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Review

Orodispersible films: Towards drug delivery in special populations

Mariagiovanna Scarpa[a], Sven Stegemann[b], Wen-Kai Hsiao[c], Heinz Pichler[c], Simon Gaisford[a], Massimo Bresciani[c], Amrit Paudel[b,c,*], Mine Orlu[a]

[a] School of Pharmacy, University College London (UCL), London, United Kingdom
[b] Graz University of Technology, Graz, Austria
[c] Research Center Pharmaceutical Engineering GmbH, Graz, Austria

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ABSTRACT

Orodispersible films (ODF) hold promise as a novel delivery method, with the potential to deliver tailored therapies to different patient populations. This article reviews the current strides of ODF technology and some of its unmet quality and manufacturing aspects. A topic highlights opportunities and limitations of inkjet printed ODF as a population-specific drug delivery. Overall, this article aims to stimulate further research to fill the current knowledge gap between manufacturing and administration requirements of ODF targeting specific patient subpopulations such as geriatrics.

Contents

1. ODF: a potential formulation strategy for special patient populations

There is an increasing need of developing new drug delivery platforms to address the needs of special patient populations. For example, the paediatric patient requires the medicine dosage to be adequate to the constantly increasing body weight. As medicinal products containing the required dosage may not be available, the practice of splitting tablets, opening capsules, or mixing powders with foods or liquids may lead to dose inaccuracy and other consequences for the safety of the patient and the efficacy of the treatment (Visser et al., 2016). Similarly, other populations may have specific needs with respect to medicine administration (Grimsrud et al., 2015; Slavkova and Breitkreutz, 2015; Stegemann

* Corresponding author at: Research Center Pharmaceutical Engineering, Inffeldgasse 13, 8010 Graz, Austria.
E-mail address: amrit.paudel@rcpe.at (A. Paudel).

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et al., 2010). Therefore, the development of drug delivery platforms that can help addressing the needs of specific patient populations is greatly needed.

Orodispersible films have been reported to contribute to an improved patient compliance by improving ease of administration and by not requiring water (Bala et al., 2013; Krampe et al., 2015). Furthermore, ODFs offer a wide range of features that can be easily adapted to the needs of individual patients or patient populations.

According to Borges and colleagues, patients suffering from dysphagia or subjected to an increased risk of chocking can benefit from the employment of ODF platforms for drug administration. As ODFs are inherently easy to administer, young and older patients can have access to a platform that can ensure a complete and precise dosing of medicines, minimising the risk of partial loss of actives due to tablet crushing or imprecise liquid administration. Moreover, medicine administration to uncooperative patients can be facilitated by the adhesion of ODFs to the oral cavity, therefore preventing the medicine to be spit out. Other ODF features such as flexibility, portability, and stability can confer superiority to other dosage forms like orodispersible tablets or liquids (Borges at al., 2015a, vol. IBorges et al., 2015aBorges at al., 2015a, vol. I). Delivering actives via ODFs through oral mucosa, can lead to rapid dissolution and fastest onset of action (Ashraf and Sayeed, 2014; Choudhary et al., 2013). Some examples of ODF products are commercially available for Alzheimer's disease (Donepezil – Labtech, Kyukyu Pharmaceuticals, Hexal Pharmaceuticals), emesis (Ondansetron – Monosol, Labtech, Aavishkar), schizophrenia (Olanzapine – Labtech, Hexal Pharmaceuticals), migraine (Zolmitriptan – Monosol, Labtech, NAL Pharma) etc. (Borges et al., 2015a). The readers are referred to a recent review by Borges et al. for a comprehensive product list of oro-mucosal film based products that are registered, launched, under (pre-) clinical development or withdrawn/discontinued.

