OrPhyllo™

A thin line between you and better medication

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personalizing medicine

Summary

1. Introduction

Innovative and personalized pharmaceutical dosage forms are essential in transforming how patients interact with their treatments. The patient-centric concept (Figure 1) has been extensively discussed during new active pharmaceutical ingredients (APIs) development focusing on patients' needs and preferences.[1,2] The patient-centric approach means that patients are at the center of their treatment and considers personal preferences, opinions, values, and circumstances. It aims to improve patients' lives and well-being.[1,3]

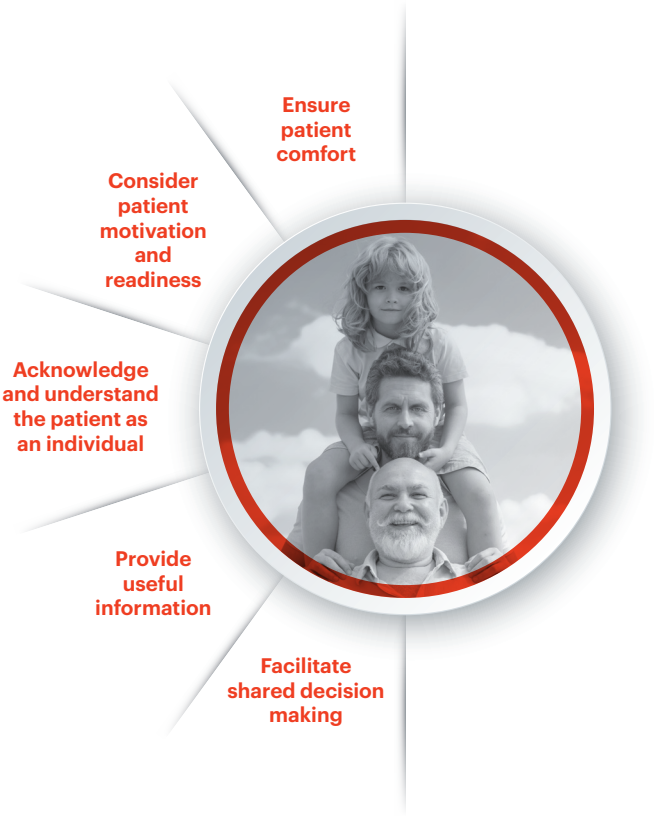

Figure 1. The patient-centric approach and its values.

Pharmaceutical dosage forms administered through the oral route are the most traditionally accepted, versatile, and convenient drug delivery system worldwide, besides having excellent treatment compliance among patients. In fact, more than 70% of the commercially available medication are for oral administration, from which most are solid dosage forms (e.g., capsules and tablets), due to their superior stability profile when compared to water-containing dosage forms.[4,5]

Although being the most prevalent route of administration, the oral route also has some limitations. For example, patients with dysphagia or other swallowing difficulties, such as those diagnosed with dementia or physical traumas, can have very low adherence to capsules or tablets. Dysphagia can occur in all age groups, but it is more common in children and elderly patients.[4,6] Other solid pharmaceutical forms such as lozenges, lollipops, gums, and chocolates, can present good alternatives for some patient groups. Nevertheless, some limitations with regard to taste, transport, and incompatibility with thermo sensitive ingredients may arise.[7] Additionally, to overcome swallowing-related problems that cannot be solved through other dosage forms, strategies such as orodispersible tablets (ODTs) were also developed.[4] This pharmaceutical form is not intended to be swallowed by the patient but to dissolve quickly once in the mouth (usually within 15 seconds). Nevertheless, some disadvantages of ODTs should also be considered. For example, difficulties in drug loading, taste masking of certain ingredients, manufacturing costs, friability of the tablets (easily breakable during transportation or when removing it from the packaging), and sensitivity to humidity.[8,9]

Advances in research and pharmaceutical technology led to a new approach known as orodispersible films (ODF). This new pharmaceutical form has gained attention in the medical community due to its unique properties of quick dissolution and disintegration. Additionally, it is highly suitable for all groups of patients, from pediatric to geriatric, and they can carry multiple APIs for different clinical conditions.[4]

Given the variety of ingredients that can be used to formulate ODFs, healthcare providers would benefit from a standardized base that maintains the reproducibility of the formulation, has a low cost per unit, is highly compatible with different APIs, and still allows for high quality, efficient, and personalized treatments.

In this brochure, we will introduce OrPhyllo™, an innovative ready-to-use base, stable and compatible with multiple APIs, developed to safely compound ODFs for different patient groups.

2. Orodispersible Films

2.1. Definitions

An ODF, also known as buccal film, oral strip, fast dissolving film, oral disintegrating film, or mouth dissolving film, is a solid pharmaceutical dosage form designed for fast delivery of active ingredients through the oral mucosa. It consists of water-soluble polymers that quickly hydrates once in contact with the saliva when placed in the oral cavity, including oral, palatal, gingival, lingual or sublingual areas (Figure 2), without the need of water intake or chewing.[5] ODFs are thin, flexible and easy to carry, with a surface area between 1 and 20 cm^2. Furthermore, they are stable to environmental conditions such as humidity and temperature and have excellent organoleptic properties (e.g., pleasant taste, no residual after-taste, and rapid administrations followed by fast disintegration).[4,5,10]

