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Oromucosal film preparations: points to consider for patient centricity and manufacturing processes

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ABSTRACT

Introduction: According to the European Pharmacopoeia, oromucosal films comprise mucoadhesive buccal films and orodispersible films. Both oral dosage forms receive considerable interest in the recent years as commercially available pharmaceutical products and as small scale personalized extemporaneous preparations.

Areas covered: In this review, technological issues such as viscosity of the casting liquid, mechanical properties of the film, upscaling and the stability of the casting solution and produced films will be discussed. Furthermore, patient-related problems like appearance, mucosal irritation, taste, drug load, safety and biopharmaceutics are described. Current knowledge and directions for solutions are summarized.

Expert opinion: The viscosity of the casting solution is a key factor for producing suitable films. This parameter is amongst others dependent on the polymer and active pharmaceutical ingredient, and the further excipients that are used. For optimal patient compliance, an acceptable taste and palatability are desirable. Safe and inert excipients should be used and appropriate packaging should be provided to produced films. Absorption through the oral mucosa will vary for each active compound, formulation and patient, which gives rise to pharmacokinetic questions. Finally, the European Pharmacopoeia needs to specify methods, requirement and definitions for oromucosal film preparations based on bio-relevant data.

1. Introduction

In the monograph “Oromucosal Preparations” (Ph. Eur. 8.0),[1] two different film formulations are defined: Mucoadhesive buccal and orodispersible films. Mucoadhesive buccal films are described as dosage forms that can be attached to the target site in the oral cavity, where they release the drug for local or systemic action. These films may dissolve, but can also consist of a nondispersible material that needs to be removed after releasing the drug.[2,3] Orodispersible films are single- or multiple-layer thin polymer sheets intended for rapid disintegration, which are usually placed onto the tongue.[2,3] Both types of films can be designated as oromucosal films. These oromucosal film preparations consist of a film-forming polymer (most common are cellulose derivatives such as hypromellose), which serves as carrier matrix for the active pharmaceutical ingredient (API); in some cases, an additional plasticizer is needed to ensure the film flexibility. Different excipients such as saliva stimulating agents, fillers, colors and flavors can be added.[2]

Oromucosal films have received increasing interest in the recent years,[4] not only as easy-to-use commercially available pharmaceutical products, but also as small scale extemporaneous pharmacy preparations suitable for personalized use. The latter creates flexibility in pharmacotherapy and may suit an individual approach for a patient in cases where commercial products are unavailable or insufficiently meet specific needs by the individual patient. Besides the dose flexibility, oromucosal films have considerable advantages compared to other oral dosage forms. The films adhere to the mucosa, cannot be spit out and usually do not require water for intake. This provides a good patient acceptance and compliance. Oromucosal films may display different biopharmaceutical characteristics as compared to other oral dosage forms. If the API is indeed absorbed directly via the oral mucosa, the first pass
Oromucosal films are gaining increasing interest both as commercially available pharmaceutical products and as extemporaneous preparations for personalized use. So far, the solvent casting method seems to be the production technique of choice. To enhance the acceptability for the patient, oromucosal films should have an acceptable taste and appearance and should not be irritable. Oromucosal films should be protected by appropriate packaging to enhance their stability. These dosage forms should possess suitable mechanical strength, which can be defined as acceptable mechanical properties for manufacturing and handling of the films. Oromucosal films offer different routes of drug absorption:

- the immediate disintegration of the film on the tongue can be considered as an oral drug delivery and absorption via the gastrointestinal route
- whereby the application of the film onto different target sites of the oral mucosa enables local drug release and action, besides systemic absorption by absorption of the active substance through the mucosa.

All production techniques mentioned are able to produce oromucosal films with adequate quality. However, all preparation processes and techniques entail some limitations that should be coped with and preferably restrained.

This review focuses on problem-solving in the pharmaceutical development of oromucosal films for small scale as well as for industrial production. Further, it addresses the problems regarding patient acceptance, safety of excipients, handling properties and biopharmaceutics.

2. Patient-related issues

2.1 Acceptance

Patient acceptance of a dosage form is of high interest for its compliance, e.g. the regular and correct intake of the dosage form. Commonly used oral dosage forms may cause problems that can be excluded by using oromucosal film preparations. Especially for children, adolescents, elderly and persons suffering from dysphagia or mental illness, swallowing deficiencies are known for tablets or capsules. This may result in nonadherence or undesired modification of the dosage form by the patient. Crushing or dissolving of the solid oral dosage form, to avoid swallowing, may affect essential performance characteristics such as the dissolution and absorption behavior or stability of the drug. Orodispersible tablets may overcome the swallowing challenges but aspiration concerns still remain. By using liquid formulations, the swallowing problems can be circumvented, but other problems like accurate dosing, taste problems and drug stability may arise.

Oromucosal films are solid forms that stick to the oral mucosa, contain a fixed dose and do not have to be swallowed at once. If adequately formulated, many of the aforementioned problems can be overcome by this dosage form. The ease of administration without water is a clear advantage of oromucosal films. A high acceptability for these novel dosage forms can thus be assumed. An orodispersible film formulation containing dexamethasone was shown to be superior regarding its taste and ease of administration compared to a tablet in an acceptability study with 19 patients.

