Journal of Pharmaceutical and Biomedical Analysis 152 (2018) 47–56

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Assessment of oral formulation-dependent characteristics of orodispersible tablets using texture profiles and multivariate data analysis

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ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 16 January 2018
Accepted 18 January 2018

Keywords:
Texture analysis
Mouth feel
In vivo evaluation
Palatability
Multivariate calibration

ABSTRACT

Orodispersible tablets (ODTs) emerged as dosage forms recommended for special groups of patients like pediatrics or geriatrics, due to their multiple advantages. Among their critical quality attributes, palatability determines patient acceptance, with high impact on treatment efficacy. The aim of this study was to develop an instrumental method to assess *in vivo* disintegration time and palatability of ODTs.

The formulation factors that can influence palatability were refined through an experimental design. The most important ones were taken forward and a calibration set was prepared for multivariate calibration model development. The ODTs were tested for their pharmaceutical properties, texture profile, followed by *in vivo* disintegration and palatability characteristics assessed by a panel of 16 healthy volunteers.

Acceptability was correlated to high palatability scores, sweet taste and long disintegration time and negatively correlated to with the bitter taste and a voluminous residue. Results revealed the importance of choosing the right type of filler or filler ratio for the oral disintegration time and associated mouth feel. The calibration set included formulations with different ratios of mannitol and microcrystalline cellulose as fillers. Regression models were built by correlating the texture profiles to the *in vivo* evaluation parameters. The model performance was good on both external prediction set formulations and on marketed ODTs, with good predictive capacity ($Q^2 > 0.7$) for most of the subjective ODTs characteristics: *in vivo* disintegration time, residual volume and palatability.

1. Introduction

In the recent years a great emphasis was made on delivering easily accepted dosage forms, especially for the groups of patients who face the lack of therapeutic efficiency due to non-adherence [1,2,3,4]. As a result, orodispersible dosage forms (ODFs) were developed, that can be swallowed with no difficulty after prior disintegration in the oral cavity, without the need of water [1–6]. The wide patient acceptance determined the pharmaceutical industry to integrate the new technologies and products, often as replacements for classical dosage forms [7]. The orodispersible tablets (ODTs) emerged as class representatives. Their preparation was rapidly transferred to the production sites due to the simple and cost-effective technological process, to the conventional equipment, common excipients and packaging.

At the same time, the pharmaceutical industry faced another shift, within the FDA and EMA's Quality by Design initiative, which focuses on ensuring the quality of the drug products, starting from the design stage, by developing in-line methods to control manufacturing processes [8]. Among the fundamentals of this paradigm are establishing the quality target product profile (QTPP) and the critical quality attributes (CQA) of the developed medicines and consequently, a set of control methods associated to each CQA. The ICH Q8 guideline [8] enforces the need of a robust control strategy adapted for the product particularities, based on formulation and

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https://doi.org/10.1016/j.jpba.2018.01.040
0731-7085/

process understanding. In what ODTs are concerned, none of these prerequisites is properly addressed [9].

The characteristic that defines ODTs is fast disintegration, therefore disintegration time is the CQA upon whose value one can decide whether a product is orodispersible or not. The United States Pharmacopoeia (USP) limits it at 30s, while the European Pharmacopoeia (EP) allows ODT disintegration in maximum 3 min [10,11]. The high differences between the two official requirements can lead to high product variability and difficulties in categorizing and comparing the ODTs. Moreover, the control method assigned for the disintegration time assessment is similar to the one applied for conventional tablets, even though the *in vivo* conditions, namely disintegration media composition, pH and volume, are poles apart. The poor *in vitro – in vivo* correlation that resides was repeatedly reported in the scientific literature and several research groups attempted to give better alternatives to the pharmacopoeia standard test.

The first shortcoming of the official disintegration test relates to the high volume of disintegration media, 900 ml compared to about 1 ml of saliva in the oral cavity conditions. Several wetting evaluation methods were proposed, that tried to simulate the *in vivo* conditions, by placing the tablet on moist tissue paper immersed in a small volume of water (2–10 ml, depending on the Petri dish diameter). The results showed good correspondence to the disintegration test; still, the method fails to reproduce the forces applied by the tongue during disintegration, which makes it difficult to correlate to *in vivo* performance [9]. On the contrary, the use of a texture analyzer as an operating structure for disintegration profile evaluation allowed exerting variable pressure on tablets during disintegration. The experimental setup reported by Abdelbary et al. [12] pictured the tablet on a mobile perforated grid that was immersed into the simulated saliva due to the force developed by the descending probe. The time-distance profiles accurately indicated both the start and the endpoint of disintegration process, with good correlation to the *in vivo* behavior. Moreover, a qualitative parameter associated to mouthfeel estimation was anticipated. Szakonyi and Zelkó [13] extended the texture approach to tablets with different disintegration mechanisms that target various groups of patients whose illnesses can modify the testing parameters. In addition to that, computational optimization was used to predict the formulation that yielded the best *in vivo* performance for patients with xerostomia.

Along with the disintegration time, palatability is another representative CQA for ODTs. It is defined as the overall appreciation of a medicinal product concerning its smell, taste, aftertaste, texture and mouthfeel [14] and it is usually marked by high variability due to the personal preferences of the volunteers, thus difficult to standardize. Progress has been made in the attempt to develop analytical methods for taste evaluation, e.g. the electronic tongue [15]. But up to date, to our knowledge, no one reported the development of an instrumental method that predicts palatability, although recent studies in children incriminated unpleasant texture and large volume medicines as reasons for medicines refusal, along with the unpleasant taste [16].

The aim of this study was to build a multivariate calibration model to predict several properties of orodispersible tablets by means of texture analysis, setting an instrumental method as an alternative for *in vivo* testing procedures.

In this respect, placebo tablets were prepared according to a 2^{6-2} screening experimental design and were analyzed in order to identify the most influential formulation factors that have an impact over pharmaceutical properties and *in vivo* characteristics. In order to reach high formulation diversity regarding disintegration time and mouthfeel, the independent variables included two superdisintegrants with different mechanisms, two fillers (one soluble and sweet, the other one insoluble in water), two sweeteners and granules prepared at two levels of the average size.

The classical pharmaceutical evaluation targeted the measurement of weight uniformity, mechanical strength, friability, disintegration time, wetting time and water absorption ratio. Texture analysis was performed using a previously reported experimental setup, modified towards a better simulation of oral conditions [13]. Moreover, 16 healthy volunteers assessed the *in vivo* disintegration time and oral tablet characteristics.

2. Materials and methods

2.1. Materials

The following excipients were used at the preparation of ODTs: sodium starch glycolate (SSG) (JRS Pharma, Germany), sodium croscarmellose (SCC) Ac-Di-Sol (FMC BioPolymer, Belgium), mannitol (Man) (Parteck M200, Merck, Germany), microcrystalline cellulose (MCC) (Avicel PH-101, Merck, Germany), polyvinylpyrrolidone (PVP) (Kollidon 25, BASF, Germany), aspartame (Ajinamoto, Japan), saccharine (Foodchem, China) and magnesium stearate (Merck, Germany). Aerius 5 mg orodispersible tablets (Merck Sharp & Dohme Ltd, United Kingdom) and Yasnal 10 mg orodispersible tablets (KRKA, Slovenia) were purchased from the local pharmacy.

2.2. ODTs preparation

The placebo ODTs were prepared by wet granulation, having the filler and the superdisintegrant within the granules and the sweetener and magnesium stearate mixed with the granules. 10% PVP in ethanol solution was used as binder solution. The filler, the superdisintegrant and the sweetener used for the preparation, are indicated in the experimental design matrix for each of the 19 formulations, together with the PVP ratio and the superdisintegrant ratio (Table 1). The sweetener ratio was kept constant, at 2% and the filler content was calculated and added as necessary, so that the total weight of a tablet would be 200 mg. Briefly, the filler and superdisintegrant were blended into a mixer (Erweka, Germany) for 2 min, at 50 rpm. The PVP solution was added, and the mixing continued for another 1 min, at 70 rpm. The wet mass was transferred into the oscillating calibrator (Erweka, Germany), equipped with a mesh of 400 μm or 800 μm, as specified in the experimental design matrix (Table 1). The granules were dried over night at room temperature and then calibrated again in the same equipment. Before compression, dried granules were blended with the sweetener and magnesium stearate using a planetary mixer, for 5 min, at 50 rpm. An eccentric tablet press (Korsch EK0, Germany) equipped with a 10 mm diameter flat punch set was used for tablet preparation, adjusted for an average weight of 200 mg/tablet.

2.3. ODTs pharmaceutical characterization

2.3.1. Disintegration time

The disintegration time was measured on six tablets, according to the European Pharmacopoeia method, in 800 ml distilled water kept at 37 °C (ZT 2 disintegration tester, Erweka, Germany). The times until complete disintegration, with no residue left on the sieves, were recorded. The results were expressed as mean disintegration times with the correspondent standard deviation.

2.3.2. Wetting time and water absorption ratio

For the wetting time measurement, two pieces of tissue paper were placed in a 4.5 cm diameter Petri dish, containing 4.5 ml distilled water, at room temperature. The tablet was placed on the tissue paper and the time until dissolution media reached the upper surface of the tablet was recorded. The tablets used in the wetting