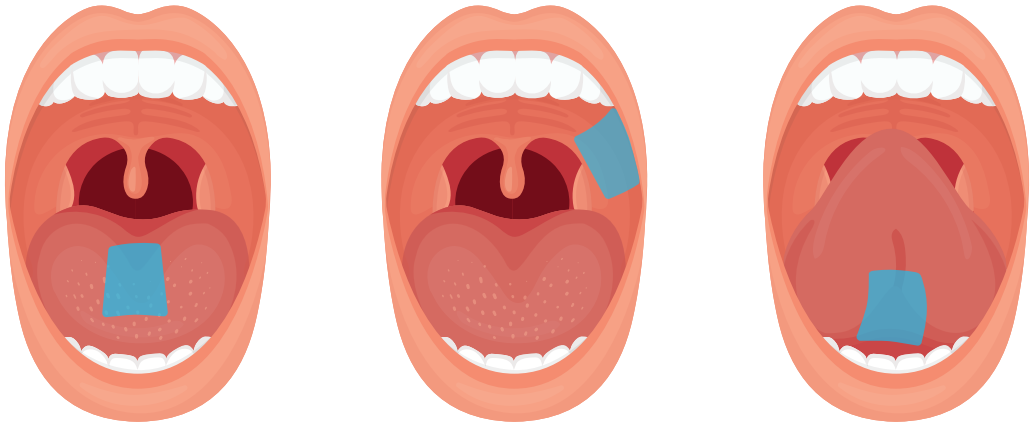

Figure 2. ODF application areas.

Officially, according to the United States Pharmacopeia (USP),[11] "Films are thin sheets that are placed in the oral cavity. They contain one or more layers. A layer may or may not contain the drug substance. [...] "Buccal films" and "sublingual films" are formulated to facilitate absorption through the proximal mucosal membranes avoiding first pass metabolism or degradation in the gastrointestinal tract and providing a quick onset of action. Films can be formulated with edible polymers such as pullulan or with water-soluble polymers such as modified cellulose, edible gums, and copolymers. The dissolution rate of the film is controlled to facilitate incorporation of the medication into saliva or for absorption by the proximal mucosa. These films must be substantial enough to maintain their integrity during manufacture and packaging, and permit handling by the patient. Because of the rapid dissolution, taste and mouth feel are important considerations."

The European Pharmacopoeia and the British Pharmacopoeia (harmonized)[12] define that orodispersible films are solid oromucosal preparations. "Oromucosal preparations are preparations intended for administration to the oral cavity and/or the throat to deliver active substances for a local or systemic effect. Preparations intended for a local effect are designed to be administered to a specific site within the oral cavity such as the gingivae (gingival preparations), the teeth (dental preparations) or the throat (oropharyngealpreparations). Preparations intended for a systemic effect are designed to be absorbed primarily at one or more sites on the oral mucosa (e.g. sublingual preparations). Mucoadhesive preparations are intended to be retained in the oral cavity by adhesion to the mucosal epithelium and may modify systemic drug absorption at the site of application. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract.

Oromucosal preparations are liquid, semi-solid or solid preparations containing one or more active substances in a suitable vehicle. They may contain preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents. Solid

preparations may in addition contain glidants, lubricants and excipients capable of modifying the release of the active substance(s)."

The choice of using ODFs offers many advantages to the patients, such as: [5,10,13]

- The fast disintegration and dissolution of the film in the oral cavity
- Rapid onset of action, which is beneficial for acute episodes (nausea, pain, allergies)
- Allow sublingual application, potencially reducing side effects related to the gastrointestinal system and decreasing hepatic first-pass metabolism
- No need for water or chewing for administration, making it suitable for rapid intake
- Greater acceptability and easy administration in dysphagic, pediatric, geriatric, and other patients with swallowing difficulties
- Dose accuracy
- Available in different sizes, allowing a wide range of applications
- Greater stability when compared to liquid dosage forms
- Flexible and portable, with minimum volume, for easy transportation during handling, use, and storage

ODFs can also have some limitations, such as being unsuitable for APIs that are irritating to the oral mucosa, sensitive to oral enzymes or unstable at the oral pH, the low maximum API loading per film, and their sensitivity to humidity if not adequately protected. Nevertheless, a wide range of clinical conditions can be addressed by using ODFs, providing increased patient comfort in relation to their therapies.[5,10,13]

Additionally, to provide a deeper insight of the advantages of using ODFs, Table 1 provides a comparison between ODFs and other traditional oral dosage forms, highlighting key features such as administration, dissolution, water requirement, patient compliance, and others.

Table 1. Comparison between ODFs and traditional oral dosage forms.

Feature	Orodispersible Films (ODFs)	Tablets/Capsules	Liquids/Syrups
Administration	Placed on tongue/oral cavity	Swallowed	Swallowed
Dissolution	Rapid dissolution (30 seconds to 2 minutes)	Dissolves ~ 30 minutes after swallowing (requires disintegration in the stomach before dissolution occurs)	Immediate
Water Requirement (for ingestion)	None	Required	Optional
Chewing	Not required	May be required	Not required
Ease of Administration	Convenient, no swallowing	May be challenging for some patients	Variable
Onset of Action	Prompt	Variable	Variable
Patient Compliance	High	Moderate	Moderate
Swallowing Difficulty	Suitable	May be challenging	Depends on viscosity
Portability and Storage	Portable, easy storage	Portable	Variable
Taste Masking	Possible for most APIs	Possible (coating)	Limited
Dosage Flexibility	Personalized by film size	Various strengths	Variable
Stability	High	High	Challenging

2.2. Potential Therapeutic Groups for ODFs

ODFs are suitable for several therapeutic classes of APIs for oral administration to obtain both local and systemic effects. These include (but are not limited to) antiulcer, antiasthma and antitussive, antihistamines, anticonvulsants, antiemetics, analgesics, non-steroidal anti-inflammatory, antidepressants, sedatives, hypnotics, diuretics, antihypertensives, antianginals, mouthwashes, vitamins, among others.[5,14] Some examples of APIs are listed in Table 2.

Table 2. Examples of active pharmaceutical ingredients for orodispersible films.[4,14]

Indication/ Therapeutic Class	Active Pharmaceutical Ingredient
Analgesic and anti-inflammatory	Ketoprofen, piroxicam, meloxicam, tramadol, indomethacin, ketorolac tromethamine, paracetamol, acetylsalicylic acid, benzydamine HCl, cefixime trihydrate, diclofenac sodium, ibuprofen, naproxen, anthraquinone, prednisolone, baclofen, ergotamine, fentanyl
Antiasthmatic	Montelukast sodium, albuterol sulfate
Antibiotics	Amphotericin B
Antidepressants	Fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, mirtazapine
Antidiarrheal	Loperamide, racecadotril
Antiemetics	Metoclopramide, dimenhydrinate, domperidone, ondansetron, granisetron, meclizine hydrochloride
Antiepileptics/ anticonvulsants	Lamotrigine, carbamazepine, clonazepam, oxcarbazepine, phenytoin, primidone, valproic acid, sodium valproate, topiramate, zonisamide, diazepam, pregabalin, gabapentin, flurazepam, olanzapine
Antiflatulent	Simethicone
Antihistamines	Loratadine, desloratadine, chlorpheniramine maleate, brompheniramine maleate, dexchlorpheniramine, cetirizine, levocetirizine, diphenhydramine hydrochloride, acrivastine, triprolidine hydrochloride, ebastine, rupatadine fumarate
Antihypertensive and heart diseases	Amlodipine besylate, valsartan, verapamil, atenolol, captopril, carvedilol, diltiazem HCl, enalapril, hydrochlorothiazide, metoprolol
Antimigraine	Naratriptan, dihydroergotamine mesylate, eletriptan hydrobromide, frovatriptan succinate monohydrate, rizatriptan, sumatriptan-prochlorperazine
Antipsychotics	Quetiapine, sulpiride, haloperidol, aripiprazole
Antitussives	Dextromethorphan
Antiulcer	Famotidine, omeprazole (powder)
Breath fresheners	Menthol, *Mentha piperita* essential oil, cinnamon essential oil
Central nervous system stimulants	Caffeine
Erectile dysfunction	Sildenafil citrate, tadalafil, vardenafil
Herbal medicines	Dry extracts: green tea (*Camellia sinensis*), guarana (*Paulinea cupana*), Korean ginseng (*Panax ginseng*), Siberian ginseng (*Eleutherococcus senticosus*), maca (*Peruvian ginseng*) (*Lepidium meyenii*), *Garcinia cambogia*, *Garcinia mangostana*, *Fucus vesiculosus, Gingko biloba*
Hypnotics/anxiolytics	Midazolam maleate, clonazepam
Hypocholesterolemic (statins)	Atorvastatin, lovastatin, pravastatin, simvastatin, cerivastatin, fluvastatin, rosuvastatin
Local anesthetics (for sore throat)	Benzocaine
Mucolytic agent	Ambroxol hydrochloride
Muscle relaxants	Baclofen, dicyclomine, tizanidine hydrochloride
Nasal decongestant for systemic use	Phenylephrine hydrochloride
Nootropics	Donepezil, memantine, piracetam, rivastigmine, vinpocetine, sulbutiamine
Nutritional supplements	Methylcobalamin, cyanocobalamin, nicotinamide, biotin, folic acid, ascorbic acid, cholecalciferol, conzyme Q10, minerals (Cr, Zn, Si, Se)
Oral antiseptics	Chlorhexidine digluconate, cetyl pyridinium chloride, triclosan, eugenol
Sialogogues (salivary stimulants)	Citric acid, malic acid, tartaric acid, pilocarpine hydrochloride
Other	Nicotine (smoking cessation), pectin (sore throat formulations), epinephrine (for severe allergic reactions), melatonin, isoniazid (tuberculosis), ledipasvir (hepatitis C), sofosbuvir (hepatitis C), ropinirole HCl (Parkinson disease), warfarin (anticoagulant), zaleplon (insomnia)

2.3. Potential Patient Groups for ODFs

2.3.1. Dysphagia and Swallowing Disorders

Dysphagia, also known as swallowing difficulties, is a symptom caused by malfunctions in any part of the swallowing mechanisms.[15,16] Although the global prevalence of dysphagia is still unclear, it is estimated that around 15% of the elderly can be affected by the condition.[17,18] Due to natural aging processes such as atrophy of the muscles and changes in the neurological system, the condition is more prevalent in these patients.[15,18]

There are a wide variety of causes for dysphagia or swallowing difficulties, but the most common ones are:[4,18]

- Neurologic or anatomic injuries on the cerebral cortex, generally associated with strokes or diseases such as Parkinson, Alzheimer and other dementias, sclerosis, myasthenia gravis, and myopathies;
- Injuries to the swallowing muscles and their structure caused by traumas, head and neck tumors, surgeries, chemoradiation-induced mucositis and edema.

Dysphagia is divided into two main types: oropharyngeal and esophageal dysphagia (Figure 3). The oropharyngeal dysphagia is split into two phases: oral and pharyngeal. [15,18]

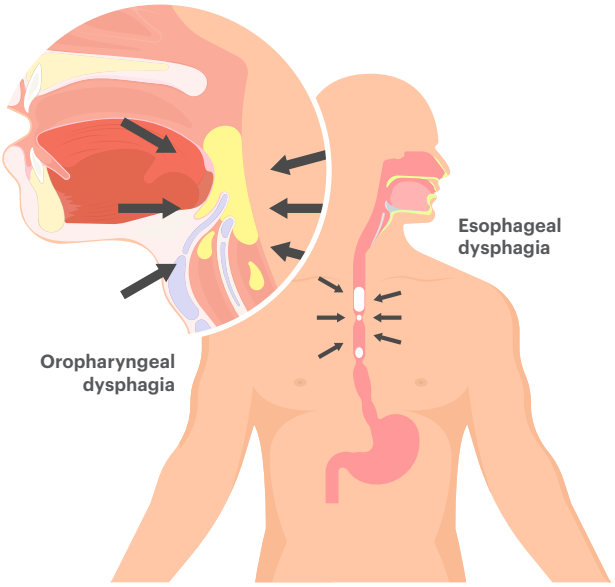

Figure 3. Types of dysphagia.

