–28].

in animals, cost-effective, biocompatible, biodegradable, and has favorable physicochemical properties (forms hydrogels 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. Zydis® 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 [30]. Quicksolv® technology also uses gelatin as matrix (Table 1, Risperidone), but relies on more excipients and a second solvent to obtain a less friable product and facilitated packaging. In exchange, it limits drug options to the ones with low doses and immiscible in the second solvent [31]. The third and last technology (Lyoc®) with commercial medicines relies on xanthan gum as the matrix polymer (Fig. 2A). This polysaccharide forms coherent and stable freeze-dried forms, with the advantage of production and sustainability of a microbial source [32]. The apparent yield stress was reported as higher than for gelatin based products,

which results in less friable wafers and facilitated storage/package conditions [33]. 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

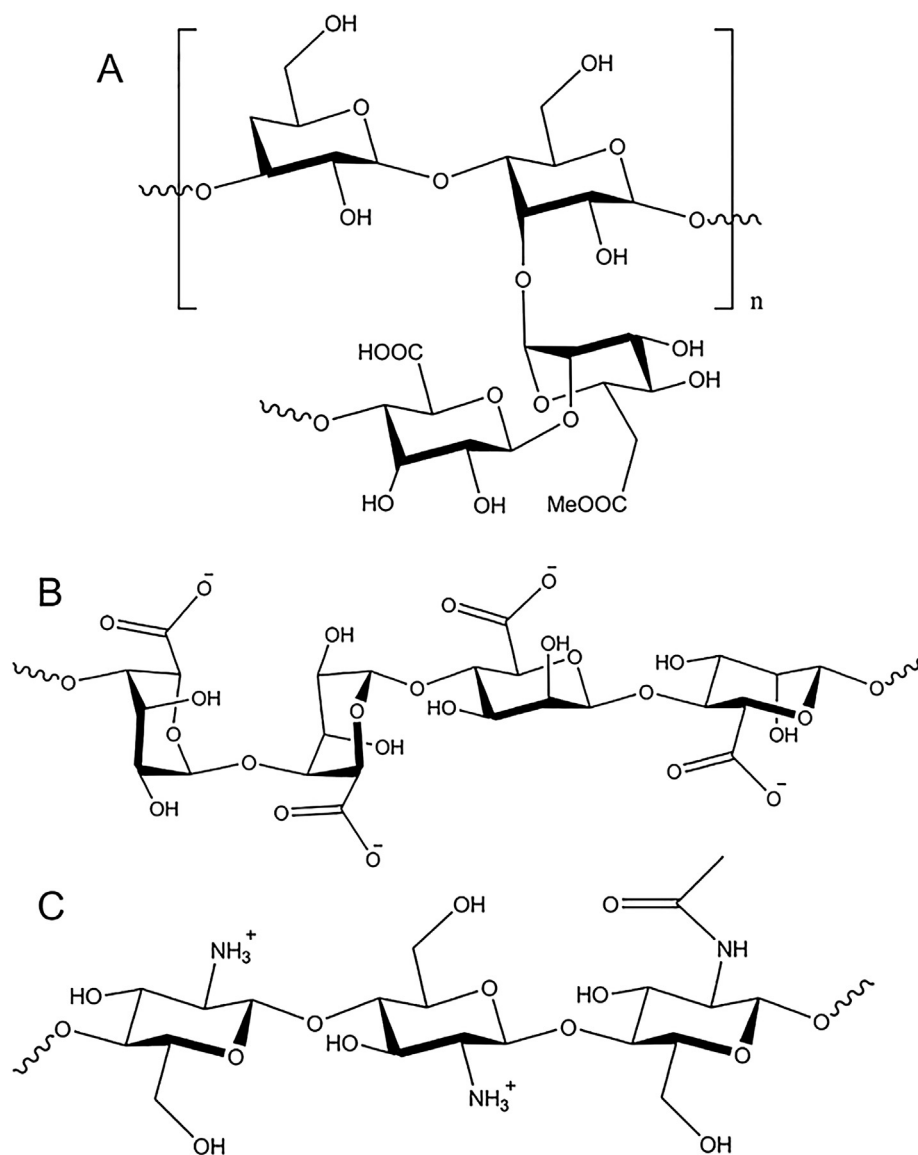


Fig. 2. Structural features of natural matrix polysaccharides. (A) Molecular structure of xanthan gum, (B) molecular structure of sodium alginate and (C) molecular structure of chitosan.

