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Bio-relevant dissolution testing of hard capsules prepared from different shell materials using the dynamic open flow through test apparatus

Grzegorz Garbacz [a,b], Dominique Cadé [c], Hassan Benameur [c], Werner Weitschies [a,*]

[a] University of Greifswald, Institute of Pharmacy, Center of Drug Absorption and Transport, Felix-Hausdorff-Strasse 3, 17487 Greifswald, Germany
[b] Physiolution GmbH, Walter-Rathenau-Strasse 49a, 17489 Greifswald, Germany
[c] Capsugel R&D, 10, rue Timken, 68027 Colmar, France

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ABSTRACT

Current compendial dissolution and disintegrating testing is unable to mimic physiological conditions affecting gastric drug release from immediate release dosage forms. In order to obtain more realistic data, a novel test setup was developed that we term a 'dynamic open flow through test apparatus'. It is based on the previously described dissolution stress test device and attempts to simulate the intra-gastric dissolution conditions pertinent to immediate release dosage forms administered under fasting conditions with respect to flow rates, intra-gastric temperature profiles and gastric motility. The concept of the dynamic open flow through test apparatus has been tested using five different types of hard capsules: conventional hard gelatin capsules (HGC), three hypromellose based capsules (Vcaps, Vcaps Plus and DRcaps) and pullulan based capsules (Plantcaps). These were of different sizes but all contained 100 mg caffeine in each formulation, adjusted to avoid buoyancy by addition of excipient. When the capsules were stressed in the apparatus under the dynamic flow conditions applying mild pressure simulating gastric motility, release from release from Vcaps Plus, Vcaps and Plantcaps capsules was very well comparable to HGC. Capsules are usually swallowed with cold water and the temperature dependency of release from gelatin was noted as a significant factor, since heat exchange in the stomach is slow.

1. Introduction

The characterisation of the drug release from immediate release tablets and capsules is usually performed using standardised dissolution or disintegration tests. Adoption of a common standardised conditions permits laboratory-to-laboratory comparison although none of the test methods has been developed with the reference to important in vivo considerations, apart from adoption of more representative media.

The initiation of disintegration of immediate release tablets and capsules generally begins in the stomach within some seconds to a few minutes after administration. The physiological conditions which are encountered likely to impact on these processes, are media flow (hydrodynamics), media temperature, frequency and magnitude of intraluminal pressure (motility), frequency and the intensity (range, duration and velocity) of intraluminal transport. This, together with media composition and volume are highly interlinked determinants of performance and are dynamic, not static, in nature.

In view of this complexity, a test setup was designed that captures the discrete simulation of the parameters hydrodynamics, media volume, media temperature, gastrointestinal motility and transport in an appropriate context. The result of this development we term the "dynamic open flow through test apparatus" (Fig. 1), designed as an accessory to the stress test dissolution apparatus that we have been working on during the last years (Garbacz et al., 2008, 2010). This allows the dissection of bio-relevant determining factors for product performance and the creation of a test protocol that allows product discrimination within the physiological range.

The novel apparatus allows the operator to handle volumes of less than 50 mL which is a realistic volume of gastric fluid in the human stomach under fasting conditions (Memiş et al., 2003, 2002; Schiller et al., 2005). To this is added 250 mL of water which will be heated to abdominal temperature at an appropriate rate. In addition the simulation of intra-gastric media flow and gastric emptying kinetics under fasting conditions is achieved.

The test items employed were hard capsules manufactured from different polymers filled with caffeine as the model drug substance. In the studies described in this paper, the simulation of the release behaviour of the tested hard capsules was limited to fasting intake conditions. This permitted the data to be linked to the scintigraphic studies which served as a reference.

* Corresponding author. Tel.: +49 3834 864813; fax: +49 3834 864886.
E-mail address: werner.weitschies@uni-greifswald.de (W. Weitschies).