Dysphagia can result in several short and long-term consequences to the patient's quality of life. For example, it is associated with constant choking, bronchospasms, nausea and vomiting, potentially leading to malnutrition, weight loss and dehydration.[15,17,19] In addition, it can directly affect the success of treatments due to suboptimal dosage ingestion or when the medication is not commercially available in a more convenient form, either for stability reasons or palatability.[15,19]

2.3.2. Pediatric Patients

Developing a suitable dosage form for pediatric patients remains challenging among healthcare professionals. The children's acceptability of the medication is not only affected by the dosage form itself but can also be influenced by age, behavior, background, and disabilities.[20,21] Most medicinal products are not commercially available in a suitable dosage form recommended for pediatric patients since most of them are solid dosage forms (e.g., capsules and tablets). In fact, there are still concerns regarding the age at which a child can safely swallow a tablet or capsule, especially among those under the age of 2, as their swallowing mechanisms are still under maturation.[21,22]

Currently, most alternative therapies for pediatric patients are developed as liquids (e.g., syrups, drops) and suppositories to increase acceptability. However, these dosage forms are dependent on proper administration. Children can still refuse liquid dosage forms due to palatability issues, potentially resulting in sub-dosing. Additionally, due to the small therapeutic dose usually prescribed for children, minimal dosing variations might affect dose accuracy, leading to suboptimal effects or intoxication.[21] Children have a low tolerance to repeated dosage administration, especially if they are unpleasant (e.g., taste), uncomfortable (e.g., suppositories, eye drops, ear drops), or painful (e.g., injections).[22]

Finally, children receiving medication will most likely require dosage administration when they are not at home, resulting in the need for dosage forms that can be easily transported and correctly administered by caregivers who are not the parents (e.g., daycare, schools). Therefore, ensuring medicine stability during transport and correct administration to the patient is paramount for the success of the therapy.[21,22]

2.4. How to use ODFs

The greatest convenience of ODFs is their easy storage and transportation and their rapid and practical administration without water or chewing (Figure 4). This is truly beneficial for administration to patients such as described above and for addressing acute episodes (e.g., allergic reactions, vomiting, seizures, etc.). Some orientations regarding the administration are detailed below:

1. Make sure your hands and fingers are dry before touching the film to avoid it adhering to the skin surface.
2. Place the film directly in the desired application area (over the tongue, under the tongue, gingiva, or touching the inside of the cheek).
3. Wait until complete dissolution (usually a few seconds).

Figure 4. How to use ODFs.

3. OrPhyllo™ • A thin line between you and better medication

OrPhyllo™ is a base specially developed for producing ODFs for applying APIs directly in the oral mucosa (Figure 5). **OrPhyllo™** is an innovative and versatile dosage form that allows the compounding of personalized treatments for patients from all age groups, including those suffering from dysphagia or other swallowing difficulties. It provides healthcare professionals with a safe, validated and standardized base to facilitate the compounding process, ensuring reproducibility and stability.

Advantages of choosing OrPhyllo™

- Produces elegant and standardized ODFs, with increased stability
- Rapid disintegration rate (< 30 seconds)
- Validated compatibility with multiple APIs
- Promote the local and systemic API absorption
- Increased stability
- Low water activity (0.49 aw)
- Produced with natural polymers
- Possible to convert into a mucoadhesive base
- Suitable to compound mono-layer or double-layer films
- USP and EFSA (European Food and Safety Authority) compliant.

Figure 5. Orodispersible film produced with OrPhyllo™.

3.1. Compounding with OrPhyllo™

ODFs are suitable for several therapeutic classes of APIs. Traditionally, ODFs can be compounded using various ingredients that need to be combined to achieve adequate viscosity of the base (prior drying), mucoadhesiveness, dissolving rate, and stability. Also, the base should not be irritant to the mucosa and must promote the proper release of the API once it is administered in the oral cavity. In the daily routine of primary healthcare establishments, it is hard to validate all of these parameters, which can represent a limitation in the production of ODFs. **OrPhyllo™**, as a ready-to-use base, has a facilitated 4-step compounding procedure (Figure 6).