Nevertheless, several other critical acceptance issues, which may seem less important for tablets, capsules or liquids, like appearance, taste, mouth feel, irritation of the mucosa or mucus formation in the oral cavity, have to be considered during the development of an oromucosal film formulation. Finally, it has to be emphasized that a formulation, which is “too acceptable”, may lead to drug abuse. This has to be
considered especially in view of the development of pediatric formulations.[21]

2.1.1 Appearance

Beside the danger of confusion, the appearance of a dosage form is also important for a satisfying compliance by the patient. The appearance of oromucosal film preparations may vary in many aspects. A dosage form with a color associating with a sweet may lead to drug abuse, especially by children. Oromucosal films should be free from air bubbles and have a smooth, soft and flexible appearance.[22,23] Sometimes the use of a different polymer may help to improve the appearance of a film or may help to reduce or modify the recrystallization of the API in the film during storage (like e.g. the use of polyvinyl pyrrolidone, hydroxypropyl methylcellulose and methylcellulose as a crystallization inhibitor).[6,22,24]

2.1.2 pH value/irritation

The incorporation into a film of acidic or alkaline APIs or excipients, like polymers or solubilizers, may influence the experienced surface pH after wetting of oromucosal dosage forms.[25,26] Alkaline or acidic properties of the surface differing from the pH of the saliva may lead to an acidic or alkaline microenvironment in the film–mucosa interface causing mucosal irritation and damage.[25,26] The resulting pain and infection risk will lead to significantly reduced acceptance and poor patient compliance. A damaged oral mucosa may also lead to an uncontrolled permeability for the drug. A pH range of 7 ± 1.5, measured on the wetted surface of the films, comparable to the human saliva pH is considered as appropriate and non-irritant for buccal adhesive patches.[27] As the pH of the human saliva is highly variable, a nonirritant surface pH is hardly to predict. Thus also films with a surface pH of 4.5–6.5 have been developed which did not elicit local irritation.[28] It should be realized that especially the strength of the buffer is an important factor in this respect. When the product has a low buffer strength, dilution with saliva buffer will reduce any potential harm rapidly. However, when there are strong buffers used, the saliva dilution will have less affect and harm may be caused. Furthermore, the type of film should be considered in this respect. Orodispersible films, where a change in pH only occurs for a few seconds, are much safer than mucoadhesive buccal films, which remain at the oral mucosa for a longer time and which should preferably cause no significant change in pH during the drug release.[29] Sometimes acidic polymers are used because of their good mucoadhesiveness. A combination with nonirritant adhesive polymers, e.g. sodium carboxymethylcellulose, could reduce the risk of irritation.[25] In addition buffers, alkaline or acid, have been incorporated into films to neutralize the films pH.[30] Also API salts may be used instead of the corresponding acid or base form.

2.1.3 Poor taste

Taste is one of the most critical aspects regarding the acceptability of a dosage form. As the API, incorporated in oromucosal films, will (partly) dissolve in the mouth, an interaction with the taste receptors is inevitable. APIs with a poor taste may lead to reduced compliance by the patient.[20,31] An effective taste masking is therefore required. A framework providing different steps during the development of palatable formulations has been designed.[32] After the first step, the taste assessment, the formulation development can be carried out by either reduction of the unpleasant taste or by addition of substances to create a favored taste. It should be realized, however, that the creation of a pleasant, candy-like taste also implicates the danger of drug abuse by children.[21] For oromucosal films, several approaches are available to improve the taste of a formulation. Table 1 gives an overview of possible taste masking techniques.

The probably easiest method to overlay the unpleasant taste of an API is the addition of sugar alcohols, flavors, nutritive or artificial sweeteners. In many cases, a combination of such excipients is used to improve the taste of oromucosal films.[20,42]

After the taste-masked dosage form is developed, the taste has to be evaluated. Human taste panels are expensive, require the authorization of an ethical assessment committee and sometimes involve API-related health risks. Therefore, electronic tongues [43] and biorelevant dissolution methods [44] are good alternatives to pretest the formulation.

2.1.4 Mouth feel

In contrast to other solid oral dosage forms, where swallowability is most important as they stay in the mouth only for a few seconds, oromucosal films dissolve or disintegrate in the mouth and may remain there for a longer time. Therefore, the texture and mouthfeel of oromucosal films have to be considered next to the size of the film.

The space provided by the oral cavity at the site of application limits the size of the dosage form. Orodispersible films with a size of $2 \times 2 \text{ cm}^2$ and a thickness of 100 µm as well as a size of $2 \times 3 \text{ cm}^2$ and a thickness of 350 µm were judged as acceptable in human volunteer studies.[20,36] Films with a size of 1–2 cm² were judged acceptable for mucoadhesive preparations,[45]
As orodispersible films differ from mucoadhesive films in their behavior in the mouth, their texture has to be evaluated for every individual dosage form. For orodispersible films, the change in the texture during dissolution or after disintegration has to be considered. Particles remaining after disintegration may negatively influence the mouthfeel and thereby the acceptability of films.[36] Small particles were preferred over large particles as especially larger particles cause a poor mouthfeel.[46] A poor mouthfeel may also occur due to a gummy nature of the films after wetting, caused by a polymer with a viscous behavior or a slow drug release.[37] Finally, excipients like polyhydric alcohols may improve the mouthfeel due to their cooling properties.[35,46]