(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 CaCl_2 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

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 15 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_{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 $-40\text{ }^{\circ}\text{C}$, nitrogen tunnels or ultra-freezers can be required for specific freezing processes.

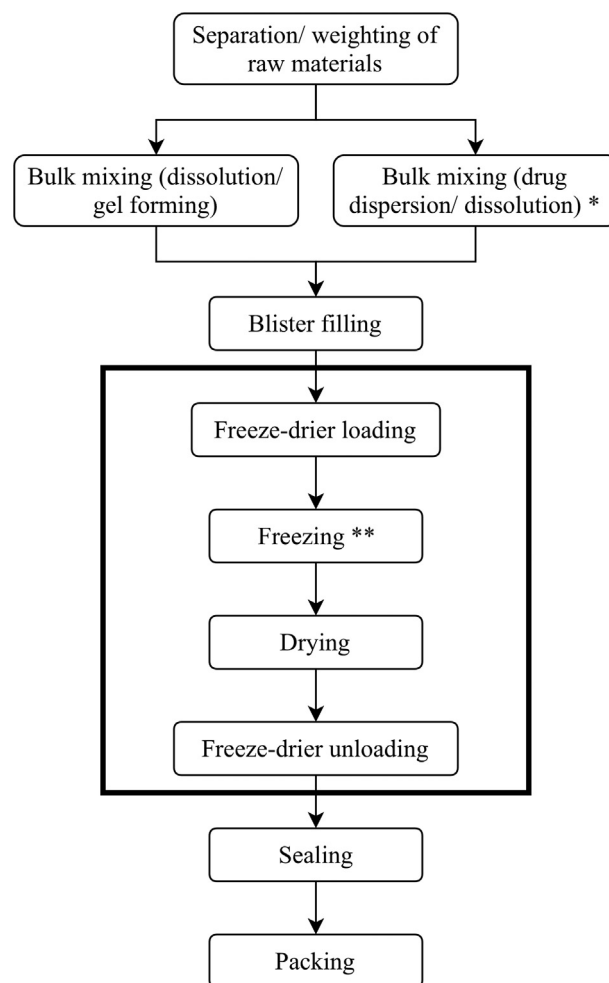


Fig. 3. Flowchart of the production process. The steps inside the highlighted box are performed inside the freeze-drier. *Drug dispersion/dissolution can be accomplished in a separate tank or directly in the gel. Liquid preparations can be solution, suspension or emulsion. Alternatively, blank wafers can be embedded in drug solutions after the lyophilization step. **Some process designs include freezing samples outside the freeze-drier (e.g. Zydis®), before the freeze-drier loading step [62].

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 (T_c) of the formulation to assure structural integrity and adequate residual moisture. Although biopolymers used in wafers have high T_c s, drugs generally have lower T_c 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 T_c is close to or lower than -40°C , reformulation often occurs. Quicksolv[®] 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 lyophilizates, Table 2 shows the common CQAs and the most relevant operation units associated with these CQAs [67].

CPPs relate to process steps that consequently impact CQAs; therefore, they must be well-established and monitored. Fig. 4 shows process parameters relevant to most common issues in wafer development and production. Cassian and coworkers observed that inadequate mixing time can lead to incomplete

polymer hydration. As a result, viscosity may be variable and affect inter/intra-batch mechanical resistance and disintegration/dissolution [44]. In addition to process parameters, CMAs affect several quality attributes. For instance, particle size and excipient solubility can influence disintegration and should be specified [14]. In the case of polymorphisms, the final product may disintegrate/dissolve slower than desired. An evaluation of gelatin-based ODTs demonstrated that low bloom strength and polymer concentration increased disintegration time. This study also showed that some saccharides confer lyoprotection and enhance hardness, but each saccharide had an optimal concentration for effective disintegration of lyophilizates. Mannitol (30–40%) was the top filler in this study for 2–5% low bloom gelatin gels [72]. Another impact of CMAs relates to process adjustments. Previous studies have demonstrated that PVP can suppress metastable forms of mannitol and eliminate the need for an annealing step in freezing [73].