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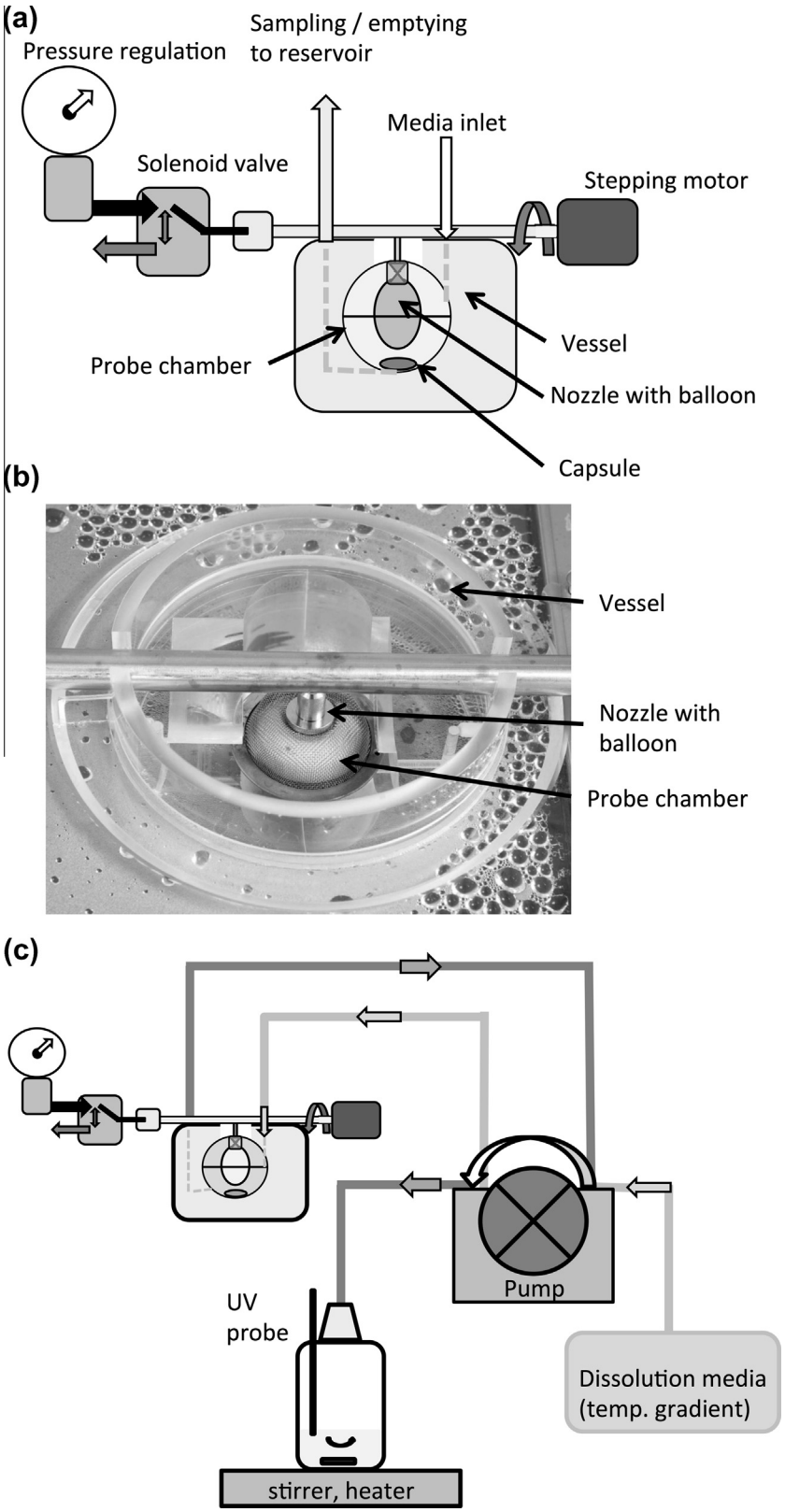

Fig. 1. Dynamic open flow through test apparatus. (A) Schematic diagram of the test apparatus. (B) Photograph of the open vessel with view on the probe chamber that is mounted on the central axis via a nozzle. (C) Schematic diagram of the test configuration with media flow.