For mucoadhesive films, in contrast, disintegration and the resulting texture are less important. Other features like sufficient mucoadhesiveness of the film, the flexibility and change in the habitus during attachment have to be considered instead regarding the residence time in the oral cavity. A high increase in film surface has been reported for buccal mucoadhesive films based on polyvinylalcohol, which may lead to an unpleasant mouthfeel.[45]

### Table 1. Possible taste masking approaches and technical implementations for use in oromucosal films.

<table>
<thead>
<tr>
<th>Taste masking approach</th>
<th>Technical implementation</th>
<th>Substances used</th>
<th>(Dis)advantages/remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste is overlaid by other substance</td>
<td>Nutritive sweetener</td>
<td>Sucrose, glucose, fructose, dextrose, maltose, stevia</td>
<td>Should be used in high amounts, which may lead to poor mechanical stability. Possess cariogenic potential. Caloretic value has to be considered especially for diabetic patients (only sucrose, glucose)</td>
</tr>
<tr>
<td>Artificial sweetener</td>
<td>Saccharine, aspartame, saccharin sodium, acesulfame potassium, neotame, alicam</td>
<td>Not cariogenic. Lower amounts are sufficient for comparable sweetening effect.[33] Bitter and metallic after taste has been reported,[34] which can be reduced by adding flavors,[35]</td>
<td></td>
</tr>
<tr>
<td>Sugar alcohols</td>
<td>Sorbitol, mannitol, xylitol</td>
<td>Less sweet than sucrose. Cooling effect possibly improving the palatability of the film formulation.[35]</td>
<td></td>
</tr>
<tr>
<td>Flavor</td>
<td>Mint, milk, fruit . . .</td>
<td>Detection by the nose after evaporation</td>
<td></td>
</tr>
<tr>
<td>Other excipients</td>
<td>Glycerol, maltodextrines</td>
<td>Glycerol tastes sweeter than propylene glycol.[36] Maltodextrine displays a sweet sensation and improves palatability of the dosage form.[23]</td>
<td></td>
</tr>
<tr>
<td>All taste overlaying substances</td>
<td></td>
<td></td>
<td>Faster speed of onset of API on the taste receptors compared to the taste masking agents. Sprinkling a flavor on top of a film may lead to faster contact of the taste buds with the flavor than with the API, by which the sweet taste is experienced before the bad taste.[37]</td>
</tr>
<tr>
<td>Bitter receptor inactivation</td>
<td>Bitter blocker</td>
<td>G – protein antagonists</td>
<td>Reduce the bitter taste of APIs. Lack the after taste sensation of artificial sweeteners.[38]</td>
</tr>
<tr>
<td>API receptor interaction interrupted</td>
<td>Particle coating</td>
<td>Saliva insoluble polymers</td>
<td>Coating or encapsulation of drug particles, which are swallowed after the film has dissolved.[37]</td>
</tr>
<tr>
<td>API not dissolved in the oral cavity</td>
<td>Incorporation in complexes or adhesion to structures</td>
<td>Cyclodextrines, maltodextrin</td>
<td>API–receptor interaction may be disturbed.[24,39]</td>
</tr>
<tr>
<td>Ionic change resins</td>
<td>Cholesteamine</td>
<td>The binding of ionic API molecules to charged moieties of excipients may decrease the amount of dissolved API in the saliva and thus the interaction with the taste receptors.[40]</td>
<td></td>
</tr>
<tr>
<td>API not dissolved in the oral cavity</td>
<td>Backing layer</td>
<td>Hypromellose + crospovidone</td>
<td>Taste masking approach by addition of a second layer that covers the active film.[3]</td>
</tr>
<tr>
<td>Salt or prodrug that is insoluble in the saliva</td>
<td></td>
<td>An insoluble salt or prodrug may not always be available, or also cause dissolution problems in the gastrointestinal tract, gritty mouth feeling.</td>
<td></td>
</tr>
<tr>
<td>Ion exchange resin</td>
<td>Chemical</td>
<td>Gritty mouth feeling of the insoluble resin</td>
<td></td>
</tr>
<tr>
<td>Prodrug</td>
<td></td>
<td>Reduction of unpleasant taste by a more rapid absorption or swallowing of the prodrug in relation to the conversion of the prodrug into its active form.[41]</td>
<td></td>
</tr>
<tr>
<td>Coating of the drug particles</td>
<td>Polycrylates or ethyl cellulose</td>
<td>Production difficulties because the coating should not dissolve during casting of the suspension. Gritty mouth feeling due to larger drug particles</td>
<td></td>
</tr>
</tbody>
</table>

As orodispersible films differ from mucoadhesive films in their behavior in the mouth, their texture has to be evaluated for every individual dosage form. For orodispersible films, the change in the texture during dissolution or after disintegration has to be considered. Particles remaining after disintegration may negatively influence the mouthfeel and thereby the acceptability of films.[36] Small particles were preferred over large particles as especially larger particles cause a poor mouthfeel.[46] A poor mouthfeel may also occur due to a gummy nature of the films after wetting, caused by a polymer with a viscous behavior or a slow drug release.[37] Finally, excipients like polyhydric alcohols may improve the mouthfeel due to their cooling properties.[35,46]

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### 2.1.5 Excipients

Nearly all excipients used for oromucosal film preparations have been previously used for other dosage forms. Many of the currently applied film-forming polymers are widely used as matrix or coating materials for
3. Development and production-related issues

3.1 Viscosity

As oromucosal films are produced from a semi-solid solution or suspension, the rheological characterization is of high interest. Viscosity is a critical factor especially for a solvent casting process, either on extemporaneous or industrial production scale; therefore, it has to be adapted to every formulation and production process individually.