Studies on wafer development that use QbD principles are scarce. A recent paper provided a complete assessment, which included risk analysis (Ishikawa-FMEA), D-optimal designs, screening of excipients, and determination of a design space for a blank formulation. These researchers found that alginate/mannitol formulations had high mechanical strength and disintegration time, whereas xanthan-gum/mannitol formulations rapidly dispersed, but maintained structural stability [44]. Another interesting study combined formulation with process parameters as the basis for developing a design space. They observed that slow freezing of methylcellulose/mannitol wafers improved mechanical strength and the dissolution profile of meloxicam [74]. In another study, an experimental design was developed to generate an optimal predicted formulation of low-methoxy amidated pectin/carboxymethylcellulose wafers to increase mucoadhesivity. The optimal polymer ratio showed similar performance to the predicted formulation, validating the mathematical approach [43].

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

Table 2
Main unit operations related to quality attributes and correlated analytical evaluations [14,68–71].

Critical Quality Attributes	Operation unit	Analytical evaluation
Appearance (macrostructure)	Primary drying	Visual analysis ¹
Microbial contamination	Transference/mixture	Microbial limits
Content uniformity	Mixture	Assay ² (10 units)
API concentration	Mixture	Assay
Drug release profile	Freezing	USP Dissolution methods ³
Oral residence time	Secondary drying	Mucoadhesiveness [*] /USP Disintegration methods ⁴
Residual moisture	Secondary drying	Karl Fischer/Thermogravimetry
Mechanical resistance	Secondary drying	Texture profile

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.

^{*} Extended release versions.

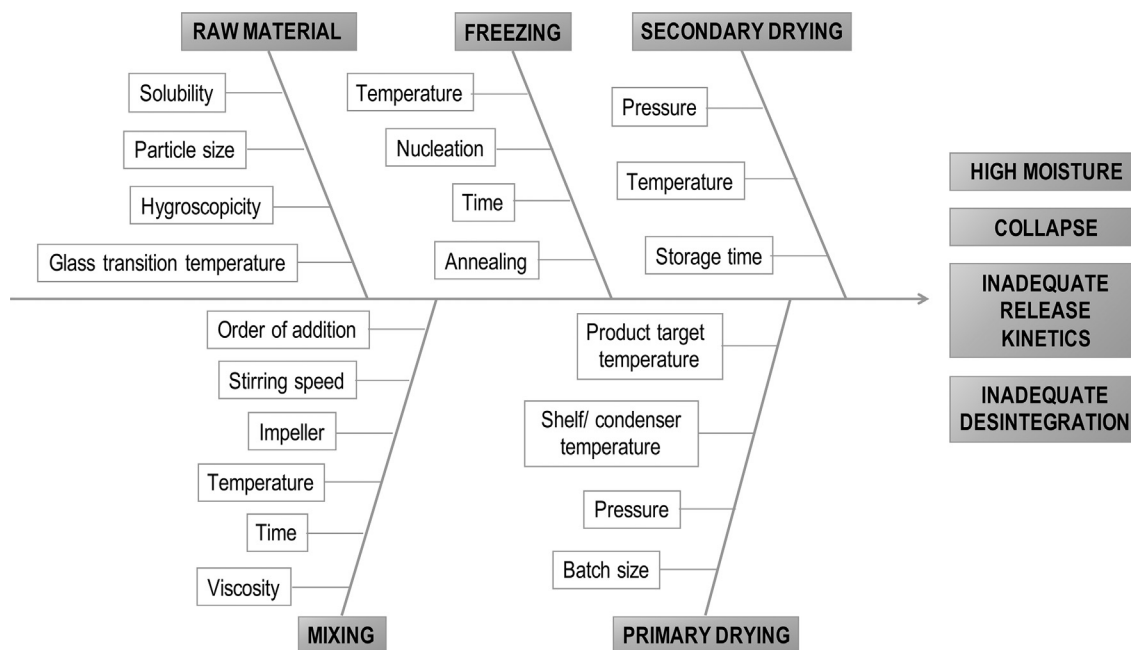


Fig. 4. Ishikawa for process parameters related to the most important quality deviations [44].

