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Experimental and computational determination of the hydrodynamics of mini vessel dissolution testing systems

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ABSTRACT

Mini vessel dissolution testing systems consist of a small-scale 100-mL vessel with a small paddle impeller, similar to the USP Apparatus 2, and are typically utilized when only small amounts of drug product are available during drug development. Despite their common industrial use, mini vessels have received little attention in the literature. Here, Computational Fluid Dynamics (CFD) was used to predict velocity profiles, flow patterns, and strain rate distribution in a mini vessel at different agitation speeds. These results were compared with experimental velocity measurements obtained with Particle Image Velocimetry (PIV). Substantial agreement was observed between CFD results and PIV data. The flow is strongly dominated by the tangential velocity component. Secondary flows consist of vertical upper and lower recirculation loops above and below the impeller. A low recirculation zone was observed in the lower part of the vessel. The radial and axial velocities in the region just below the impeller are very small especially in the innermost core zone below the paddle, where tablet dissolution occurs. Increasing agitation speed reduces the radius of this zone, which is always present at any speed, and only modestly increases the tangential flow intensity, with significant implication for dissolution testing in mini vessels.

1. Introduction

In recent years, dissolution testing has become a powerful tool in the evaluation of different solids dosage formulations during drug product development and therefore in the improvement of the whole development process. For this purpose, numerous dissolution test devices exist, although the USP Apparatus 2 system is still the most commonly used device in industry, particularly for the immediate release (IR) of solid dosage forms (U.S. FDA, 2000; U.S. FDA, 1997; USP 38-NF 33, 2015). Generally, successful dissolution testing during product development is preceded by the preparation of test drug products and is followed by drug analysis of the samples collected during the dissolution tests. Often, even at this initial stage, dissolution testing is conducted in a standard dissolution apparatus, such as the USP 2 system, for which an extensive literature exists, also covering the complex hydrodynamics of this apparatus (Baxter et al., 2005; Bocanegra et al., 1990; Kukura et al., 2004; Bai et al., 2007a; Bai et al., 2007b; Bai and Armenante, 2008; Bai and Armenante, 2009).

In most pharmaceutical companies, the use of the standard USP Apparatus 2 is well established, and this system is typically the first choice for dissolution testing of solids dosage forms (USP 38-NF 33, 2015; Cox et al., 1984; Inman et al., 2001; Moore, 1996; Qureshi and Shabnam, 2001; Wang et al., 2013; Zhang et al., 2013). However, this approach may not be appropriate for all dissolution situations, especially during the early stages of product development. For example, initially the availability of Drug Substance (DS) is often limited: therefore, testing drug products may contain only microgram quantities of the active ingredient. Upon dissolution in a conventional USP Apparatus 2, this in turn results in very low concentrations of the dissolved drug. In fact, available analytical methods may not be sensitive enough for such low-dose dissolution testing, and this approach may not be practical to obtain reliable dissolution testing data. Low drug concentrations in the dissolving medium may additionally result from the development of more potent drug substances. Specifically, for some bio-relevant studies during drug formulation, dissolution should be ideally conducted in a specific dissolution medium, such as the animal gastrointestinal medium, with a similar dissolution medium as in animal

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physiology (Amidon et al., 1995; Gu et al., 2004; U.S. FDA, 1997; Avdeef, 2007; Klein, 2006). If the USP 2 standard system is used, this may require large volume of expensive bio-relevant dissolution medium, with additional costs.