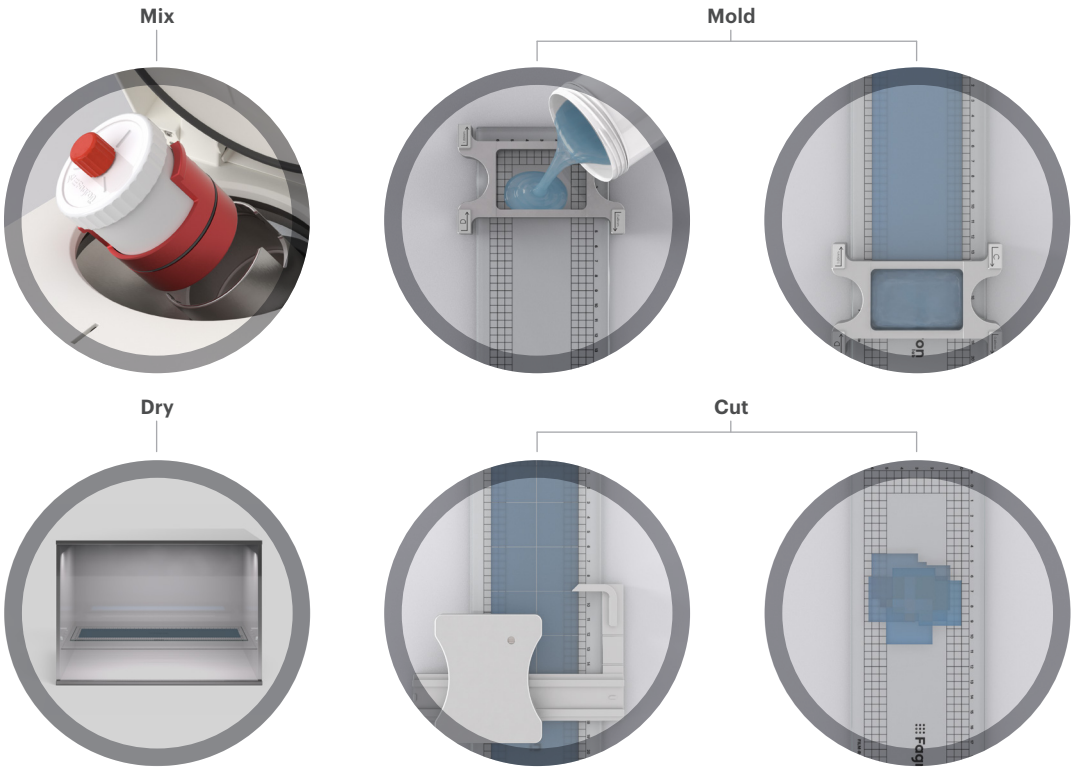

Figure 6. Step-by-step preparation procedure of ODFs.

1. Mix
All ingredients in the formulation, including APIs, inert ingredients, and the film base, must be thoroughly mixed according to the specified quantities outlined in the formulation. It is crucial to conduct the mixing process while ensuring the avoidance of air entrapment. The use of a **FagronLab™ PM140** is highly recommended.

2. Mold
The **FILM-Rx Applicator** is positioned on the **FILM-Rx Glass Plate**, with the desired thickness facing upwards **(C)**, and aligned from the top. The mixture prepared in the previous step is poured into the cavity of the **FILM-Rx Applicator**. Subsequently, the **FILM-Rx Applicator** is slowly and continuously slid across the surface of the **FILM-Rx Glass Plate**, aligning from one side without stopping or reversing the movement. The **FILM-Rx Mat** under the plate keeps the movement smooth.

3. Dry
The drying process can be conducted overnight in a laminar-flow cabinet at room temperature, ensuring a contamination-free environment. This cabinet maintains a contamination-free environment. Alternatively, a ventilated drying cabinet can be used, with the recommended drying time being **40 minutes** at **40 °C**.

4. Cut
After drying, the films are precisely cut while still positioned on the **FILM-Rx Glass Plate** using the **FILM-Rx Cutter.** The **FILM-Rx Cutter** is aligned with the engraved graduations on the **FILM-Rx Glass Plate**, allowing reproducible cutting into predefined dimensions and ensuring accurate dosage administration. Once cutting is completed, the individual film units are carefully removed from the **FILM-Rx Glass Plate**.

In addition to compounding ODFs, **OrPhyllo™** base can also be easily converted in to a mucoadhesive buccal film (MBF) base. The buccal area is an attractive alternative as a drug-delivery route thanks to the easiness of patient administration and the increased possibility of bypassing gastrointestinal enzymatic and acidic degradation.[23] Differently from ODFs, with a fast disintegrating profile, the capacity of MBF to adhere to the buccal mucosa aims to retain the medication inside the buccal cavity for a longer period, also allowing for the slow-release of the API.[24]

Finally, **OrPhyllo™** also allows for compounding double-layer films, which can be used to increase the API load per film and to associate different APIs, especially those with physicochemical incompatibilities between each other. Additionally, different disintegration profiles can be combined (e.g., one layer of ODF, and one layer of MBF), allowing for different drug-release profiles in the same formulation.[25,26]

For a complete step-by-step guide on how to compound ODFs and MBFs, both as a mono-layer or double-layer film (Figure 7), with **OrPhyllo™**, you can consult the **"OrPhyllo™ - How to Compound"** document available at **fagron.com**.

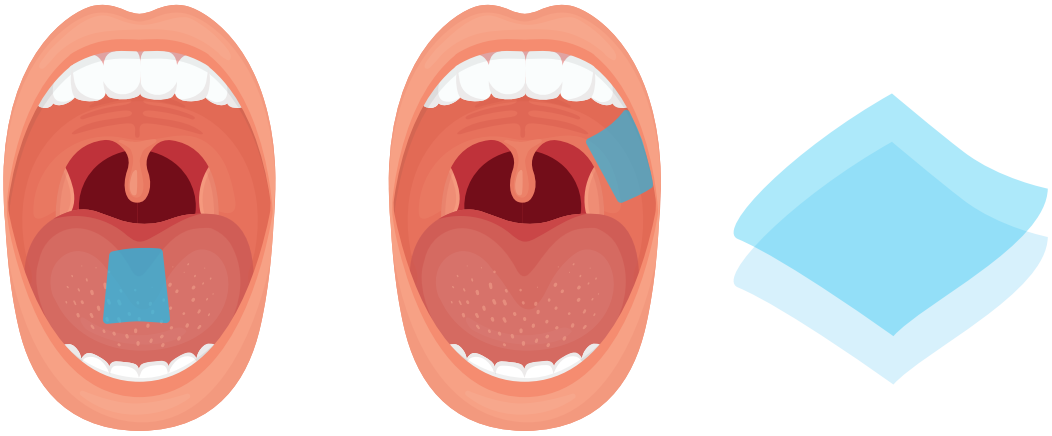

Figure 7. Types of oral films.

