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Assessment of disintegration of rapidly disintegrating tablets by a visiometric liquid jet-mediated disintegration apparatus

Parind M. Desai, Celine V. Liew, Paul W.S. Heng*

GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Singapore

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ABSTRACT

The aim of this study was to develop a responsive disintegration test apparatus that is particularly suitable for rapidly disintegrating tablets (RDTs). The designed RDT disintegration apparatus consisted of disintegration compartment, stereomicroscope and high speed video camera. Computational fluid dynamics (CFD) was used to simulate 3 different designs of the compartment and to predict velocity and pressure patterns inside the compartment. The CFD preprocessor established the compartment models and the CFD solver determined the numerical solutions of the governing equations that described disintegration medium flow. Simulation was validated by good agreement between CFD and experimental results. Based on the results, the most suitable disintegration compartment was selected. Six types of commercial RDTs were used and disintegration times of these tablets were determined using the designed RDT disintegration apparatus and the USP disintegration apparatus. The results obtained using the designed apparatus correlated well to those obtained by the USP apparatus. Thus, the applied CFD approach had the potential to predict the fluid hydrodynamics for the design of optimal disintegration apparatus. The designed visiometric liquid jet-mediated disintegration apparatus for RDT provided efficient and precise determination of very short disintegration times of rapidly disintegrating dosage forms.

1. Introduction

Conventional tablets and capsules sometimes are difficult to be administered to certain groups of patients including those on the move, those with swallowing difficulties, geriatric, pediatric, bedridden and mentally challenged patients (Fu et al., 2005; Giri et al., 2010; Goel et al., 2008; Jeong et al., 2005; Pfister and Ghosh, 2005; Saigal et al., 2008; Sandri et al., 2006). Rapidly disintegrating tablets (RDTs) can be regarded as an effective alternative in such situations. RDT is an oral solid dosage form which disintegrates or disperses instantly upon wetting with saliva in the buccal cavity and can be ingested without the need of water (Battu et al., 2007; Giri et al., 2010; Goel et al., 2008; Jeong et al., 2005; Saigal et al., 2008; Sandri et al., 2006). Thus, RDTs provide convenience of both solid and liquid dosage forms. From the pharmaceutical industry's point of view, RDTs can potentially offer an option to extend the patent life and market exclusivity of a product (Giri et al., 2010; Saigal et al., 2008).

One of the most important features of the RDT is its short disintegration time (Narazaki et al., 2004). Disintegration time could be evaluated *in vivo* by the methods described in the literature (Bi et al., 1996; Ishikawa et al., 1999; Koizumi et al., 1997; Watanabe et al., 1995). Results of such *in vivo* tests are not as reproducible for RDTs in comparison with conventional tablets because disintegration times of RDTs generally differ only by seconds. Also, *in vivo* disintegration testing requires demanding regulatory approvals. Thus, a reliable *in vitro* disintegration test for RDT is required especially for routine quality control purposes. However, no specific pharmacopeial apparatus has been identified for determining the disintegration time of RDTs. As reported, the conventional disintegration time measurement appears inappropriate for RDTs since it is unable to discriminate the disintegration ability of various RDTs (El-Arini and Clas, 2002; Harada et al., 2006; Morita et al., 2002; Narazaki et al., 2004; Shukla et al., 2009). Several new methods have been proposed. A modified dissolution apparatus was suggested where the disintegration medium was stirred using a paddle and the time required for the tablet fragments to pass through the screen of the sinker was determined as disintegration time (Bi et al., 1996). Morita et al. (2002) developed an approach to determine the RDT disintegration time in a sophisticated disintegrating test apparatus equipped with a CCD camera. Both methods showed potential but RDTs were evaluated without considering possible mechanical stress induced by the tongue and movements in the oral cavity. Therefore, a disintegration apparatus was developed with the application of mechanical stress (Narazaki et al., 2004). The RDT on a stainless steel wire gauze was slightly immersed in

* Corresponding author. Tel.: +65 65162930; fax: +65 67752265.
E-mail address: phapaulh@nus.edu.sg (P.W.S. Heng).

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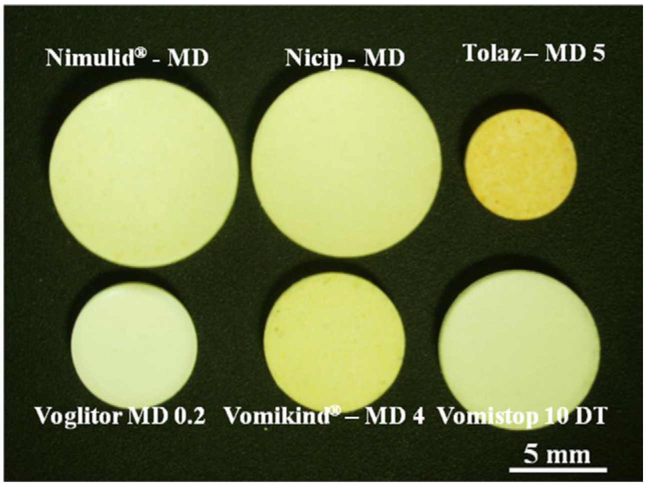