High viscosity of the casting solution prolongs the production time, due to entrapped air bubbles and a hindered homogenization. Air bubbles affect the mechanical properties and the drug release from the films and thus have to be avoided. The incorporation of air bubbles, using a highly viscous formulation, could be reduced by stirring the solution under vacuum, centrifugation, using degased water, sonication of the solution or storing the solution in a refrigerator. In some cases, the separate production of the film-forming solution and solution containing excipients with surface activity (causing air bubbles) can help to avoid entrapped air. On the other hand, low viscosity causes problems regarding uniformity of content when suspensions are used as rapid sedimentation may occur.

Regarding the casting process, viscosity levels have to be considered for each production scale individually. For the small scale, working with a petri dish, the viscosity is less important, as spreading of the solution is bordered by the petri dish wall. Nevertheless, problems regarding uniformity of content caused by low viscosity and impeded pouring out of the beaker, where the film casting solution is prepared, have been reported. The viscosities as observed for the small scale production in a petri dish differ over a wide range, from 1.7 to 64.8 mPa*s, to 207 mPa*s, Using a film coating bench, the film solution can spread over the entire intermediate liner. A low viscosity leads to variations in film thickness at different sites and thereby to poor drug uniformity. A high viscosity may interfere with a free flow of the solution through the gap of the coating applicator and thus hamper the coating process. Viscosities ranging from 0.3 Pa*s to 6.2 Pa*s have been reported in the literature to be feasible for a coating process using a coating knife. The problems described for the coating bench also apply for a continuous coating process used in the industry or on a lab scale continuous coater. In addition, a low viscosity may lead to running of the solution in the direction opposite to the coating process directly after releasing the coating mass to the intermediate liner. On the other hand, the viscosity of the solution must enable a free flow through the pumps and the coating dispenser.

Viscosity of the casting solution can be enhanced by increasing the polymer content, using polymers with a higher viscosity or adding thickening agents like xanthan gum. Woertz et al. showed increased content uniformity after adding thickening agents. Finally, surfactants or different laminated intermediate liners can help to improve the spreading of the casting mass over the film and decrease variability of the solution volume applied on the intermediate liner.

3.2 API suitability and drug load

Oromucosal films are manufactured to contain a precise drug load, which offers an improved dosing accuracy over solutions and suspensions. Complete uniformity within a single dosage form is important if the films are cut into smaller pieces for dose adjustment. In case APIs (e.g. enalapril, prednisolone) or co-solvents (e.g. ethanol) influence the physical properties of the casting solution or the films, the polymer formulation needs to be adjusted to achieve the required precision of drug load. Application of drug solutions or suspensions on plain films by the printing technology method may become a good alternative to achieve precise drug load.
around 50 mg [62]) can be achieved by increasing the surface area and/or the thickness of the films, although the acceptability and patient convenience have to be considered. A high drug load may result in a thick film, which disintegrates slowly [63] as well as recrystallization of the API, leading to loss of transparency and increased brittleness.[2,9] In some cases (e.g. dimenhydrinate as API), the recrystallization can be prevented by the addition of maltodextrin or cyclodextrine (HP-β-CD, sulfobutyl ether-β-cyclodextrin).[39]

The maximum drug load of poorly water soluble APIs can be increased by the formation of water soluble complexes with cyclodextrins.[39,64] However, in most cases, a large amount of cyclodextrins is needed to form a soluble complex, thereby negatively influencing the mechanical properties of the films. Besides, complexation with cyclodextrins is not applicable for all poorly water soluble APIs, which makes them less suitable for film production.[65] For such APIs, as well as for peptides, the use of nanosuspensions may overcome the problem related to poor water solubility. [2,53,64–66]

Both API and added excipients influence the mucoadhesive properties of the film, generally in a negative way. The effect is dependent on the API (and its dose), excipients and nature of the film-forming agent.[67]

### 3.3 Mechanical strength

According to the Ph. Eur. 8.0, oromucosal films should ‘possess suitable mechanical strength to resist handling without being damaged’. [1] Therefore, the question rises how ‘suitable strength’ can be defined. It could be argued that acceptable mechanical properties are given when it is possible to manufacture and handle the film. From a scientific point of view, it is inevitable to assess the strength-related properties such as tensile strength or elastic behavior using experimental data. Furthermore, it helps to evaluate deviations within and between batches and enables the comparison of different films, e.g. marketed products against novel small-scale formulations.[48]

The literature reveals multiple approaches to assess mechanical strength of films such as tensile strength tests, where the film is clamped in a universal testing apparatus or a Texture Analyser [6,68,69] or folding endurance testing.[70]

It has been concluded that the careful selection of the plasticizer is important, since the plasticizer type and content, as well as the storage conditions, in particular humidity, influenced the properties of the ethylcellulose films and their mechanical strength.[71] Furthermore, the impact of unstable plasticizers, resulting in brittle films after prolonged storage, has been discussed.[71] Sufficient elasticity of films appears beneficial when it comes to small-scale manufacturing. [48] With respect to pilot- and production scale, manufacturing elasticity might lead to unintended stretching of the films, e.g. during the transfer over conveyor belts, which may result in waving of the thin film due to rebound effects and yield irregular drug content. Brittle films, on the other hand, may provoke ruptures during production and cutting.