In order to address these issues, in the industrial practice the standard USP Apparatus 2 dissolution method has been modified, and a small volume dissolution vessel with a mini paddle has been suggested as an alternative to standard dissolution equipment during these early stage studies, when tablets only contain very small amounts of active ingredient, or when extended release tablets are tested in which small amounts are released and may be difficult to detect using conventional analytical methods. This "mini vessel" system consists of a small volume vessel (typically about 100 mL) with a small-size impeller similar in shape to the USP Apparatus 2, as shown in Fig. 1. This type of apparatuses is now widely used in industry and routinely available commercially from a number of vendors. However, such mini vessel dissolution apparatus and the associated dissolution method are not yet included in the US Pharmacopoeia (i.e., this is not a "compendial" method), although Section ⟨1092⟩ mentions that the mini-paddle and mini vessel apparatus may have some utility "with proper justification, qualification, and documentation of superiority over the standard equipment" and that they "may be considered for low-dosage strength products."

Although growing, the literature on mini vessels is still in general quite limited (Crist, 2009; Klein and Shah, 2006; Scheubel et al., 2010; Sree Lakshmi and Badarinath, 2013; Stamatopoulos et al., 2015). This implies that some important issues must still be addressed, such as apparatus calibration, reliability reproducibility, and method validation before this approach can be more widely used. In addition, it is unclear how dissolution tests conducted in mini vessels compare to those obtained in the standard USP Apparatus 2. This in turn requires a more fundamental understanding of the hydrodynamics of mini vessel systems, which has received even less attention until very recently (Stamatopoulos et al., 2015).

Therefore, the overall objective of this work is to quantify the hydrodynamics of mini vessels by determining the flow characteristics, velocity profiles, and strain rate distribution in a mini vessel dissolution system under different operating conditions. This was accomplished here by conducting Computational Fluid Dynamics (CFD) simulations and Particle Image Velocimetry (PIV) experiments to obtained detailed information on the hydrodynamics of mini vessels. The hydrodynamics of a specific mini vessel was studied in detail at four different agitation speeds, with special attention paid to the determination of the velocity distribution in the region below the impeller since this is where dissolving tablets can be found during the dissolution testing process.

2. Experimental equipment, materials, and method

2.1. Mini vessel dissolution system

The mini vessel apparatus used here consisted of the most common commercially available mini vessel system, i.e., a cylindrical glass vessel with a hemispherical bottom and a working volume of 100 mL provided with a mini paddle impeller placed centrally in the vessel. The exact dimensions of the mini vessel system studied here are given in Table 1 and Fig. 2. These dimensions were obtained by directly measurements of a mini vessel provided by the Merck Company, Rahway, NJ (courtesy of Mr. Gerard Bredael). The mini vessel was mounted in a commercial USP Apparatus 2 system (Distek 5100 Bathless Dissolution Apparatus; Distek Inc., North Brunswick, NJ) using a round mounting plate with a central opening to accommodate the mini vessel inside the round opening where the 1-L vessel is typically placed in a dissolution test (Fig. 1). The mini impeller was similarly assembled on the same system by unscrewing the larger Apparatus 2 paddle and replacing it with the entire mini paddle impeller/shaft instead.

The off-bottom impeller clearance used in this work (measured from the bottom of the paddle to the bottom of the vessel) was 10 mm, which, when appropriately scaled, is very close to that of the standard USP Apparatus 2 system. This is the clearance commonly used in industry (and depth setting tools for this clearance can be purchased commercially), and it was recommended by the manufacturer of the dissolution testing equipment (Distek Company).

In order to minimize optical distortion effects during the velocity measurements, the mini vessel was suspended inside a 203-mm square Plexiglas box filled with water placed under the mounting plate of the Distek dissolution testing system. After assembling the apparatus, the mini vessel was filled with distilled water at room temperature.

Table 1
Dimensions of mini impeller (mini paddle) in mini vessel system.

Component	Dimension (mm)
Shaft Diameter	6.40
Length of Top Edge of Impeller Blade	27.58
Length of Bottom Edge of Impeller Blade	17.00
Height of Impeller Blade	8.08
Thickness of Impeller Blade	1.60

Fig. 1. Mini vessel dissolution apparatus, including the small volume vessel, mini paddle impeller, small lid, and the mounting plate to adapt the mini vessel to the standard opening for the USP 2 vessel in a typical dissolution testing system.