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A Novel Disintegration Tester for Solid Dosage Forms Enabling Adjustable Hydrodynamics

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ABSTRACT

A modified *in vitro* disintegration test device was designed that enables the investigation of the influence of hydrodynamic conditions on disintegration of solid oral dosage forms. The device represents an improved derivative of the compendial PhEur/USP disintegration test device. By the application of a computerized numerical control, a variety of physiologically relevant moving velocities and profiles can be applied. With the help of computational fluid dynamics, the hydrodynamic and mechanical forces present in the probe chamber were characterized for a variety of device moving speeds. Furthermore, a proof of concept study aimed at the investigation of the influence of hydrodynamic conditions on disintegration times of immediate release tablets. The experiments demonstrated the relevance of hydrodynamics for tablet disintegration, especially in media simulating the fasted state. Disintegration times increased with decreasing moving velocity. A correlation between experimentally determined disintegration times and computational fluid dynamics predicted shear stress on tablet surface was established. In conclusion, the modified disintegration test device is a valuable tool for biorelevant *in vitro* disintegration testing of solid oral dosage forms.

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Introduction

PhEur, USP, and other Pharmacopoeias describe simple devices to investigate solid oral dosage form disintegration and dissolution *in vitro*. During the last years, the knowledge of the *in vivo* hydrodynamic and mechanical conditions in the gastrointestinal (GI) tract increased making it possible to challenge the biorelevance of the devices proposed by the pharmacopoeias.

Tablet disintegration has recently been described to be dependent on 4 mechanisms comprising surface erosion, fraction, rupture, and dissolution of the drug and/or excipients.[1] Particularly, surface erosion and fraction depend on hydrodynamic conditions. During the passage through the GI tract, solid dosage forms experience a wide range of hydrodynamic and mechanical forces that may influence their disintegration and the dissolution of active ingredients. Depending on the position of the dosage form in the stomach, it experiences different loads. Although the proximal part of the human stomach is characterized by low shear stress and little dosage form movement, high shear stress and strong mixing are observed in the distal part.[2] The stress exerted on the dosage form is furthermore dependent on the prandial state of the stomach. During the fasted state, the interdigestive migrating motor complex occurs. These cyclic contractions are characterized by 3 to 4 phases of different contraction strength and duration.[3] During phase 3, where the most powerful contractions occur, all undigested material is emptied from the stomach. Meal ingestion interrupts the migrating motor complex and initiates the fed pattern (digestive motor activity). Incoming food is transported to the antrum by slow fundic contractions where it is mixed and digested by antral contraction waves. Reaching the pylorus, fluid, and small particles up to approximately 2 mm are emptied into the duodenum, whereas undigested material is retained and further grinded. During gastric digestion, considerable mechanical forces are acting on solid objects, food particles, or dosage forms, provoking their disintegration.

Clearly, these changing mechanical and hydrodynamic conditions cannot be reproduced by the static *in vitro* test devices currently described by USP, PhEur, and other pharmacopoeias. For example, results of a computational fluid dynamics (CFD) study recently published by our group[1] suggest that the compendial disintegration test device is not accurately reproducing the *in vivo*

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conditions leading to *in vitro* disintegration times of limited value with respect to predict the *in vivo* situation. Similar lack of predictable and biorelevant hydrodynamic conditions based on advanced computational calculations has been shown for the USP I and II dissolution apparatuses.[4-7]

Therefore, during the last years, several attempts were undertaken improving *in vitro* dissolution testing. The rotating beaker, introduced by Abrahamsson et al.,[8,9] aims to better simulate the shear stresses present in the postprandial human stomach. A close relationship between measured erosion rates of hydroxypropyl methylcellulose tablets and calculated shear stress was found for varying conditions. The dissolution stress test device was designed to mimic GI movement and mechanical stresses acting on the dosage form during GI transit.[10] Similarly, the fed stomach model was developed to simulate the conditions present in the postprandial state with particular focus on mechanical aspects.[2]

The applicability of these recently developed methods described earlier are limited due to complexity of setups and restriction to certain type of dosage forms. Additionally, these methods with focus on dissolution behavior of solid dosage forms do not consider disintegration, neither fluid movement, which is responsible for hydrodynamic conditions in the vicinity of the dosage form. Depending on the prandial state, fluid movements and velocities change *in vivo* leading to diverse hydrodynamic conditions that may influence disintegration of solid dosage forms. Therefore, there is still a need for new, simple tests providing different and controllable hydrodynamic conditions to enable biorelevant disintegration testing, especially because there is increasing evidence for the importance of disintegration characterization in solid dosage form development and quality control.[11]

Results of a CFD study recently published by our group[1] suggest that the compendial disintegration test device is not accurately reproducing the *in vivo* conditions leading to *in vitro* disintegration times of limited value with respect to predict the *in vivo* situation.