The combination of polymers in a single formulation can improve the mechanical properties. This is illustrated with alginate films when combined with different amounts of hypromellose. In contrast, Skullason et al. showed that hypromellose did not lead to increased strength in combination with polyacrylic acid.[69] These findings point out once more that polymer interactions as well as plasticizing effects of APIs cannot be described in general and need thorough individual investigations.

### 3.4 Drug release rate

For mucoadhesive buccal films as well as for orodispensible films, Ph. Eur. 8th edition demands a dissolution test, showing the release of the API from the dosage form. The Ph. Eur. 8th edition does not describe how such a test should look like. In literature, usually paddle or basket apparatuses of the Ph.Eur. are described.[44] For orodispensible films, a high dissolution rate is preferred in most cases, while a sustained release of the drug may be desired for a buccal film formulation. As films have a matrix-like structure and display swelling in water, the typical release profile is nonlinear and shows profiles between Fickian diffusion and zero order.[72] The release rate of the API from a film can, however, be changed via different approaches. The use of polymers with a different viscosity affects the release rate. Polymers generating a thick gel layer with a high viscosity after wetting will lead to a slower release than from polymers with a low or intermediate viscosity.[73] The incorporation of the highly water permeable Eudragit RL will show a faster release than the less water permeable Eudragit RS.[72] Sometimes polymers can lead to complexation or ionic binding of the API, reducing the dissolution rate.[73] The addition of cyclodextrins, surfactants, the use of (poorly) water soluble APIs or incorporation of coated drug particles may alter the release rate.[74,75] Finally, also recrystallization may influence the release rate of the API. The use of different polymers may influence the recrystallization [6] and thus the release rate.
3.5 Upscaling

Upscaling of extemporaneously prepared oromucosal films offers various challenges. Most problems with the manufacturing process as mentioned in the previous sections apply to both small scale and industrial production of the films. But also specific problems are encountered that relate to larger scale processes. The industrial production of oromucosal films differs from small scale production, including the use of huge drying tunnels and rapid conveyor belts.[5] For small scale production, the drying procedure may be as long as necessary, although it should be kept in mind that a prolonged drying time facilitates the growth of microorganisms. An industrial process would not allow a time-consuming drying procedure.[76] Increasing the drying temperature reduces the drying time but may influence the stability of the films. The drying procedure may also cause the so-called ripple effect. Drying with hot air causes solvents to evaporate immediately. This results in a thin dry polymer layer covering the wet cast which may rupture and cause uneven surfaces during further drying.[77] Therefore, the end point of drying has to be defined and controlled carefully.[68]

The use of several windings during the manufacturing process requires the films (or large strings) to possess a suitable mechanical strength, which may significantly differ from the preparation on film applicators on small scale.[5] During manufacturing, stretching of long pieces of films is inevitable. This may cause problems when the films are cut per length, resulting in variations in drug load. To overcome this problem, the films should be cut per weight providing a fixed dose per film. Homogeneous spread of the API over the film is of course a prerequisite.

The quality by design (QbD) approach can be a useful tool for optimizing a film formulation and production process that may also be suitable for large scale production.[78] The QbD approach is a systematic approach to optimize pharmaceutical preparations and to improve the control over and the quality of the production process [79] and includes the establishment of a quality target product profile. This starts with defining critical quality attributes and finding and identifying critical process parameters that affect the final product quality; from there a design space can be created.[78]

4. Stability, storage and packaging

Manufacturing of oromucosal films with the solvent casting method comprises a drying step, usually at temperatures between 30 and 40°C. In general, increasing the drying temperature or drying time can negatively influence the stability of APIs and excipients such as sweeteners.[80] Reduction of the drying temperature to 20°C results in a long drying time, which is far from ideal for extemporaneous and rapid manufacturing approaches and also disadvantageous in terms of (microbiological) stability challenges.[78] Using HME omits the drying step, but the process-specific melting step may influence API, flavor and polymer stability. [2,80] In literature, several stability studies have been described according to either the ICH guidelines (25°C/60% RH and 40°C/75% RH) [12,81] or deviating conditions, e.g. storage in aluminium packages at room temperature.[65] All studies showed that the films were stable in terms of physical characteristics as well as drug content during a storage period of up to 6–9 months. However, prolonged stability testing is essential, and regarding the drug content, the outcome is of course fully API-specific.

4.1 Light sensitivity

Exposure to light may result in an unacceptable change of APIs and/or excipients during manufacturing, packaging, storage or administration of the oromucosal films. Photodegradation is often seen as a color change (e.g. bleaching) but may also elicit other effects such as a change in viscosity of the casting solution or an unexpected precipitation of the API.[82] Photodegradation during manufacturing can be limited by avoiding direct sunlight and artificial light (at specific wavelengths). For pharmaceutical preparations, it is known that the addition of pH-modifying compounds (e.g. citrate – or phosphate buffer), antioxidants and chelators (e.g. ascorbic acid, disodium edetate) or UV absorbers (e.g. vanillin) may enhance the stability.[83] The addition of photo stability enhancers is not common in the manufacturing of the films but this approach may be an interesting option. In case a photosensitive API is manufactured into a film, a photo stability test according to the ICH guidelines [84] should be part of the stability testing protocol. Of course, light sensitivity problems can be adequately tackled by adequate packaging approaches.

