European Journal of Pharmaceutical Sciences 57 (2014) 273–279

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Bio-predictive tablet disintegration: Effect of water diffusivity, fluid flow, food composition and test conditions

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ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 27 August 2013
Accepted 29 August 2013
Available online 11 September 2013

Keywords:
Hydrodynamics
GI tract
Biopredictive conditions
Food effect

ABSTRACT

Food intake may delay tablet disintegration. Current in vitro methods have little predictive potential to account for such effects. The effect of a variety of factors on the disintegration of immediate release tablets in the gastrointestinal tract has been identified. They include viscosity of the media, precipitation of food constituents on the surface of the tablet and reduction of water diffusivity in the media as well as changes in the hydrodynamics in the surrounding media of the solid dosage form.

In order to improve the predictability of food affecting the disintegration of a dosage form, tablet disintegration in various types of a liquefied meal has been studied under static vs. dynamic (agitative) conditions. Viscosity, water diffusivity, osmolality and Reynolds numbers for the different media were characterized. A quantitative model is introduced which predicts the influence of the Reynolds number in the tablet disintegration apparatus on the disintegration time.

Viscosity, water diffusivity and media flow velocity are shown to be important factors affecting dosage form disintegration. The results suggest the necessity of considering these parameters when designing a predictive model for simulating the in vivo conditions. Based on these experiments and knowledge on in vivo hydrodynamics in the GI tract, it is concluded that the disintegration tester under current pharmacopoeial conditions is operated in an unphysiological mode and no bioprediction may be derived. Recommendations regarding alternative mode of operation are made.

1. Introduction

The disintegration test is a simple test to control the quality of pharmaceutical products. It provides information about the time that is required for the solid dosage form to break up in a given medium. Fast tablet disintegration facilitates drug dissolution by increasing the contact surface between the drug and the media. Any delay in tablet disintegration, will affect the overall release of the active pharmaceutical ingredient (API) from the dosage form. Recently, attention has been paid for using disintegration as a surrogate test for dissolution of BCS class 1 compounds (Gupta et al., 2009).

Food consumption is known to significantly retard the disintegration of immediate release tablets. Decreased tablet disintegration in canine stomach was reported under fed compared to fasted conditions (Kalantzi et al., 2005). Prolonged disintegration time of fosamprenavir tablets immersed in nutritional drink compared to simulated gastric fluid was due to impaired water ingress (Brouwers et al., 2011). Abrahamsson et al. (2004) explained the postprandial delay in tablet disintegration in vitro and in vivo by precipitation of a protein film on the tablet surface. Galia et al. (1998) attributed the delay in drug dissolution in milk to the interaction between tablet excipients and medium without providing further mechanistic explanation. The prolonged disintegration time in milk compared to simulated gastric fluid (SGF) was ascribed to its relatively high viscosity (Anwar et al., 2005).

Disintegration is largely dependent on the media physicochemical properties such as viscosity and water diffusivity. The elevation in media viscosity has been shown to significantly delay tablet disintegration (Parojčić et al., 2008; Radwan et al., 2012, 2013). The effect was mediated through reduced water penetration rates into tablets (Radwan et al., 2012). Reduced water diffusivity in sucrose solutions was shown to be the reasonable explanation for increased disintegration time in these media compared to equal osmolality sodium chloride solutions (Radwan et al., 2013).

The delay in tablet disintegration times may have clinical implications, especially for drugs with low bioavailability or when a rapid onset of action is desired. For example, trospium chloride, which is classified as BCS III drug, has low bioavailability (about 10%). Site dependent and low permeability was shown to be

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http://dx.doi.org/10.1016/j.ejps.2013.08.038

responsible for its poor bioavailability (Doroshyenko et al., 2005). Trospium chloride exhibits a negative food effect: concomitant food intake had been reported to reduce its bioavailability (AUC) by 70–80% compared to the fasted state (Hotha et al., 2010).

Current compendial disintegration media and disintegration test conditions do not reflect the actual conditions of the GI and will not be suitable to predict the effect of food on dosage form performance (Anwar et al., 2005). Several biorelevant models have been proposed to more accurately simulate the gastric environment under fast and fed conditions (Jantratid et al., 2008; Klein, 2010). However, the influence of media hydrodynamics was not considered in these reports.

