Orodispersible Films as a Solution to Drug Acceptability Issues: A Short Review

Mohamed Yafout¹*, Hicham Elhorr¹, Amine Ousaid¹, Ibrahim Sbai El Otmani¹ and Youssef Khayati¹

¹Laboratory of Drug Sciences, Biomedical and Biotechnological Research, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, 19, Tarik Ibnou Ziad Street, P.O.Box 9154, Casablanca, Morocco.

Authors' contributions

This work was carried out in collaboration among all authors. Authors MY and HE designed the study, carried out the literature search, and wrote the first draft of the manuscript. Authors AO and ISEO revised the first draft of the manuscript and supervised the work. Author YK presented the idea and supervised the work. All authors read and approved the final manuscript.

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ABSTRACT

Despite the fact that the tablets are the most widely used dosage form, they are not suitable for young children and patients with swallowing difficulties, especially the elderly. Orodispersible films (ODFs) dissolve rapidly in the mouth and deliver an accurate amount of the active ingredient, which makes them an easy-to-use dosage form that can improve drug acceptability and, therefore, treatment adherence. The findings of the 4 studies that we discussed in this review prove that ODFs have experimentally-proven good acceptability in all age groups and that they are clinically superior to tablets and syrups in terms of acceptability. Therefore, despite some limitations, ODFs are still an innovative and patient-centered dosage form that can contribute to improving drug acceptability and treatment adherence particularly in children and elderly patients. Pharmaceutical companies should focus on developing more ODF-based drugs and also other innovative dosage forms that can make the drug-taking experience even-easier.

*Corresponding author: E-mail: yafoutm@yahoo.fr
Keywords: Orodispersible films; drug acceptability; treatment adherence; pediatric patients; geriatric patients; innovative dosage forms; swallowing difficulty.

1. INTRODUCTION

Patient acceptability is defined as “the overall ability and willingness” of the patients and their caregivers to administer the medicines as intended [1]. It is closely linked to palatability which is the overall appreciation of a medicine’s properties, such as its appearance, smell, taste, mouthfeel, and aftertaste [2]. These properties can have a major effect on compliance and, therefore, on the success of treatments. Geriatric and pediatric patients have the most compliance issues related to the lack of suitable formulations matching their specificities [3]. Studies showed that children’s refusal to take the drug is one of the most common reasons for non-adherence to medication [4,5]. In geriatric patients, safe swallowing is the key formulation factor in drug design [3]. The reflection paper on the pharmaceutical development of medicines for use in the older population issued by EMA in 2020 clearly specifies that older patients’ needs may require specific measures in the pharmaceutical design of medicines. It also encourages a patient-centric approach to medicine’s pharmaceutical development [6].

Tablets and other solid oral dosage forms have always been the most attractive forms for drug administration [7]. However, these dosage forms are not suitable for patients having swallowing difficulty or vomiting issues and, in general, geriatric and pediatric patients for which liquid dosage forms have always been preferred [8,9].

Orodispersible films (ODFs) are defined by the European Pharmacopoeia as “single or multilayered sheets of suitable materials, to be placed in the mouth where they disperse rapidly” [10]. The United States Pharmacopoeia uses different terminology and calls them “Oral soluble films” which are defined as “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” [11].

ODFs are a versatile dosage form that can be formulated in such a way that the tastes are masked, and that do not require water to be taken [12]. They also have no risk of choking and offer a better dose accuracy in comparison to syrups. Compared to other systems, they have a larger surface area that allows for faster wetting, disintegration, and dissolution. This means patients don’t need to chew or swallow to ingest the drug. These attributes could make them suitable for all patients who have difficulty taking medication [13]. Since they dissolve rapidly in the oral cavity and deliver an accurate amount of the active ingredient, they combine dose accuracy of solid oral forms and ease of use of liquid oral forms [14]. These remarkable properties can be used to improve the acceptability of drugs, particularly in children and other patients experiencing difficulties in solid oral forms administration.

Therefore, this review aims to describe the contribution of orodispersible films in improving patient's acceptability of drugs through a search in the available scientific references.

2. METHODS

We searched Science Direct, Web of Sciences, and PubMed databases for articles published between 2010 and 2021 and containing clinical data on ODFs’ acceptability, using the keywords “Orodispersible film”, “Thin-film”, “Oral film”, and “Acceptability”. We only retained articles reporting strong clinical studies on the acceptability or ease of use of ODFs administered alone or in comparison with other oral dosage forms.

3. RESULTS

The search that we performed yielded 4 articles whose contents were deemed relevant and corresponding to our inclusion criteria. The main findings of the studies described in these articles are as follows:

In the STAMP study that was conducted in The United Kingdom [15], placebo ODFs were administered to children aged 6 months to 5 years. The acceptability of ODFs was assessed using direct observation and questionnaires for both caregivers and children aged 3 and over. Seventy-eight percent of children aged 3 years and over gave a positive rating to ODFs; Seventy-nine percent and 86% of infant caregivers and caregivers of preschool children respectively expressed a positive opinion about children’s acceptance of ODFs. Another study tested the acceptability of ODFs in 50 healthy adult volunteers using a 5-point hedonic scale [16]. Results of this study showed high modal
<table>
<thead>
<tr>
<th>Reference and authors</th>
<th>ODFs characteristics</th>
<th>Comparator</th>
<th>Participants</th>
<th>Number of participants</th>
<th>Assessment method</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (Orlu et al. 2017)</td>
<td>• Placebo • 6 cm²/film • 85 mg/film</td>
<td>None</td>
<td>Children aging 6 months to 5 years</td>
<td>110</td>
<td>- Pre-administration caregiver questionnaire - Post-administration children’s questionnaire - Post-administration caregiver questionnaire - Observation</td>
<td>Positive opinion about ODFs’ acceptability of both caregivers and children aged 3 and over</td>
</tr>
<tr>
<td>16 (Abdelhakim et al. 2017)</td>
<td>• Placebo • Electrospun films: - 6 cm²/film - 25 mg/film • Cast films: - 3.4 cm²/film - 25 mg/film</td>
<td>None</td>
<td>Adults aged 18 to 60</td>
<td>50</td>
<td>Five-point hedonic scale to assess 6 acceptability criteria: stickiness, thickness, disintegration time, saliva thickening effect, and handling</td>
<td>High modal values (4 to 5) for all mouthfeel attributes except for stickiness (2)</td>
</tr>
<tr>
<td>17 (Klingmann et al. 2020)</td>
<td>Placebo 6 cm²/film</td>
<td>Glucose syrup</td>
<td>Neonates and infants aged 2 days to 12 months</td>
<td>150</td>
<td>- Observation. - Acceptability was defined as an aggregate of two evaluation criteria: “everything swallowed” and “chewed/partially swallowed”</td>
<td>ODFs were superior to syrup in terms of overall acceptability (95.3% vs 80.7%) and overall swallowability (70% vs 48.7%).</td>
</tr>
<tr>
<td>18 (Nishigaki et al. 2012)</td>
<td>4 cm² cast films containing 4 mg of Dexamethasone</td>
<td>Dexamethasone tablets (4 mg)</td>
<td>Adults aged 41 to 70 (Breast cancer patients)</td>
<td>20</td>
<td>Self-check sheet. Each attribute is scored on a three-point scale (1: bad, 2: medium, 3: good)</td>
<td>Patient’s impressions on taste and ease in taking were significantly better for films than for tablets</td>
</tr>
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</table>
Table 2. Comparison of the main attributes of tablets, oral liquids, and orodispersible films

<table>
<thead>
<tr>
<th></th>
<th>Tablets</th>
<th>Oral liquids</th>
<th>Orodispersible films</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for water</td>
<td>Yes</td>
<td>When liquid needs to be diluted</td>
<td>No</td>
</tr>
<tr>
<td>Administration to children and elderly</td>
<td>Difficult</td>
<td>Medium</td>
<td>Easy</td>
</tr>
<tr>
<td>Dose accuracy</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Risk of choking</td>
<td>High</td>
<td>Medium</td>
<td>None</td>
</tr>
<tr>
<td>API dose range</td>
<td>High</td>
<td>High</td>
<td>Limited</td>
</tr>
<tr>
<td>Acceptability in children and elderly</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Disintegration and solubilization</td>
<td>Slow</td>
<td>Already in liquid form</td>
<td>Fast</td>
</tr>
<tr>
<td>Suitable when vomiting issues</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Suitable when xerostomia</td>
<td>Yes (if water is available)</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

values (4 to 5) for all mouthfeel attributes except for stickiness (2). In a clinical trial carried out in Germany, ODFs were compared to syrup in terms of acceptability, swallowability, and palatability in 150 neonates and infants [17]. The ODFs were superior to syrup in terms of overall acceptability (95.3% vs 80.7%) and overall swallowability (70% vs 48.7%). The palatability assessments were also in favor of the ODFs. A Japanese study aimed to investigate the clinical effect of ODFs containing dexamethasone as an antiemetic and compare it to the effect of tablets containing the same amount of the active ingredient [18]. Among the outcomes of this study, the oral acceptability of ODFs particularly regarding taste and ease of administration was significantly better for films than for tablets. These 4 studies are summarized in Table 1.

4. DISCUSSION

The 4 studies summarized in Table 1 allow us to draw 2 main facts: 1) ODFs have good acceptability in all age groups (from neonates to 70 years old adults); 2) ODFs are superior to syrups and tablets in terms of acceptability in all age groups. These findings are consistent with those of many other reviews that emphasize the patient-friendly nature of ODFs and their potential usefulness as a solution to acceptance and adherence issues [19-21]. ODFs are therefore the ideal dosage form that meets the most the recommendations of EMA guidelines and reflection papers on pharmaceutical development of medicines for pediatric and geriatric use [15,16]. Moreover, solvent casting technology allows easy manufacturing of personalized ODFs that meet the specific needs of particular patients in hospital pharmacies and community pharmacies [22]. Therefore, there is no doubt that ODFs will be one of the most attractive dosage forms across all age groups. Their enhanced acceptability gives them the full potential to gain patient compliance in all physiological conditions. Nevertheless, ODFs are not a universal remedy for acceptability issues as they still carry some limitations such as the impossibility to load them with large amounts of active ingredients and their non-suitability for patients suffering from xerostomia (Table 2).

5. CONCLUSION

Given the multiple benefits of ODFs that we have discussed throughout this review, it seems clear that this dosage form can bring a significant contribution to improving drug acceptability and treatment adherence particularly in children and elderly patients. Pharmaceutical companies should focus not only on developing more ODF-based medicines but also in the research and development of other innovative pharmaceutical forms which could transform taking a drug into an easy and pleasant experience for all age groups and all patient's conditions.

CONSENT AND ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES

