European Journal of Pharmaceutics and Biopharmaceutics 125 (2018) 131–140

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Key acceptability attributes of orodispersible films

Mariagiovanna Scarpa[a], Amrit Paudel[b], Frank Kloprogge[c], Wen Kai Hsiao[b], Massimo Bresciani[b], Simon Gaisford[a], Mine Orlu[a,*]

[a] UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom
[b] Research Centre for Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria
[c] UCL Institute for Global Health, 30 Guilford Street, London WC1N 1EH, United Kingdom

ARTICLE INFO

Keywords:
Orodispersible film
Acceptability
Stickiness
Disintegration time
In vitro method
Human panel

ABSTRACT

The features rendering orodispersible films (ODFs) patient-centric formulations are widely discussed in the scientific literature. However there is a lack of research studies exploring ODF characteristics with a potential impact on end-user acceptability. The aim of this study was to identify the key ODF characteristics affecting end-user acceptability by developing *in vitro* test methods for the prediction of ODFs acceptability and correlate these formulation characteristics with the data obtained from a human panel study. Four drug-free single-polymer films were prepared by solvent casting. Solutions of poly(vinyl) alcohol (PVOH) 39 KDa (P1), PVOH 197 KDa (P2), carboxymethylcellulose (CMC) 395 KDa (C1), and CMC 725 KDa (C2) were prepared. Texture analysis and Dynamic Mechanical Analysis (DMA) were used to assess film tack. Petri dish and drop methods were used to assess disintegration time. A human panel of 24 healthy young adults was employed to identify end-user acceptability criteria of the four study film samples. Texture analysis data of ODF tack were not found to be in agreement with the *in vivo* perceived stickiness in the mouth. However, measurement of the area under the adhesive force curve obtained by DMA correlated with *in vivo* perceived stickiness data for all samples. The disintegration times obtained by drop method were more comparable to human panel data than the petri dish method. Hence DMA and drop methods proved to be promising methodologies for the prediction of the end-user acceptability. The type and molecular weight of the film-forming polymer had a strong influence on stickiness perception, whereas only polymeric molecular weight influenced perceived disintegration time. The human panel study showed that Participant Reported Outcomes (PROs) for the perceived stickiness in the mouth and disintegration time of test films received significantly different scores between samples, and thus were identified as the key attributes with the potential to affect the end-user acceptability. ODF stickiness and disintegration time should therefore be evaluated at an early stage of the drug product design.

1. Introduction

The term patient-centricity is currently used to describe drug products with characteristics that meet the needs of patient groups [1]. The quality attributes of pharmaceutical products should be optimised to ensure appropriate patient acceptability [2]. Orally administered pharmaceutical formulations, such as multiparticulates, orodispersibles, buccal tablets, buccal films, and chewable formulations, have been evaluated for their potential patient-centric features [3–5]. However, a harmonised approach towards the end-user acceptability testing of pharmaceutical formulations has not yet been fulfilled [1]. Recently, a definition of patient-centric drug product design was proposed [1]. In the manuscript, it was suggested to test a drug product for acceptability/usability in the personal health and environmental context of the target patient population, or to collect such information during clinical trials, where appropriate. Design drivers could then be identified and used to achieve the desired design outputs of the drug product [1].

Orodispersible films (ODFs) are stamp-size polymeric thin films that rapidly dissolve upon contact with saliva. Although ODFs have been reported to contribute to improved patient compliance [6], and offer a wide range of characteristics with the potential of addressing the needs of different patient populations [7], their acceptability has not been explored in the context of final dosage form characteristics [8–10]. Patient acceptability has been defined as the ability and willingness to take a medication as intended [2].

As ODFs reside in the mouth until complete disintegration, taste, mouthfeel and texture are considered as the characteristics that are very

* Corresponding author.
E-mail address: m.orlu@ucl.ac.uk (M. Orlu).

https://doi.org/10.1016/j.ejpb.2018.01.003
Received 16 August 2017; Received in revised form 25 December 2017; Accepted 7 January 2018
Available online 31 January 2018

likely to affect patient acceptability [11]. Moreover, the standard requirement for the disintegration time of orodispersible formulations is 3 min or less [12]. This guideline was introduced in order to allow a clear differentiation between dispersible and non-dispersible dosage forms. However, it also points to the central role played by disintegration time on patient preferences potentially affecting on the willingness of the patient to take and adhere to their medicine. Therefore, the disintegration time could also affect the acceptability of ODFs.

The assessment of the end-user acceptability of ODFs should focus on the identification of the needs of the patient/caregiver and key acceptability attributes of the test product. Human panels have been widely used in food science in order to determine the customer acceptability of specific food products [13]. Techniques such as hedonic scales have also been used for the acceptability assessment of pharmaceutical products, especially in children [9], allowing the identification of patient needs. However, knowing whether a specific ODF product is acceptable to patients does not provide any information on how to identify the formulation attributes that can influence the acceptability of the end-user. For this purpose, human panels should be designed to allow the identification of ODFs key acceptability attributes through an appropriate selection of the test samples.

Such selection needs to account for the acceptability attribute being studied, and how this can be influenced by modifying the formulation and/or process parameters of the particular product. For example, establishment of acceptability criteria of ODFs perceived stickiness requires the test samples to be prepared with different types of polymers at varying molecular weights. This stems from the fact that the adhesive properties of the film forming polymer depend, among other parameters, on the molecular weight and type of polymer [14]. Once a certain attribute is found to influence patients‘ perception, it should be also aimed to develop an *in vitro* methodology to predict the end-user‘s acceptability at an early stage of the drug product development. Ideally, such methodology should allow the assessment of an outcome measure capable of describing the acceptability attribute in a quantitative way. In the case of perceived stickiness, one of the appropriate methods would be measuring the adhesive force of the ODF sample upon detachment from a surface under hydrated conditions as a measure of tack. The adhesive force values of the test ODF samples measured at different time points can potentially describe how ODF tack changes over its disintegration time.

The aim of this study was to identify the key ODF characteristics affecting end-user acceptability by developing *in vitro* test methods for the prediction of ODFs acceptability and correlate these formulation characteristics with the data obtained from human panel study. Dynamic Mechanical Analysis (DMA) and texture analysis methods were developed to assess ODF tack while petri dish and drop methods were used to assess the ODF *in vitro* disintegration time. A human panel study was conducted in order to evaluate the perception of the healthy young adults about the stickiness and disintegration time of ODFs. The key acceptability attributes of polymeric ODFs were thereby established by assessing the relevant *in vitro* film properties and *in vivo* perceptive data.

2. Materials and methods

2.1. Materials

EMPROVE® poly(vinyl) alcohol 40–88 (39 KDa) and 40-–88 (197 KDa) were purchased from Merck Millipore (Darmstadt, Germany). Aqualon Blanose carboxymethylcellulose 12M31P (395 KDa) and 7HF-PH (725 KDa) were provided by Ashland Aqualon Functional Ingredients (Wilmington, Delaware, U.S.). Sterile water for injection was purchased from Gibco (Grand Island, New York, U.S.) Listerine PocketPacks® breath strips (Listerine®) and NiQuitin® strips (NiQuitin®) were purchased from Johnson & Johnson (New Brunswick, New Jersey, U.S.), and Omega Pharma (Brentford, Middlesex, U.K.) respectively.

2.2. ODF preparation by solvent casting

Four single-polymer test samples were prepared by solvent casting. Two samples were made of poly(vinyl) alcohol (PVOH) 39 KDa (P1), and 197 KDa (P2) respectively. Two samples were prepared with carboxymethylcellulose (CMC) 395 KDa (C1) and 725 KDa (C2) respectively. The solvent casting method described by Birck and colleagues [15] was adapted to prepare PVOH-based films. A 5% (w/v) PVOH solution was prepared in sterile water under stirring. The solution was heated to 75–90 °C (depending on PVOH grade) until a visible clarity was obtained, and then allowed to cool to room temperature. A 1% (w/v) CMC solution was prepared in sterile water and stirred until clear. 7.5 mL of PVOH or 15 mL of CMC solution were poured in a casting mould comprising a 8 cm diameter silicone ring (Shenzhen Yimeifen Technology, Guangdong, China) placed on top of a food safe acetate sheet (Tierrafilm - Nac Industrial, London, U.K.). The mould was then heated to 50 °C on a hot plate (IKA Labotechnik, Staufen, Germany) for two hours. The film was then peeled off, cut to size, and stored in a 10% RH and room temperature for at least one week before *in vitro* measurements were performed.

2.3. Measurement of drug-free ODF thickness

ODF thickness was measured using a thickness gauge (Mercer Ltd, Manchester, U.K.). Thickness measurements were taken on 5 different location (at the four corners and at the centre) of 3 × 2 cm cast films, as reported by Liew and colleagues [16].

2.4. Adhesive force measurements of ODFs by texture analysis

The adhesive force of drug-free ODF samples was measured using a TA.XT Plus texture analyser (Stable Microsystems Ltd., Godalming, Surrey, U.K.) equipped with a 30 kg load cell. The testing method was adapted from Hall et al., and Dave et al. [17,18]. A 1 × 1 cm^2 film with a thickness of 60 µm for PVOH films and 20 µm for CMC films was cut and placed on a non-conductive double-sided adhesive tape (SPI supplies, West Chester, Pennsylvania, U.S.) and attached to a microscope slide (Thermo Scientific, Braunschweig, Germany). The microscope slide was positioned under the TA.XT probe (6 mm cylindrical) and 200 µL of warm water (37 °C) was deposited on top of the film. The probe was lowered at a test speed of 0.4 mm/s. A force of 2.308 N was applied to the sample and maintained for 12 s, before the probe was withdrawn at 0.4 mm/s. Data were visualised using Exponent software (Exponent v6, Stable Microsystems Ltd., Godalming, Surrey, U.K.).

2.5. Adhesive force measurements of ODFs by dynamic mechanical analysis (DMA)

The adhesive force of drug-free and commercial test ODF was analysed using a Q800 Dynamic Mechanical Analyser (TA Instruments Delaware, US) equipped with 1.5 cm diameter steel compression clamps. The DMA was operated in controlled force mode. The film sample was cut into a circle of 1.5 cm diameter, mounted onto the lower clamp and secured by non-conductive double-sided adhesive tape. The clamps were kept separated by applying a negative force of −0.8 N, until the initial temperature of 37 °C was reached. A 450 µL of warm water (37 °C) was deposited on top of the film. Immediately after, the clamps were brought together and a force of 2.649 N was applied. The clamps were then withdrawn by ramping the force at −25 N/min to −8 N. Data were analysed using Universal Analysis 2000 v.4.5A (TA Instruments Waters LLC, Delaware, US). The adhesive force values were obtained at the intersection between the force curve and the ordinate of the displacement ramp at its onset point. The area under the curve (AUC) of the adhesive force versus time plot was calculated from time 0