An early review reported prolonged tablet disintegration times in vivo vs. in vitro (Steinberg et al., 1965). In addition to media composition, the poor IVIV correlation was attributed to the difference in the agitation intensity between in vitro and in vivo. While the literature data revealed very low in vivo hydrodynamic flow (Katori et al., 1995; O'Grady, 2010; Pal et al., 2004), the disintegration apparatus was shown to produce the highest hydrodynamic flow between the disintegration, paddle, basket and flow-through pharmacopeial tests (Morihara et al., 2002). In order to obtain a more physiologically relevant test from the hydrodynamic flow point of view, it is important to simulate the in vivo physiological Reynold's numbers. Reynold's numbers for gastric flow around a tablet of 1 cm in diameter were determined to be 0.01–30 (Abrahamsson et al., 2005). The in vivo physiological flow velocity is much lower than that within the disintegration device. The hydrodynamic flow velocity around a tablet in the GI tract was estimated to be less than 0.89 cm/min (Katori et al., 1995). Gastric flow velocity is induced by propagation of wave contractions. High-resolution mapping was applied to study the activity of the slow waves in the human stomach. The mean velocity of propagation in the corpus was 3 mm/s compared to 5.9 mm/s in the antrum with a maximum velocity of 8 mm/s in the pacemaker region (near the mid to upper corpus) (ÓGrady et al., 2010). Computational fluid dynamics were useful for modeling gastric mixing and evaluating in vivo gastric flow rates. Using two dimensional numerical simulations, Pal et al. (2004) estimated the average velocity of gastric flow to be 2–3 mm/s with a maximum up to 7.5 mm/s. Ferrua and Singh (2010) developed a 3-D geometrical model of the stomach to characterize the fluid dynamics of the gastric contents at different viscosities. The flow velocity was shown to be site dependent with the strongest fluid motion in the antrum region of the stomach. Similarly, Kozu et al. (2010) showed the highest velocity of gastric flow in the occluded region of the antrum of approximately 12 mm/s.

The aims of this work were to study the impact of food composition, fluid flow and media water diffusivity on tablet disintegration and to improve the predictability of the disintegration test by matching the in vitro flow velocities and Reynold's numbers with the physiological values using theoretical calculations. A model for predicting tablet disintegration based on media hydrodynamics was developed by modeling tablet disintegration rates as a function of Reynold's number.

2. Materials and methods

2.1. Materials

2.1.1. Dosage forms

Three dosage forms containing trospium chloride were used in this study: Spasmolyt® 30 mg tablet (Madaus, Germany), Spasmex® 30 mg (Dr. R. Pfleger, Germany) and Trospi® 30 mg (Medac, Germany). Spasmolyt® and Spasmex® were film-coated tablets, whereas Trospi® was a non-coated tablet.

2.1.2. Study media

- Simulated gastric fluid (SGF) (0.1 N HCl) and simulated intestinal fluid (SIF) were used as a reference media to represent the fasted state. SIF was prepared by dissolving 6.8 g KH_2PO_4 and 0.2 M NaOH in 1000 ml distilled water.
- Various types of liquid and liquefied meals were used to investigate the effect of food on tablet disintegration: orange, grape, apple juices (Riodoro, Rinteln) and Coca Cola were obtained from local markets. Champignon and tomato soups (Le Guto, Dr. Lange & co., GmbH, Düsseldorf) were prepared by dissolving the contents of the packets in 500 ml water and heating until boiling. Standard FDA meal was prepared by mixing thoroughly the following constituents using a Waring blender: 2 slices of toast with butter, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, 8 oz of whole milk and 240 ml water (CDER, 2002). The final volume of the homogenised FDA meal was 700 ml, which is composed of 460 ml of the homogenised diet and 240 ml of water that is recommended to be administered with the meal. Due to its high viscosity and in an attempt to account for the dilution process by GI secretions; the mixture was then diluted with 200 ml of water. The dilution factor of 200 ml was selected based on a previous in vivo study (Marciani et al., 2001), which reported a gastric dilution factor of 130–165 ml/80 min. And since the gastric emptying time was estimated to range between 70 and 130 min following solid meal ingestion (Dressman, 1986), a volume of 200 ml will be appropriate. Water was used instead of buffers for the dilution process, since the drug in this study and formulation disintegration is not affected by pH. The homogenisation of the FDA meal was done to enhance the uniformity of the sample and to reduce the variability in the measurements. This may represent the situation after a perfectly chewed meal. However, the situation might be different in real life; MRI images showed poor food mixing after ingestion of a viscous meal (Ferrua and Singh, 2010; Marciani et al., 2001) such that, after intake of an FDA meal, one might expect also the gastric content to be a heterogeneous mixture of different food particles suspended in a low viscosity medium. Probably the real situation lies in between these extremes.

2.2. Density determination

A pycnometer was used to determine the density of the various media. The density values were calculated by dividing the difference in the mass of the pycnometer before and after filling it with the investigated solution by its volume. Density determination was performed in triplicate at 37 °C.

2.3. Viscosity determination

The dynamic viscosity of the different samples was measured using a capillary viscometer (Schott-Geraete, Germany) at 37 °C. The rheological profile for the diluted FDA meal viscosity measurements was determined by a rotational rheometer RV 12 (HAAKE, Germany) using the MV DIN Sensor system. Measurements were made in triplicate.

2.4. Osmolality determination

The osmolality of the different media was measured using a Wescor vapour pressure osmometer (MA, USA) calibrated with standard solutions of known osmolality. Osmolality was measured in duplicate.