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

Acknowledgments

This study was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. We thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2014/14457-5 and 2017/06613-5) for the financial support, MPhil. Luiz Gonzaga Camargo Nascimento for the critical reading and Ana Thereza Fiori Duarte for the illustration of chemical structures.

References

- [1] U.S. Department of Health and Human Services. Guidance for industry – size, shape, and other physical attributes of generic tablets and capsules; 2015.
- [2] Spain CV, Wright JJ, Hahn RM, Wivel A, Martin AA. Self-reported barriers to adherence and persistence to treatment with injectable medications for type 2 diabetes. *Clin Ther* 2016;38(1653–1664):e1.
- [3] Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur J Pharm Biopharm* 2009;71:505–18.
- [4] Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. *Adv Drug Deliv Rev* 2005;57:1666–91.
- [5] Ayensu I, Mitchell JC, Boateng JS. Development and physico-mechanical characterisation of lyophilised chitosan wafers as potential protein drug delivery systems via the buccal mucosa. *Colloids Surf B Biointerfaces* 2012;91:258–65.
- [6] Montero-Padilla S, Velaga S, Morales JO. Buccal dosage forms: general considerations for pediatric patients. *AAPS PharmSciTech* 2017;18:273–82.
- [7] Laffleur F. Mucoadhesive polymers for buccal drug delivery. *Drug Dev Ind Pharm* 2014;40:591–8.
- [8] Aher BD, Shinkar DM, Kothawade PD, Maru AD. A review on mucoadhesive buccal drug delivery system. *World J Pharm Pharm Sci* 2018;7:305–20.
- [9] Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: *in vitro/in vivo* performance and effect of ageing. *Int J Pharm* 2003;264:1–14.
- [10] Mukherjee D, Bharath S. Design and characterization of double layered mucoadhesive system containing bisphosphonate derivative. *ISRN Pharm* 2013. doi: <https://doi.org/10.1155/2013/604690>.
- [11] Boateng JS, Auffret AD, Matthews KH, Humphrey MJ, Stevens HNE, Eccleston GM. Characterisation of freeze-dried wafers and solvent evaporated films as potential drug delivery systems to mucosal surfaces. *Int J Pharm* 2010;389:24–31.
- [12] Nagar P, Singh K, Chauhan I, Verma M, Yasir M, Khan A, et al. Orally disintegrating tablets: formulation, preparation techniques and evaluation. *J Appl Pharm Sci* 2011:35–45.
- [13] WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report - Annex 5: development of paediatric medicines: points to consider in formulation; 2012.
- [14] U.S. Department of Health and Human Services. Guidance for industry – orally disintegrating tablets; 2008.
- [15] Hoffman AS. Hydrogels for biomedical applications. *Adv Drug Deliv Rev* 2012;64:18–23.
- [16] Lerner EI, Rosenberger V, Flashner M. Pharmaceutical oral patch for controlled release of pharmaceutical agents in the oral cavity. US6197331B1; 2001.
- [17] Hay E, Rodrig J, Hussain A, Derazon H, Kopelovitch G, Dashkovsky E, et al. Rizatriptan RPD for severe migraine in the emergency department—a multicenter study. *J Emerg Med* 2003;25:245–9.
- [18] Evans RW, Mathew NT. Handbook of headache. 2nd ed. Lippincott Williams & Wilkins; 2005.
- [19] Grover VK, Mathew PJ, Hegde H. Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study. *Anaesthesia* 2009;64:595–600.
- [20] Troester MM, Hastriter EV, Ng Y-T. Dissolving oral clonazepam wafers in the acute treatment of prolonged seizures. *J Child Neurol* 2010;25:1468–72.
- [21] Center for Drug Evaluation and Research. Clinical pharmacology review: claritin® Reditab® 12 hour tablet; 2006.
- [22] El-Feky GS, Abdulmaguid RF, Zayed GM, Kamel R. Mucosal co-delivery of ketorolac and lidocaine using polymeric wafers for dental application. *Drug Deliv* 2018;25:35–42.
- [23] Ghosh TK, Pfister WR. Drug delivery to the oral cavity: molecules to market. CRC Press; 2005.
- [24] Barua S, Kim H, Jo K, Seo CW, Park TJ, Lee KB, et al. Drug delivery techniques for buccal route: formulation strategies and recent advances in dosage form design. *J Pharm Investig* 2016;46:593–613.
- [25] Datapharm Communications Limited, Medicines and Healthcare products Regulatory Agency, European Medicines Agency. Electronic Medicines Compendium (eMC) [homepage on the Internet]; 2019. <https://www.medicines.org.uk/emc/> [accessed January 29, 2019].