4.2 Microbiological stability

Microbiological stability is one of the critical factors during oromucosal film preparations because they are usually produced from aqueous solutions or suspensions.

To prevent or minimize the growth of microorganisms, the casting solution can be heat sterilized and
stored in sealed containers before use. The solubility of some film-forming agents, like hypromellose, displays reverse temperature sensitivity, which may hamper heat sterilization.[74] The redispersion after sterilization can, however, be enhanced by constant shaking during the cooling process. Thermostable APIs can be added to the casting solution prior to sterilization. To prevent microbiological contamination, the addition of thermostable APIs should be carried out after the sterilization step in a cleanroom class D. The constant shaking or addition of thermostable APIs after sterilization may, however, cause the introduction of air bubbles in the viscous liquid, which are difficult to remove.

The microbiological stability has to be considered during the casting and drying process as the water content is still high in these phases, and although the water activity of the film is generally low after manufacturing, it may increase upon storage. Moisture adsorption or relatively high amounts of residual water may facilitate the growth of micro-organisms, influence the integrity and microbiological safety of the films during shelf life. Moreover, a high water content may result in decomposition of the API.[5] Oromucosal films can also be prepared by freeze drying aqueous gels or polymers. Freeze-dried formulations have several advantages: they offer stable products, extend shelf life and allow storage of products at room temperature.[85] However, it is a complex and expensive procedure, and it is important to realize that certain sugars (used for e.g. taste masking) can stabilize some bacteria during freeze drying.[86] The application of freeze drying for the production of oromucosal films is still relatively unexploited.

The use of preservatives is rarely reported in literature and is generally not necessary. Preservatives may cause adverse effects in neonates and infants due to an immature metabolic system and should be avoided if possible.[6,49] However, industrially prepared films sometimes contain a preservative, generally 0.01–1 wt % of the film. Preservatives of choice are benzalkonium chloride, benzyl alcohol or parabens.[6]

4.3 Storage and packaging

Stability testing is an inevitable last step in the development of new films. The impact of storage over time on the mechanical properties and stability of the oromucosal films has already been addressed. The packaging of the films plays an important role in the final stability of the product, and an adequate packaging can be of significant help to ensure the formulations maintain their initial properties such as the drug dissolution rate.[87] Furthermore, storage and stability testing of the film products may be used to assess the behavior of the ingredients of the formulation and possible degradations and interactions, e.g. the moisture uptake by hygroscopic excipients or the active substance incorporated in the film base.[36]

Film preparations that should rapidly disperse or dissolve in the mouth when having contact with saliva are highly sensitive to humid conditions. Air-tight primary packaging materials, such as aluminum sachets, have been shown as necessary to maintain the integrity of the films and are frequently used when a long storage period is required.[2] However, these sachets are expensive. Foil, paper or plastic pouches can be considered as secondary packaging material. However, their suitability needs to be evaluated carefully before they are applied for a specific formulation including aspects such as the film’s stability and packaging materials suitability for pharmaceutical use.[88] An alternative packaging of multiple films of the size of a credit card, where films can be taken out individually, has been described.[89]

5. Biopharmaceutics

Oromucosal films are intended to cause either a systemic or a local effect. For local treatment, absorption of the API is undesired, as side effects may occur. Transmucosal absorption of a local anesthetic released from a film may be toxic for children.[90] This requires sub-effective plasma concentrations, whereas at the same time, effective concentrations are desired in the oral cavity. The use of oromucosal films may be superior to other local dosage forms, like oral gels or liquids. Due to a constant API release from the films, no burst effect will occur, and the time with effective salivary concentration may be prolonged.[91]

If a systemic effect is desired, the API can either be swallowed and absorbed via the gastrointestinal tract or be absorbed via the oromucosal membrane. Absorption via the oromucosal membrane may increase the bioavailability of the API incorporated in a film compared to oral application, when the API suffers from a significant first-pass effect. Such an improvement of the bioavailability may be advantageous for new products but may also cause problems regarding generic film products when referring to classical oral dosage forms in a bioequivalence study. Therefore, the focus of an oromucosal film development may either be an increased bioavailability, due to oromucosal absorption, or the absence of permeation through the oral mucosa, hence following the oral route.

The two types of oromucosal film dosage forms, orodispersible or mucoadhesive buccal preparations,
have to be discussed separately as they behave differently in the oral cavity. The biopharmaceutical differences are shown in Table 2.

For orodispersible films, an uncontrolled absorption through the oral mucosa may be prevented by excipients like ion exchange resins or particle coatings.

For oromucosal mucoadhesive films, various possibilities regarding the film composition, the API and the specific site of application can be considered to increase the usually intended absorption of the API through the oral mucosa.

