

Orodispersible films as a solution to drug acceptability issues: a short review

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.

Keywords: Orodispersible films; drug acceptability; treatment adherence; pediatric patients; geriatric patients; Innovative dosage forms; Swallowing difficulty

26 **1. Introduction**

27 Tablets and other solid oral dosage forms have always been the most attractive forms for drug
28 administration [1]. However, these dosage forms are not suitable for patients having
29 swallowing difficulty or vomiting issues and, in general, geriatric and pediatric patients for
30 which liquid dosage forms have always been preferred [2,3]. Orodispersible films (ODFs) are
31 defined by the European Pharmacopoeia as “single or multilayered sheets of suitable
32 materials, to be placed in the mouth where they disperse rapidly” [4]. The United States
33 Pharmacopoeia uses different terminology and calls them “Oral films” which are defined as
34 “Thin sheets that are placed in the oral cavity. They contain one or more layers. A layer may
35 or may not contain the drug substance” [5].

36 Since ODFs dissolve rapidly in the oral cavity and deliver an accurate amount of the active
37 ingredient, they combine dose accuracy of solid oral forms and ease of use of liquid oral
38 forms [6]. These remarkable properties can be used to improve the acceptability of drugs,
39 particularly in children and other patients experiencing difficulties in solid oral forms
40 administration.

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

43 **2. Method**

44 We searched Science Direct, Web of Sciences, and PubMed databases for articles published
45 between 2010 and 2021 and containing clinical data on ODFs' acceptability, using the
46 keywords “Orodispersible film”, “Thin-film”, “Oral film”, and “Acceptability”.

47 **3. Results**

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

51 In the STAMP study that was conducted in The United Kingdom [7], placebo ODFs were
52 administered to **children aged 6 months to 5 years**. The acceptability of ODFs was assessed
53 using direct observation and questionnaires for both caregivers and **children aged 3** and over.
54 Seventy-eight percent of children aged 3 years and over gave a positive rating to ODFs;
55 Seventy-nine percent of infant caregivers and 86% of caregivers of preschool children
56 expressed a positive opinion about children's acceptance of ODFs. Another study tested the
57 acceptability of ODFs in **50 healthy adult volunteers using a 5-point hedonic scale**[8]. Results
58 of this **stud** showed high modal values (4 to 5) for all mouthfeel attributes except for
59 stickiness (2). In a clinical trial carried out in Germany, ODFs were compared to syrup in
60 terms of acceptability, swallowability, and palpability in **150 neonates and infants**[9]. The
61 ODFs were superior to syrup in terms of overall acceptability (95.3% vs 80.7%) and overall
62 swallowability (70% vs 48.7%). The palatability assessments were also in favor of the ODFs.
63 A Japanese study aimed to investigate the clinical effect of ODFs containing dexamethasone
64 as an antiemetic and compare it to the effect of tablets containing the same amount of the
65 active ingredient [10]. Among the outcomes of this study, the oral acceptability of ODFs
66 particularly regarding taste and ease of administration was significantly better for films than
67 for tablets. These 4 studies are summarized in table 1.

68 **4. Discussion**

69 Patient acceptability is defined as "the overall ability and willingness" of the patient and their
70 caregiver to administer the medicines as intended [11]. It is closely linked to palatability which
71 is the overall appreciation of a medicine's properties, such as its appearance, smell, taste,
72 mouthfeel, and aftertaste [12]. These properties can have a major effect on compliance and,
73 therefore, the success of treatments. Geriatric and pediatric patients have the most compliance
74 issues related to the lack of suitable formulations matching their specificities[13]. Studies
75 showed that children's refusal to take the drug is one of the most common reasons for non-

Table 1: Summary of the 4 studies

Reference	ODF characteristics	Comparator	Participants	Number of participants	Assessment method	Main outcomes
7	<ul style="list-style-type: none"> ● Placebo ● 6 cm²/film ● 85 mg/film 	None	Children aging 6 months to 5 years	110	<ul style="list-style-type: none"> - Pré-administration caregiver questionnaire - Post-administration children's questionnaire - Post-administration caregiver questionnaire - Observation 	Positive opinion about ODFs' acceptability of both caregivers and children aged 3 and over
8	<ul style="list-style-type: none"> ● Placebo ● Electrosun films: <ul style="list-style-type: none"> - 6 cm²/film - 25 mg/film ● Cast films: <ul style="list-style-type: none"> - 3.4 cm²/film - 25 mg/film 	None	Adults aged 18 to 60	50	Five-point hedonic scale to assess 6 acceptability criteria: stickiness, thickness, disintegration time, saliva thickening effect, and handling	High modal values (4 to 5) for all mouthfeel attributes except for stickiness (2)
9	Placebo 6 cm ² /film	Glucose syrup	Neonates and infants aged 2 days to 12 months	150	<ul style="list-style-type: none"> - Observation. - Acceptability was defined as an aggregate of two evaluation criteria: "everything swallowed" and "chewed/ partially swallowed" 	ODFs were superior to syrup in terms of overall acceptability (95.3% vs 80.7%) and overall swallowability (70% vs 48.7%).
10	4 cm ² cast films containing 4mg of Dexamethasone	Dexamethasone tablets (4 mg)	Breast cancer patients	20	Self-check sheet. Each attribute is scored on a three-point scale (1: bad, 2: medium, 3: good)	Patient's impressions on taste and ease in taking were significantly better for films than for tablets

adherence to medication [14,15]. In geriatric patients, safe swallowing is the key formulation factor in drug design [13]. 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 [16].

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 [17]. 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 (Table 2). These attributes make them suitable for pediatric and geriatric drug delivery and, in general, for all patients who have difficulty taking medication [18]. 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 [11,16]. 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: Comparison of the main attributes of tablets, oral liquids, and orodispersible films

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

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.

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