- [26] U. S. Food and Drug Administration. U. S. Food and Drug Administration [homepage on the Internet]; 2019. <https://www.fda.gov/> [accessed February 5, 2019].
- [27] RxMed. RxMed: Diseases and Preparations' Description [homepage on the Internet]; 2018. <https://www.rxmed.com/> [accessed August 2, 2018].
- [28] EMA. European Medicines Agency [homepage on the Internet]. European Medicines Agency; 2019. <https://www.ema.europa.eu/en> [accessed February 11, 2019].
- [29] Xing Q, Yates K, Vogt C, Qian Z, Frost MC, Zhao F. Increasing mechanical strength of gelatin hydrogels by divalent metal ion removal. *Sci Rep* 2014;4:4706.
- [30] Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems. *Crit Rev Ther Drug Carrier Syst* 2000;17:61–72.
- [31] Current Saharan VA. Advances in drug delivery through fast dissolving/disintegrating dosage forms. Bentham Science Publishers; 2017.
- [32] Matthews KH, Stevens HNE, Auffret AD, Humphrey MJ, Eccleston GM. Lyophilised wafers as a drug delivery system for wound healing containing methylcellulose as a viscosity modifier. *Int J Pharm* 2005;289:51–62.
- [33] Matthews KH, Stevens HNE, Auffret AD, Humphrey MJ, Eccleston GM. Gamma-irradiation of lyophilised wound healing wafers. *Int J Pharm* 2006;313:78–86.
- [34] Boateng JS, Matthews KH, Auffret AD, Humphrey MJ, Eccleston GM, Stevens HN. Comparison of the *in vitro* release characteristics of mucosal freeze-dried wafers and solvent-cast films containing an insoluble drug. *Drug Dev Ind Pharm* 2012;38:47–54.
- [35] Boateng JS, Matthews KH, Auffret AD, Humphrey MJ, Stevens HN, Eccleston GM. *In vitro* drug release studies of polymeric freeze-dried wafers and solvent-cast films using paracetamol as a model soluble drug. *Int J Pharm* 2009;378:66–72.
- [36] Aravamudhan A, Ramos DM, Nada AA, Kumbar SG. Chapter 4 - natural polymers: polysaccharides and their derivatives for biomedical applications. In: Kumbar SG, Laurencin CT, Deng M, editors. Natural and synthetic biomedical polymers. Oxford: Elsevier; 2014. p. 67–89.
- [37] Boateng JS, Areago D. Composite sodium alginate and chitosan based wafers for buccal delivery of macromolecules. *Austin J Anal Pharm Chem* 2014;1:1022.
- [38] Cohen B, Pinkas O, Fox M, Zilberman M. Gelatin–alginate novel tissue adhesives and their formulation–strength effects. *Acta Biomater* 2013;9:9004–11.
- [39] Bae SK, Sung T-H, Kim J-D. A soft-tissue gelatin bioadhesive reinforced with a proteinoid. *J Adhes Sci Technol* 2002;16:361–72.
- [40] Shaikh RP, Pillay V, Choonara YE, Toit LCD, Ndesendo VMK, Kumar P, et al. The application of a crosslinked pectin-based wafer matrix for gradual buccal drug delivery. *J Biomed Mater Res B Appl Biomater* 2012;100B:1029–43.
- [41] Ullah F, Othman MBH, Javed F, Ahmad Z, Md Akil H. Classification, processing and application of hydrogels: a review. *Mater Sci Eng C Mater Biol Appl* 2015;57:414–33.
- [42] Seager H. Drug-delivery products and the Zydys fast-dissolving dosage form. *J Pharm Pharmacol* 1998;50:375–82.
- [43] Sznitowska M, Płaczek M, Klunder M. The physical characteristics of lyophilized tablets containing a model drug in different chemical forms and concentrations. *Acta Pol Pharm* 2005;62:25–9.