As the API should dissolve prior to absorption, an adjustment of the dissolution profile can have a high impact on the pharmacokinetic profile. Zero order kinetics or a combination of zero order and Fickian diffusion was observed for the dissolution of mucoadhesive buccal films containing chlorpheniramine or caffeine.[8,72] The reason for increased $T_{\text{max}}$ values, was found in the slower dissolution of the films compared to oral immediate release formulations.[8,12] Nevertheless, an increased dissolution rate does not necessarily increase the permeation through the oral mucosa. An API present in its ionized form will show a faster dissolution rate, but less permeation compared to its unionized more lipophilic form. An adjustment of the pH of the formulation may thus influence the pharmacokinetic profile. Finally, a compromise between dissolution and absorption has to be found. It was found that films containing fentanyl with a pH close to neutral had the highest $C_{\text{max}}$ and AUC$_{\text{oo}}$ and fastest $T_{\text{max}}$.[94] A high molecular weight polymer, which impedes the diffusion of the API through the polymeric network of the film, induced a slow release rate. On the other hand, it may cause hydration of the mucosa membrane, which may balance the slower dissolution rate.[97] Hydration of the mucosa may also be achieved by adding a backing layer generating an occlusion effect. The backing layer may further reduce the amount of API lost to the oral cavity and thus absorbed via the gastrointestinal route.[98] Another approach to increase drug permeation through the oral mucosa is the use of permeation enhancers such as bile salts and other steroidal detergents, surfactants (nonionic, cationic, anionic) or chelating agents.[99,100] However, the use of these permeation enhancers may lead to tissue damage and may cause toxicity.[100] Finally also the exact site of application has to be mentioned when the absorption of an API through the oral mucosa is considered. The structure of the oral mucosa differs at the different sites of the oral cavity regarding its level of keratinization or blood circulation. [31] Different plasma concentration time curves were observed when solutions and patches were administered to different sites in a dog’s mouth.[101] Therefore, it is highly recommended to exactly specify the site of administration to avoid undesired plasma concentration profiles.

No matter whether oromucosal permeation is desired or not, the developer needs to know if absorption through the oral mucosa occurs. Several tests are available to analyze the absorption or permeation of the API, released by a film formulation, through oral mucosa. Biorelevant dissolution tests provide information about the amount of dissolved API under consideration of in vivo conditions.[44] By means of tissue studies, the suitability of an API molecule to be absorbed through the oral mucosa was assessed.[98] Finally, animal [92] and human volunteer [102] studies generated plasma concentration curves to compare the film formulations to other dosage forms containing the same API. A further aim will be to create computer-based models considering all relevant parameters mentioned above to predict plasma curve levels without the need of animal or human volunteer studies. By predicting an individual plasma profile for each patient, the administered dose can be adjusted individually, by just cutting the films into different sizes. This flexibility distinguishes oromucosal films from conventional dosage forms. 

### Table 2. Biopharmaceutical differences in the behavior in the oral cavity between orodispersible and mucoadhesive buccal films.

<table>
<thead>
<tr>
<th>Orodispersible film</th>
<th>Mucoadhesive buccal film</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Are commonly administered to the tongue (and sometimes on the buccal surface), they disintegrate within a few seconds.</td>
<td>- Are directly attached to the oral mucosa and release the API via the oromucosal absorption border and the oral cavity.</td>
</tr>
<tr>
<td>- A release of the major amount of API into the oral cavity and dispersion in the saliva may occur, but this may not happen per se.</td>
<td>- The intention of this product type is to have the largest part of the API absorbed via the oral mucosa.</td>
</tr>
<tr>
<td>- The major amount will be swallowed with the saliva and will be absorbed from the gastrointestinal tract,[92,93] resulting in the following:</td>
<td>- Higher bioavailability may occur compared to oral dosage forms.[12,45,94–96]</td>
</tr>
<tr>
<td></td>
<td>- Higher $C_{\text{max}}$ values have been observed for fentanyl and domperidone films.[12,96]</td>
</tr>
<tr>
<td></td>
<td>- Higher [8] or lower [94,96] $T_{\text{max}}$ values compared to oral immediate release dosage forms may occur. Possible reasons are reduced first pass effect.[45,95]</td>
</tr>
<tr>
<td></td>
<td>- Drug accumulation in the buccal epithelium.[56]</td>
</tr>
</tbody>
</table>

...
6. Conclusions

Oromucosal films are easy to administer, and their administration does not require the intake of large fluid volumes. Moreover, the option that these films can be cut into virtually every size gives them an enormous flexibility for individual dosing. These aspects make oromucosal films a highly acceptable novel dosage form especially for patient groups that require personalized medicine or adjusted doses (e.g. children, elderly). Essential performance characteristics of oromucosal films include an acceptable taste, appearance and