The aim of the current work was to develop and test a biorelevant disintegration test method for solid dosage forms in the stomach. A modified disintegration test device was used enabling the investigation of the influence of hydrodynamic conditions on solid oral dosage form disintegration by optimizing probe chamber design and its movement and velocity pattern. Furthermore, this study characterized fluid velocities and forces present in the modified device under various operating conditions allowing to compare with corresponding values for the stomach and, thereby, define biorelevant conditions.

Materials and Methods

Modified Disintegration Test Device

The modified disintegration test device represents an improved derivative of the compendial PhEur/USP apparatus. It is intended to investigate the effect of hydrodynamic conditions on disintegration times of oral solid dosage form. Similar to the compendial test device, the modified system comprises the probe chamber, a beaker to accommodate the test medium, and a thermostatic water bath (Figs. 1a and 1b). However, the probe chamber was modified. The compendial basket-rack assembly described in the pharmacopoeias comprises 6 circular arranged open-ended glass tubes that are limited by a wire mesh at the bottom. This design restricts the fluid to the tubes and does not allow horizontal fluid flow. The in-house built probe container of the modified device consists of 3 quadratic probe chambers (dimensions: 22 × 25 mm, solid walls made of polyethylene). The bottom and the front and back side are constructed of a wire mesh (mesh size: 2 mm; EKA, Bergisch Gladbach, Germany) allowing 2-sided fluid flow.

The movement of the probe container is accomplished by a computerized numerical control (CNC). This approach allows for the variation of moving speed and moving direction. Although the compendial device is limited to the vertical movement following a sinusoidal velocity profile (Fig. 1c, solid line), various velocity profiles in all 3 dimensions can be generated with the modified device. In this study, we focused on the vertical movement with different moving velocities. However, the moving speed was linear and constant over the moving distance (moving profile exemplarily shown in Fig. 1c for moving velocities of 40 and 80 mm/s, dashed lines). Nevertheless, a later development toward complex 3-dimensional moving profiles is possible. The movement is accomplished by a thooted belt CNC drive (LEZ 1; Isel Germany AG, Eichenzell, Germany) with high-torque stepping motor (MS045HT; Isel Germany AG) and 1:2 gear, that is controlled by a 4-axis stepping motor controller (CSD 405-IMC; Isel Germany AG). The program coding for the movement of the drive is written in ProNC (Isel Germany AG).

Fluid Flow Simulations

We applied CFD software SolidWorks (Dassault Systèmes SolidWorks Corporation, Waltham, MA) to reconstruct the geometry of the modified disintegration test device and to characterize the hydrodynamic and mechanical forces present. The principles of the software and the governing equations used have been described earlier.[1]

The beaker was constructed with 145 mm height and an inner diameter of 103 mm. Because the requirement for an internal fluid flow analysis is a closed geometry, the beaker was closed with a lid at the top. Each of the 3 probe chambers is a rectangle of 22 × 25 mm. The solid boundaries of the chambers are 84 mm in height with a thickness of 0.7 mm. The mesh at the front and back of each probe chamber was constructed with a mesh size of 2 mm and a wire diameter of 0.5 mm. A tablet of 9 mm diameter and 5 mm height was placed in the middle probe chamber.

CFD simulations were run under the condition that the tablet is fixed at the wire mesh. Although this assumption does not necessarily mimic the actual situation in the disintegration tester, it should be preferable due to the defined position of the tablet when exposed to the hydrodynamic conditions.

By default, the velocity boundary condition at all solid walls is set to nonslip. Atmospheric pressure was applied to the top lid of the beaker. The bottom of the beaker was defined as fluid inlet. The fluid velocity at the inlet was set to 80 mm/s for the first examinations of the fluid flow field and the shear stress on the tablet surface. The fluid flow condition was set to fully developed.

To examine the influence of device moving speed on hydrodynamics and forces, the inlet velocity was varied between 20 and 100 mm/s in steps of 20 mm/s.

CFD simulations were performed for 2 model fluids, namely simulating gastric fluid (SGF), representing the fasted state, and 1.4% hydroxylpropylmethylcellulose (HPMC) solution, recently proposed as model fluid representing the fed state.[12] Both fluids were created into the CFD software by providing their physicochemical characteristics. Simulating gastric fluid was, thereby, defined as a Newtonian fluid with a density of 0.999 g/mL and a viscosity of 0.817 mPa·s. Because 1.4% HPMC solution shows no-Newtonian flow behavior, the rheologic profile was experimentally measured using a Haake Rheostress 1 viscosimeter (Thermo Fisher Scientific, Karlsruhe, Germany), operating at room temperature at shear rates in the range of 0 to 600 s^{-1}. Data from rheologic measurements were evaluated using the attached RheoWin 4 data manager software. The shear stress–viscosity rheograms were loaded into the CFD software. The software corrects the inserted values for the 37°C used in this study and adjusts

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