- [44] Casian T, Iurian S, Bogdan C, Rus L, Moldovan M, Tomuta I. QbD for pediatric oral lyophilisates development: risk assessment followed by screening and optimization. *Drug Dev Ind Pharm* 2017;43:1932–44.
- [45] Tawakkul MA, Shah RB, Zidan A, Sayeed VA, Khan MA. Complexation of risperidone with a taste-masking resin: novel application of near infra-red and chemical imaging to evaluate complexes. *Pharm Dev Technol* 2009;14:409–21.
- [46] Måsson M, Loftsson T, Måsson G, Stefánsson E. Cyclodextrins as permeation enhancers: some theoretical evaluations and *in vitro* testing. *J Control Release* 1999;59:107–18.
- [47] Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. *Asian J Pharm Sci* 2014;9:304–16.
- [48] Mura P, Mennini N, Kosalec I, Furlanetto S, Orlandini S, Jug M. Amidated pectin-based wafers for econazole buccal delivery: formulation optimization and antimicrobial efficacy estimation. *Carbohydr Polym* 2015;121:231–40.
- [49] Jain AC, Aungst BJ, Adeyeye MC. Development and *in vivo* evaluation of buccal tablets prepared using danazol-sulfobutylether 7 β -cyclodextrin (SBE 7) complexes. *J Pharm Sci* 2002;91:1659–68.
- [50] Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. *Expert Opin Drug Deliv* 2007;4:403–16.
- [51] Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm Sin B* 2015;5:442–53.
- [52] Hazzah HA, Farid RM, Nasra MMA, EL-Massik MA, Abdallah OY. Lyophilized sponges loaded with curcumin solid lipid nanoparticles for buccal delivery: development and characterization. *Int J Pharm* 2015;492:248–57.
- [53] El-Mahrouk GM, El-Gazayerly ON, Aboulwafa AA, Taha MS. Chitosan lactate wafer as a platform for the buccal delivery of tizanidine HCl: *In vitro* and *in vivo* performance. *Int J Pharm* 2014;467:100–12.
- [54] Ng S-F, Jumaat N. Carboxymethyl cellulose wafers containing antimicrobials: a modern drug delivery system for wound infections. *Eur J Pharm Sci* 2014;51:173–9.
- [55] Davidson R, Rousset J. Oral films – a multi-faceted drug delivery system and dosage form. *CURE Pharm* 2018:14–7.
- [56] Ishii T, Ishii Tomo. Water-bearing gel and its production method. JP2006321792A; 2006.
- [57] Amos S, Goldwater FA. Gelating adhesive pharmaceutical preparations. US3029187A; 1962.
- [58] Bunte H, Drooge DJ, Ottjes G, Roukema R, Verrijck R, Yessine M. Key considerations when developing freeze-dried formulation and current trends. *Pharm Technol Europe Dig* 2010;22:2–4.
- [59] Kianfar F, Antonijevic M, Chowdhry B, Boateng JS. Lyophilized wafers comprising carrageenan and pluronic acid for buccal drug delivery using model soluble and insoluble drugs. *Colloids Surf B Biointerfaces* 2013;103:99–106.
- [60] Konstantinidis AK, Kuu W, Otten L, Nail SL, Sever RR. Controlled nucleation in freeze-drying: effects on pore size in the dried product layer, mass transfer resistance, and primary drying rate. *J Pharm Sci* 2011;100:3453–70.
- [61] Geidobler R, Winter G. Controlled ice nucleation in the field of freeze-drying: fundamentals and technology review. *Eur J Pharm Biopharm* 2013;85:214–22.
- [62] Kearney P, Wong SK. Method for making freeze dried drug dosage forms. US5631023A; 1997.
- [63] (Charlie) Tang X, Pikal MJ. Design of freeze-drying processes for pharmaceuticals: practical advice. *Pharm Res* 2004;21:191–200.
- [64] Gole DJ, Levinson RS, Carbone J, Davies JD. Preparation of pharmaceutical and other matrix systems by solid-state dissolution. US5215756A; 1993.
- [65] U.S. Department of Health and Human Services. Guidance for industry – Q8 (R2) pharmaceutical development; 2009.
- [66] Yu LX. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm Res* 2008;25:781–91.
- [67] Maguire J, Peng D. How to identify critical quality attributes and critical process parameters North Bethesda, Maryland, USA. AAPS J 2015. doi: <https://doi.org/10.1208/s12248-016-9874-5>.
- [68] Suci T, Iurian S, Bogdan L, Moldovan M, Tomu I. QbD approach in the development of oral lyophilisates with ibuprofen for paediatric use. *Farmacia* 2018;66:10.
- [69] Patel SM, Pikal MJ. Lyophilization process design space. *J Pharm Sci* 2013;102:3883–7.
- [70] Patel SM, Nail SL, Pikal MJ, Geidobler R, Winter G, Hawe A, et al. Lyophilized drug product cake appearance: what is acceptable? *J Pharm Sci* 2017;106:1706–21.
- [71] Jug M, Hafner A, Lovrić J, Lusina Kregar M, Pepić I, Vanić Ž, et al. *In vitro* dissolution/release methods for mucosal delivery systems. *ADMET DMPK* 2017;5:173–82.
- [72] AlHusban F, Mohammed AR, Perrie Y. Preparation, optimisation and characterisation of lyophilised rapid disintegrating tablets based on gelatin and saccharide. *Curr Drug Deliv* 2010;7:65–75.
- [73] Borges PF, García-Montoya E, Pérez-Lozano P, Jo E, Miñarro M, Manich A, et al. The role of SeDeM for characterizing the active substance and polyvinylpyrrolidone eliminating metastable forms in an oral lyophilizate—a preformulation study. *PLoS ONE* 2018;13:e0196049.
- [74] Iurian S, Tomuta I, Bogdan C, Rus L, Tokes T, Barbu-Tudoran L, et al. Defining the design space for freeze-dried orodispersible tablets with meloxicam. *Drug Dev Ind Pharm* 2016;42:1977–89.
- [75] Elwerfalli AM, Ghanchi Z, Rashid F, Alany RG, ElShaer A. New generation of orally disintegrating tablets for sustained drug release: a propitious outlook. *Curr Drug Deliv* 2015;12:652–67.



Juliana Souza Ribeiro Costa is a pharmacist (University of Campinas, Unicamp, 2011), and a doctorate student at the same University. She received her Master degree in Sciences from Unicamp (Brazil, 2014) and has experience in pharmaceutical technology, acting on modified drug release systems, nanoparticles, and buccal delivery.



Karen de Oliveira Cruvinel is an undergraduate Pharmacy student at the University of Campinas (Brazil). Her research focuses on the development of a new pharmaceutical form to deliver drugs through the oral mucosa. She currently works in pharmaceutical industry.



Laura de Oliveira Nascimento is a pharmacist (USP, Brazil -2007), with a PhD in Pharmaceutical Sciences (USP, Brazil - 2011) and doctorate Sandwich at Boston University, MA, USA (2009). She is a Professor of Pharmaceutical Technology of the University of Campinas for the last 4 years (Unicamp, Brazil). Her research focused on delivery of pharmaceutical active ingredients by nanostructured and lyophilized systems. She has over 10 years of experience in the pharmaceutical technology and biotechnology field, industrial and academic, with several published articles that, together, were cited over 350 times.