3.2. Ideal Characteristics of APIs for ODFs

There are some characteristics of APIs being compounded in ODFs that can be considered ideal – although they are not required, they may improve the performance of the pharmaceutical form and increase the chance of optimal therapeutic effect:[4,5,27]

- Have a pleasant or non-bitter taste
- Low therapeutic dose (ideally up to 100 mg)
- Good stability and compatibility with the saliva
- Short half-life with frequent administrations
- Low to moderately low molecular weight
- Good permeability in the oral mucosa

These ideal characteristics will allow ODFs produced with **OrPhyllo™** to be considered highly efficient and have adequate attributes. Table 3 summarizes some key points regarding ODFs' ideal characteristics.

Table 3. Key points for orodispersible films.

API Load	• For high-dose APIs, you can increase the film surface area or divide the dose into two or more films. • For APIs associations, a double-layer film is also a possibility (dissolution time may be affected due to different thickness).
Appearance	• Oral films can be compounded even if the API is not soluble in the base. It can be a suspension. • To avoid the appearance of "dots" in the films for some APIs (e.g., vitamin B12), a dye can be used.
Flavor	• You can always use water-soluble flavors to mask bitter APIs. • You can also use taste maskers/taste-blockers or technologies such as including the API in cyclodextrins.
Texture	• Crushing and sieving the APIs before mixing them with the base is paramount to ensure a homogeneous and even film texture. • Always mix the base well with the APIs, using a mortar and pestle to decrease particle size.
Mouth Feel	• Always check the pH of the APIs + vehicle before lamination and check if it's compatible with buccal use. • Saliva pH is 6.8 - 7.2. You can also use a buffering agent if needed.
Absorption	• Be sure to correctly label the film's use (buccal/sublingual). • Pay attention to the pH (ionization of the API) and use permeation enhancers when needed (e.g., menthol).

3.3. FagronLab™ FILM-Rx™

The **FagronLab™ FILM-Rx™** is a kit that offers a comprehensive solution for standardizing the entire compounding process of film formulations. By allowing to compound films in just 4 steps (refer to section 3.1.), this equipment line is indispensable for efficient production. This comprehensive solution ensures standardized compounding of high-quality films while addressing common challenges like shaking during molding or film adherence issues. Its optimized design enables seamless operation and consistent results with minimal effort.

The **FagronLab™ FILM-Rx™** kit comprises distinct products, which are also available for individual purchase:

- FagronLab™ FILM-Rx Applicator
- FagronLab™ FILM-Rx Glass plate
- FagronLab™ FILM-Rx Cutter
- FagronLab™ FILM-Rx Mat

This comprehensive kit features essential components that play key roles in the molding step. Additionally, other products included in the kit are designed to enhance standardization and streamline the formulation process (Figure 8).

3.4. Stability and beyond-use date of OrPhyllo

The **OrPhyllo™** base was developed to be compatible with a wide range of APIs for oral administration, with particular attention to those recommended for dysphagic patients or patients with swallowing difficulties, children, and the elderly.

Different APIs have already been evaluated for their compatibility and stability in **OrPhyllo™**, and a beyond-use date (BUD) of up to 180 days at room temperature was accessed for most of them. In the absence of stability tests, according to the USP,[28] the BUD assessed to non-aqueous formulations after compounding should be no later than the earliest expiration date of any API in the formulation or 6 months, whichever is earlier. After compounding, the formulation should be stored at room temperature (20 to 25 ºC) protected from humidity. The packaging should be well-sealed and resistant to light and moisture.

Given Fagron's commitment to science and quality, stability tests with APIs prone to oxidation or with challenging stability profiles are being conducted. The updated Compatibility Table with the most recent BUD data, and a complete Formulary with the suggested formulations compounded with **OrPhyllo™** are available at **fagron.com**.

Figure 8. The overview of the FagronLab™ FILM-Rx™.

3.5. Content uniformity

Formulations produced with **OrPhyllo™** in combination with the FagronLab™ FILM-Rx™ laminator and Drying cabinet have been previously validated to ensure that adequate content uniformity among individual films is obtained (Figure 9).

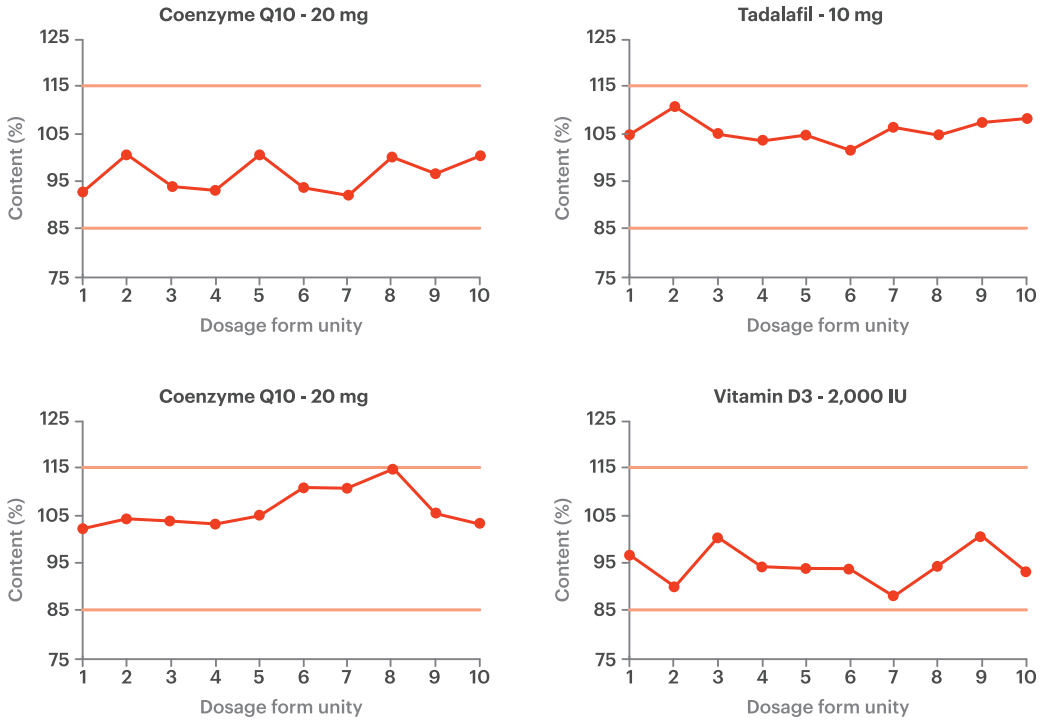

Figure 9. Content uniformity of selected ODFs produced with OrPhyllo™ and FagronLab™ FILM-Rx™ laminator.