<table>
<thead>
<tr>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td><strong>Drug load</strong></td>
</tr>
<tr>
<td>- Increase surface area and increase thickness</td>
</tr>
<tr>
<td>Too thick → problems with acceptance and non-acceptable disintegration time</td>
</tr>
<tr>
<td><strong>Taste</strong></td>
</tr>
<tr>
<td>- Add substances that overlay API taste (e.g. sweetener)</td>
</tr>
<tr>
<td>- Bitterness blocker / Interruption of API receptor interaction</td>
</tr>
<tr>
<td>- Reduction of release via the oral cavity (backing layer)</td>
</tr>
<tr>
<td>- Conversion of the API to less soluble/insoluble form</td>
</tr>
<tr>
<td>- Prodrugs</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
</tr>
<tr>
<td>- Change polymer</td>
</tr>
<tr>
<td>- Plasticizers</td>
</tr>
<tr>
<td>- Use of colorants</td>
</tr>
<tr>
<td><strong>Mucosal irritation</strong></td>
</tr>
<tr>
<td>- Limit surface pH around salivary pH</td>
</tr>
<tr>
<td>- Use of non-irritant polymers (e.g. sodium carboxymethyl cellulose)</td>
</tr>
<tr>
<td>- Add buffers</td>
</tr>
<tr>
<td>- Limit amount of API</td>
</tr>
<tr>
<td>- Smooth surface of film</td>
</tr>
<tr>
<td><strong>Texture and mouth feel</strong></td>
</tr>
<tr>
<td>- Use small particles</td>
</tr>
<tr>
<td>- Add cooling agent (e.g. polyhydric alcohols)</td>
</tr>
<tr>
<td>- Change nature of polymer</td>
</tr>
</tbody>
</table>

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**Inadequate absorption via the oromucosal route from mucoadhesive films**

- Reduce dissolution to the oral cavity side (e.g. use of backing layer)
- Add buffers to change the pH considering both dissolution and membrane permeation
- Pro-drug with better penetration over the mucosa

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**Manufacturing**

<table>
<thead>
<tr>
<th>Mechanical properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Careful selection of plasticizer</td>
</tr>
<tr>
<td>- Appropriate storage and packaging</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upscaling: Stretching – uniformity of content not reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Application of quality by design</td>
</tr>
<tr>
<td>- Cut by weight</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>→ Too low – uniformity of content not reached</td>
</tr>
<tr>
<td>→ Too high – entrapment of air bubbles</td>
</tr>
<tr>
<td>Both: unsuitable for casting</td>
</tr>
<tr>
<td>- Change amount or nature of polymer</td>
</tr>
<tr>
<td>- Add stabilizers e.g. xanthan gum</td>
</tr>
<tr>
<td>- Add surfactants</td>
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</table>

<table>
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<tr>
<th>Stability (also light sensitive and microbiological)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Limit influence of day (and artificial) light</td>
</tr>
<tr>
<td>- Add antioxidants</td>
</tr>
<tr>
<td>- Sterilize the casting solution</td>
</tr>
<tr>
<td>- Work in a clean room</td>
</tr>
<tr>
<td>- Add preservatives</td>
</tr>
<tr>
<td>- Appropriate packaging</td>
</tr>
<tr>
<td>- Appropriate storage conditions</td>
</tr>
</tbody>
</table>

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Figure 1. Critical attributes to meet patient needs and possible solutions.
mouthfeel, and the absence of irritation of the mucosa. They should contain only safe excipients, easy to produce, when considered for extemporaneous preparations, have good handling properties and be stable during storage.

7. Expert opinion

Oromucosal films are gaining more interest as extemporaneous as well as commercially available dosage forms. They offer extended possibilities for individualized pharmacotherapy. However, compared to conventional oral dosage forms, they pose new problems to the pharmaceutical developer (Figure 1A, B). Problemsolving requires a good understanding and expertise regarding the dosage form, its production process and the effects of formulation or process condition variations.

Different methods of manufacturing are used which present different challenges that have to be encountered. For the manufacturing process, the viscosity of the casting solution is the key factor for producing suitable films. Solutions with too low viscosity are difficult to cast and yield films that do not meet uniformity of content requirements, and solutions with too high viscosity are difficult to handle due to entrapment of air bubbles. In literature, different viscosity limits are mentioned, but these limits cannot be used as a general guideline, since the required viscosity depends strongly on the production method and equipment used. The viscosity not only depends on the amount of polymer used, but also on the type of polymer used. For each polymer or combinations of polymers, new limits need to be set. Also the API may influence the viscosity. This needs to be determined for each individual API and concentration.

Safe excipients should be used and optimal patient acceptances are necessary requirements to increase compliance. An acceptable taste and palatability are requirements to improve patient acceptance and can be achieved with appropriate excipients especially when a bitter API is involved. However, to prevent drug abuse, it is important not to make oromucosal films too attractive in terms of taste and appearance. As any variation of an acceptability parameter will change the characteristics of the formulation, an in-depth knowledge on the relation between the physico-chemical and physiological behavior of the film and patient acceptance and perception is required to predict outcome parameters and to produce tolerable oromucosal films. In all cases, the right balance has to be found, not only regarding the acceptance parameters, but also regarding mechanical behavior, dissolution, disintegration and stability.

This new dosage form will give rise to pharmacokinetic questions, as the absorption through the oral mucosa will vary for each formulation and for each patient, especially for orodispensible films. Here the suppression of permeation by using appropriate excipients is recommended.

Finally, more research is needed regarding patient acceptance, manufacturing and bioavailability of oromucosal films. Also the Ph. Eur. needs to specify methods, requirements and definitions based on bio-relevant data for oromucosal preparations.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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• of interest
→ of considerable interest

  → Overview on orodispensible dosage forms.

- Considerations on the characterization of mucoadhesive films.


- Discussion on dosage form-related swelling issues.


**Overview on issues regarding taste-masking assessment.**


**Amongst other, decision tool for the use of excipients in medicines for pediatrics.**


**Application of quality by design in the development of film preparations.**


**Investigations on the biopharmaceutical performance of a buccal film.**