The acceptability of ODFs was described in a recent paper considering the features of the final product including appearance, composition, taste and mouthfeel (Krampe et al., 2015). ODFs are considered to be age-appropriate oral dosage forms mainly with respect to its disintegration in the oral cavity upon administration without water. Furthermore, ODFs offer the possibility to implement taste masking technologies in order to minimise the averseness of the taste of the Active Pharmaceutical Ingredient (API). Mouthfeel and texture are also considered key characteristics potentially affecting the acceptability of ODFs, particularly with regards to the presence of residual particles following disintegration (Krampe et al., 2015). Mouthfeel in the sensory evaluation of foods has been related to the primary role of the saliva function. A reduced salivary production could therefore alter the mouthfeel of a product in specific patient groups such as patients under treatment for HIV, or older patients subjected to polypharmacy (Gupta et al., 2006; López-Verdín et al., 2013; Stokes et al., 2013). Other features like appearance, mucosal irritation, and API absorption are also considered relevant features to take into consideration when designing an ODF formulation (Krampe et al., 2015).

In addition to the aforementioned ODF characteristics, other features could potentially positively or negatively affect the patient acceptability of the dosage form, and should be further explored. As proposed in Fig. 1, the handling, placement and disintegration of ODFs are key stages to identify the full product features with high potential impact on patient experience. For example, the "stickiness/adhesiveness" of the film potentially contributes to placement in the mouth and subsequently the overall mouthfeel of the product. Krampe and colleagues have referred to the "gummy" nature of the films after wetting as potentially contributing to the mouthfeel of the dosage form (Krampe et al., 2015). Moreover, in the case of patients experiencing poor manual dexterity, poor hand sensitivity or reduced pinch strength (Stegemann et al., 2016), high ODF stickiness may result in the inability to properly handle the dosage form. These properties are largely related to the intrinsic properties of the carrier polymers, e.g. hygroscopicity and interfacial attributes. The ODF formulation is designed to disintegrate fast once placed in the mouth. Wettability, disintegration, and dissolution time of the film may change depending on the saliva production rate of the user. These parameters are considered to govern the performance of ODF drug products. Therefore, in the case of patients affected by severely impaired saliva production (dry mouth syndrome), ODFs may not be the dosage form of choice for drug administration.

2. Formulation, process and quality considerations of orodispersible films products

ODF products are conventionally manufactured via film casting of solution, suspension or melt using diverse technologies such as solvent casting, semisolid casting, rolling, coating and hot melt sheet extrusion (Borges et al., 2015a; Krampe et al., 2015). In these cases, the API(s) is/are dispersed in a feedstock with the suitable excipients, formulation and/or process aids and processed to yield films of desired dimensions and mechanical properties. Typically, therefore, ODF formulations have the structure of a matrix-based composite film. The current co-matrix formulation and process platforms intrinsically harbour some limitations in terms of content uniformity and the ability to combine and diversify doses because the final formulation is homogeneous. Furthermore, due to their moderate size and thickness ODFs can typically be loaded only with limited drug concentrations per unit volume and surface area (Bala et al., 2013). Therefore, oral films are not generally suitable for treatments requiring high dosages, although up to 50% drug loading in an ODF (Gas-X Strips®, Novartis) has been reported (Siddiqui et al., 2010).

The ODF design process should take several parameters into consideration: therapeutic target, patient population, safety, appropriateness and compatibility of API and excipients, processability of the polymeric mixture, impact on stability, physicochemical and mechanical characteristics of the final product, residual solvent/water content, drug release profile, packaging, and acceptability to the end user. Each pharmaceutical development stage can have a deep impact on the quality of the final product and must be carefully evaluated.

2.1. Manufacturing technologies

The most widespread technologies for ODF manufacture include solvent casting and semi-solid casting as broadly described by Hoffmann et al. (2011). These generally include feed stock of drug-excipient solution or suspension in aqueous and/or non-aqueous media. The use of organic solvents in solvent casting can improve the solubility of some APIs. Conversely, residual amounts of solvents could remain in the final product. Other manufacturing parameters, such as casting solution homogeneity, stability and film thickness, must be accurately monitored to ensure a smooth process.

Hot melt extrusion (HME) offers the advantage of a solvent-free process for ODF manufacturing (Palem et al., 2016, 2013; Park et al., 2015; Repka et al., 2003). Yet, poor availability of suitable polymers and high temperatures may pose stability issues to the active (Hoffmann et al., 2011). HME is a continuous manufacturing process. The scaling up/down for ODF manufacturing via hot melt sheet/film extrusion can depend upon the capacity of downstream shaping process. Other recently developed technologies offer alternatives to ODF manufacturing. Electrospinning of drug-loaded polymeric solutions has increased in popularity in the