3.6. Quality control of ODFs

The USP recommends various quality tests for drug products to ensure their safety and efficacy over time. These include tests for description, identification, assay, impurities, physicochemical properties, particle size, dosage unit uniformity, water content, microbial limits, preservative content, sterility, dissolution, breaking force, friability, leachables, and others depending on the dosage form.

For compounded ODFs, additional tests may be necessary in the absence of specific recommendations:[4,11]

- **Assessment of organoleptic properties**:
  - Appearance: Each ODF must be visually inspected for transparency or opacity, the undesirable presence of blisters, cuts, or tears, and variations in thickness;

- Taste: An essential factor for acceptance by the patient. The film should ideally have a pleasant or at least an acceptable taste;
- Color: Correlated with product identification and essential for acceptance by the patient. The color of the product must be uniform;
- Smell: Also influences acceptance by the patient. It may provide an indication of the quality of the ODF, such as the presence of odor indicating stability issues in a given batch. However, the smell may be typical of the formulation's active ingredient (e.g., vitamins) or the excipient (e.g., flavoring agents).

- **pH of the film surface**: The pH of the formulation must be checked since extreme values may irritate the mucosa, especially if it is a mucoadhesive preparation. The pH can be determined by allowing the film to swell moderately in an aqueous solution.
- **Weight variation**: Must be checked for each batch using an analytical precision electronic balance. The test may be conducted with the individual weight of 10 samples of each prepared batch.
- **Assay/content uniformity**: Determined via a standardized analytical method for the API conveyed, as described in officially recognized pharmacopeias. Content uniformity is determined by the API content in each film through the appropriate assay of the substance or estimated through the analysis of weight variation among individual units. The limits of content uniformity should be between 85% and 115%.
- **Disintegration test**: Disintegration time is the time (in seconds) for the film to break up or disintegrate when in contact with water or saliva. The disintegration time limit for ODFs should be no more than 30 seconds; a maximum of 90 seconds for specific formulations could be acceptable. The typical disintegration time ranges typically between 5 and 30 seconds. Although no official method is described for ODFs, a pharmacopeial test with a disintegration apparatus can be used for this test with some adaptations. Alternatively, the disintegration time may be visually determined in a 25 mL Petri dish at 10-second shaking intervals. The disintegration time is determined when the film starts to break up or disintegrate. The *in vivo* disintegration time in the oral cavity may also be determined by administering randomly selected films to six male volunteers at one-hour intervals. The time required for complete disintegration in the oral cavity should be recorded.
- **Dissolution test**: A test to measure the release of the drug from the dosage form. The dissolution test can be conducted with a dissolution apparatus (using paddles as the mixing accessory) as described in pharmacopeias. For example, the test can be conducted at 37 °C ± 0.5 °C in 900 mL phosphate buffer pH 6.8 as a dissolution medium at 75 rpm agitation. Collect aliquots containing 5 mL at 2-, 4-, 6-, 8-, and 10-min intervals replacing the buffer with the same volume. The concentration is determined in the collected samples using an appropriate analytical method for the APIs. The determination is usually done by UV-visible spectrophotometry.

4. Safety of OrPhyllo™

The safety of **OrPhyllo™** was evaluated through an *in vitro* study regarding its cytotoxicity, genotoxicity, and cell-inducing effects on oral mucosa cells (fibroblasts and gingival keratinocytes). The results indicate that **OrPhyllo™** did not demonstrate either cytotoxicity or genotoxicity. In short, the analysis demonstrated that:

- Cytotoxicity evaluation tests such as MTT, Neutral Red Uptake, and lactate dehydrogenase (LDH) enzyme assay showed that, even at high doses, **OrPhyllo™** was not able to significantly affect the viability of the studied cell lines.
- The same test mentioned above, with various exposure times (24, 48, 72 and 96 hours) also revealed that **OrPhyllo™** did not induce cytotoxicity in the studied cell lines.
- The micronucleus test, used to assess genotoxicity, did not show a significant increase in the presence of micronuclei compared to the control cell group (untreated cells). It is worth noting that the cells used in the genotoxicity test were cells derived from the periodontal ligament, which are more sensitive than the established cell lines used in the cytotoxicity tests.
- The evaluation of the ability of **OrPhyllo™** to induce cell death, using the Annexin/7-AAD assay to assess the following modes of cell death: apoptosis, late apoptosis, and cell necrosis, did not demonstrate that **OrPhyllo™** was capable of inducing cell death in the studied cell line.

OrPhyllo™ was formulated as biocompatible with the oral environment and non-irritant to the oral mucosa. **OrPhyllo™** contains soy lecithin in its composition and is free from allergens and controversial ingredients such as artificial colorants, artificial flavoring, artificial sweeteners, gluten, lactose, benzyl alcohol, dextrose, glycerin, propylene glycol, sorbitol, sucrose, xylitol, and parabens. The ingredients contained in **OrPhyllo™** are USP, EP and EFSA-compliant, with no safety concerns associated with any of its components.

OrPhyllo™ is alcohol-free, cruelty-free, and BSE/TSE-free (Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy). There are no ingredients from animal sources in the composition of **OrPhyllo™**; therefore, the product is safe for use by vegetarian/vegan patients.

References

1. Yeoman, G. *et al*. Defining patient centricity with patients for patients and caregivers: A collaborative endeavour. *BMJ Innov* **3**, 76–83 (2017).
2. Page, S. *et al*. Annual Review of Pharmacology and Toxicology Patient Centricity Driving Formulation Innovation: Improvements in Patient Care Facilitated by Novel Therapeutics and Drug Delivery Technologies. (2022) doi:10.1146/annurev-pharmtox-052120.
3. Robbins, D. A., Curro, F. A. & Fox, C. H. Defining patient-centricity: Opportunities, challenges, and implications for clinical care and research. *Ther Innov Regul Sci* **47**, 349–355 (2013).
4. Oliveira, A., Polonini, H. & Brandão, M. *Practical Guide of Pharmaceutical Compounding*. vol. 1 (Editar, Juiz de Fora, MG, Brazil, 2023).
5. de Oliveira Ferreira, A. *et al*. Orodispersible Films for Compounding Pharmacies. *Int J Pharm Compd* **21**, 454–461 (2017).
6. Flynn, E., Smith, C. H., Walsh, C. D. & Walshe, M. Modifying the consistency of food and fluids for swallowing difficulties in dementia. *Cochrane Database of Systematic Reviews* vol. 2018 Preprint at https://doi.org/10.1002/14651858.CD011077.pub2 (2018).
7. Oliveira, A., Polonini, H. & Brandão, M. *Practical Guide of Pharmaceutical Compounding*. vol. 2 (Editar, Juiz de Fora, MG, Brazil, 2023).
8. v. Allen, J. L. & C. Ansel, H. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. (Lippincott Williams & Wilkins, Baltimore, MD, 2014).
9. Desai, A. & Lee, M. *Gibaldi's Drug Delivery Systems in Pharmaceutical Care*. (American Society of Health-System Pharmacists, 2007).
10. Gupta, M. S., Kumar, T. P., Gowda, D. V. & Rosenholm, J. M. Orodispersible films: Conception to quality by design. *Adv Drug Deliv Rev* **178**, 113983 (2021).
11. U.S. Pharmacopeial Convention. *<1151> Pharmaceutical Dosage Forms*. (2023). doi:10.31003/USPNF_M99860_08_01.
12. British Pharmacopoeia. *Oromucosal Preparations*. (2023).
13. Morath, B., Sauer, S., Zaradzki, M. & Wagner, A. H. Orodispersible films – Recent developments and new applications in drug delivery and therapy. *Biochem Pharmacol* **200**, 115036 (2022).
14. Ferlak, J., Guzenda, W. & Osmałek, T. Orodispersible Films—Current State of the Art, Limitations, Advances and Future Perspectives. *Pharmaceutics* **15**, 361 (2023).
15. McCarty, E. B. & Chao, T. N. Dysphagia and Swallowing Disorders. *Medical Clinics of North America* vol. 105 939–954 Preprint at https://doi.org/10.1016/j.mcna.2021.05.013 (2021).
16. NHS inform. Dysphagia (swallowing problems). *https://www.nhsinform.scot/illnesses-and-conditions/stomach-liver-and-gastrointestinal-tract/dysphagia-swallowing-problems#:~:text=Dysphagia%20is%20the%20medical%20term,up%2C%20sometimes%20through%20the%20nose* (2023).
17. Sura, L., Madhavan, A., Carnaby, G. & Crary, M. A. Dysphagia in the elderly: Management and nutritional considerations. *Clinical Interventions in Aging* vol. 7 287–298 Preprint at https://doi.org/10.2147/CIA.S23404 (2012).
18. Wilkinson, J. M., Codipilly, C. & Wilfahrt, R. P. *Dysphagia: Evaluation and Collaborative Management*. vol. 103 www.aafp.org/afp (2021).
19. Sheikhany, A. R., Shohdi, S. S., Aziz, A. A., Abdelkader, O. A. & Abdel Hady, A. F. Screening of dysphagia in geriatrics. *BMC Geriatr* **22**, (2022).
20. Bracken, L. *et al*. Can children swallow tablets? Outcome data from a feasibility study to assess the acceptability of different-sized placebo tablets in children (creating acceptable tablets (CAT)). *BMJ Open* **10**, e036508 (2020).
21. Klingmann, V. *et al*. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. *Journal of Pediatrics* **201**, 202-207.e1 (2018).
22. European Medicines Agency. *Commitee for Medicinal Products for Human Safe Use (CHMP), Reflection Paper: Formulations of Choice for the Paediatric Population*. http://www.emea.europa.eu (2006).
23. Abruzzo, A. *et al*. Mucoadhesive Buccal Films for Local Delivery of Lactobacillus brevis. *Pharmaceutics* **12**, 241 (2020).
24. Montenegro-Nicolini, M. & Morales, J. O. Overview and Future Potential of Buccal Mucoadhesive Films as Drug Delivery Systems for Biologics. *AAPS PharmSciTech* **18**, 3–14 (2017).
25. Satishbabu, B. & Srinivasan, B. Preparation and evaluation of buccoadhesive films of atenolol. *Indian J Pharm Sci* **70**, 175 (2008).
26. Speer, I., Preis, M. & Breitkreutz, J. Novel Dissolution Method for Oral Film Preparations with Modified Release Properties. *AAPS PharmSciTech* **20**, 7 (2019).
27. Visser, J. C., Wibier, L., Mekhaeil, M., Woerdenbag, H. J. & Taxis, K. Orodispersible films as a personalized dosage form for nursing home residents, an exploratory study. *Int J Clin Pharm* **42**, 436–444 (2020).
28. United States Pharmacopeial Convention. <795> Pharmaceutical Compounding - non-sterile preparations. in *United States Pharmacopeia* (2023).

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