Fig. 1. Different types of commercial RDTs used in the study.

the disintegration medium and then compressed by a shaft, crushing the disintegrating RDT through the gauze into the medium. The endpoint was determined by a manual timer. Improvements were made later by introducing a conductive metal sponge at the shaft base to improve substrate attachment (Harada et al., 2006). A stainless steel perforated plate replaced the wire gauze and an electrical sensor was added for the detection of shaft-stainless steel plate contact. The texture analyzer instrument was also utilized by applying a constant force on the tablet, attached to the bottom of a cylindrical probe and immersed in distilled water (Dor and Fix, 2000). The distance traveled by the probe due to the applied force was measured. The major disadvantage of applying mechanical force with the probe or shaft is the inherent errors with very soft compacts or small dosage forms.

Computational fluid dynamics (CFD) is ideal for the characterization of fluid hydrodynamics (Lee, 2011). CFD has been used in the pharmaceutical and food industries, for simulation of flow in dissolution apparatus, pumps, mixers and spray driers (Chen, 2011; Kuriakose and Anandharamakrishnan, 2010; McCarthy et al., 2003; Pires et al., 2008) but to date, no disintegration apparatus has been characterized and simulated using CFD.

In the present study, a combined computational and experimental approach was used to characterize RDT disintegration using high speed video imaging. Three RDT disintegration compartment designs were tested and their functionality validated by CFD for the best design. Disintegration times of RDTs upon wetting were then evaluated using the most suitable compartment for the visiometric liquid jet-mediated disintegration apparatus by real time video imaging. The term visiometric is coined to describe the process of capturing the images of in-process condition (visio) and extracting the measurements (metric) from the captured images at different time points. Disintegration times of RDTs were also determined in the United States Pharmacopeia (USP) disintegration apparatus to ensure good correlation between the two methods. Six types of commercial RDTs were purchased and used to validate the viability of the visiometric liquid jet-mediated disintegration apparatus.

2. Materials and methods

2.1. Materials

Different types of commercial RDTs used in the study are shown in Fig. 1 and listed in Table 1. The results are the mean of 6 samples. The RDTs were all cylindrical tablets with either flat or bi-convex surfaces. RDTs were concealed during the experiment (random inscription from A to F) and 6 samples of each type of RDTs were used for each apparatus.

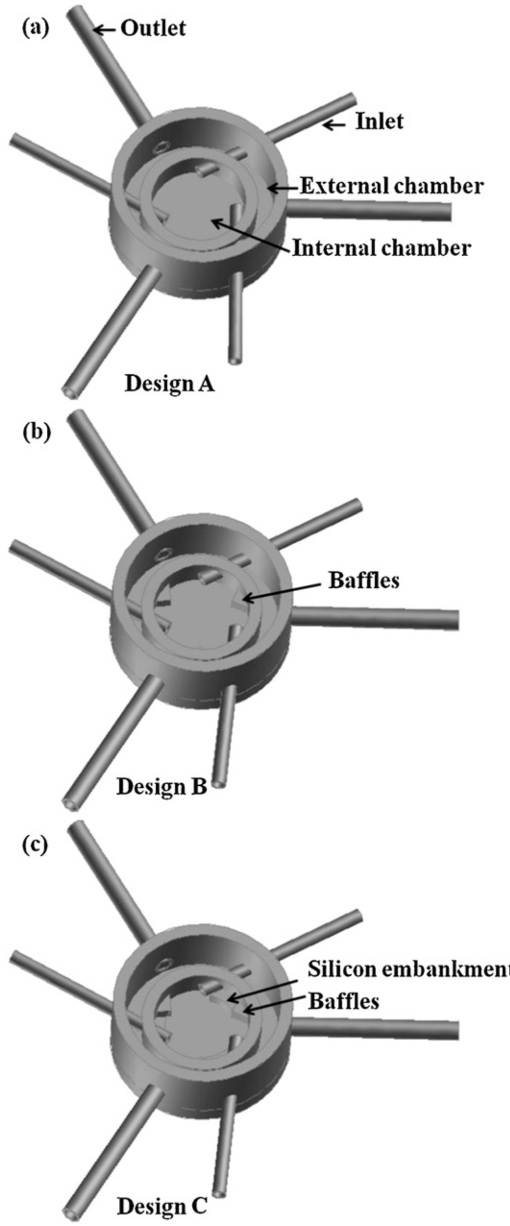

Fig. 2. Designs of the simulated and fabricated disintegration compartments of the visiometric liquid jet-mediated disintegration apparatus.

2.2. Simulation of the visiometric liquid jet-mediated disintegration apparatus

Three designs of RDT disintegration compartment (Fig. 2) with progressive modifications were prepared and simulated using CFD software packages as follows. The prototype was designed as design A, improved version as design B and accepted version as design C.

2.2.1. Governing equations

CFD software packages were used to determine numerical solution to the equations governing the fluid flow inside the defined flow geometry at different stages of apparatus design. These equations were considered as mathematical formulations of the conservation laws of fluid dynamics. Each continuous fluid flow problem was discretized with a grid or mesh to define the flow