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Note

Reciprocating dialysis tube method: Periodic tapping improved in vitro release/dissolution testing of suppositories

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Abstract

The reciprocating dialysis tube (RDT) method can be used for in vitro release/dissolution testing of suppositories and has been reported to show good in vitro and in vivo correlation. However, for suppositories with viscous excipients, the result remains variable and generally under-predicts in vivo absorption. The purpose of this study was to assess whether periodic tapping of the closure of the RDT could improve in vitro release testing of suppositories. Two commercially available acetaminophen suppositories (A and B) that showed characteristic release behavior under normal rectal temperatures (37 and 38 °C) were chosen as test suppositories. In the absence of tapping, suppository A showed different release profiles at 37 and 38 °C, but the difference disappeared with periodic tapping. This finding was consistent with minimum temperature effect in the rectal absorption of suppository A in rabbits. Suppository B showed distinct release profiles at 37 and 38 °C irrespective of tapping, and the rectal absorption of suppository B in rabbits was affected by temperature. The test variability (CV% and ranges of release values) was substantially reduced in the presence of tapping. In conclusion, the addition of periodic tapping to RDT method developed in this study could improve in vitro release testing of suppositories.

Keywords: In vitro and in vivo correlation; IVIVC; In vitro release; Dissolution test; Dialysis membrane; Suppository; Acetaminophen

1. Introduction

In vitro release/dissolution tests are widely recognized as a quality control procedure to assure lot-to-lot uniformity for pharmaceutical dosage forms as well as a predicative tool for in vivo absorption. In spite of their importance, compendial tests are mainly limited to solid oral dosage forms. For other dosage forms such as suppositories, numerous methods have been published for testing in vitro release, but such testing remains a challenge in terms of their variability and predictability [1,2]. A recent guideline [1] stated that no single test method will be suitable for all suppository formulations. The recommendation is to begin with the basket or paddle method in the case of hydrophilic suppositories and with the modified flow-through cell in the case of lipophilic formulations [1]. Therefore, a more robust in vitro release/dissolution test for suppositories is needed, which may obviate the need to employ different techniques on a case-by-case basis.

Dialysis membrane has been used for in vitro release testing of suppositories. Lootvoet et al. [3] reported that the dialysis rotating cell method (Pharmatest®) showed better in vitro and in vivo correlation than the flow-through method (Dissotest®) [2] using three commercially available indomethacin suppositories. In our previous studies [4–6], the reciprocating dialysis tube method showed the highest correlation between in vitro release and in vivo absorption in rabbits for seven commercially available indomethacin suppositories (two water-soluble, three oleaginous base

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and two rectal capsules), while a lower correlation was obtained using other apparatus such as the TMS-103 suppository dissolution apparatus (Toyama Sangyo Co., Ltd., Osaka, Japan), rotating dialysis cell, and dialysis tube. Both the TMS-103 apparatus and rotating dialysis cell methods use membranes with $\geqslant 0.45$ μm pore size, which are much larger than those of dialysis membranes. Aoyagi et al. [7] reported higher in vitro release and in vivo bioavailability in rabbits and pigs using the dialysis tube method for three oleaginous indomethacin suppositories than by using the TMS-103 apparatus. However, they cautioned that the presence of a small quantity of fluid in the dialysis tube would result in substantially delayed drug release and consequently low reproducibility. In short, a conventional dialysis tube method, in which a dialysis tube is immersed in dissolution vessel with a hemispherical bottom (USP Dissolution Test Apparatus I), has several drawbacks: (a) difficulty in controlling aqueous fluid volume in the dialysis tube, (b) heterogeneous agitation of dissolution medium, (c) off-center position and/or swaying of the dialysis tube and agitator in the reservoir resulting in non-uniform distribution of drug concentration in the medium and (d) slower release rates compared to in vivo absorption. These problems could largely be alleviated by installing a reciprocating dialysis tube to the disintegration apparatus, but the problem of reproducibility and slower release still remains to be overcome.

The aim of this study was to assess the effect of periodic tapping of the closure (which closes the lower end of the dialysis tube) of the reciprocating dialysis tube on the reproducibility and predictability of the in vitro release of suppositories. In the study, two commercially available acetaminophen suppositories, which had characteristic release profiles reported by our group [6], were chosen as test suppositories. Our long-term goal is to develop a robust in vitro release test for suppositories that could predict the in vivo bioavailability in humans.

2. Materials and methods

2.1. Materials

Two commercially available acetaminophen suppositories with oleaginous base (suppositories A and B) were purchased [6]. Each suppository contained 100 mg of acetaminophen. The dialysis tube (membrane size 27) was purchased from Viskase Sales (IL, USA). The molecular weight cut-off of the dialysis membrane is 12,000–14,000 Da. Acetaminophen standard and all other reagents were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan).

2.2. Reciprocating dialysis tube (RDT) method

The reciprocating dialysis tube method developed by our group for testing the in vitro release of suppository is shown in Fig. 1. The apparatus consists of a stainless steel

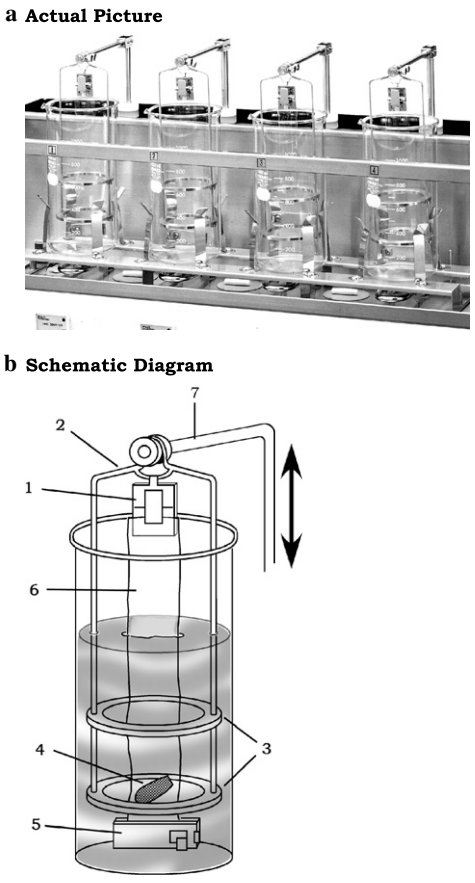

Fig. 1. Actual picture (a) and schematic diagram (b) of the reciprocating dialysis tube method for the in vitro release/dissolution test for suppositories. 1: clip, 2: agitator, 3: ring, 4: suppository, 5: closure, 6: dialysis tube and 7: arm of disintegration apparatus.

agitator, a clip that suspends a dialysis tube from an arm of a disintegration apparatus, a plastic closure (Spectra/Por® No. 132736, Spectrum Laboratories, Inc., CA, USA) attached to a weight (5 g) which closes the lower end of the dialysis tube, a 1 L beaker (20 cm of height, 9.2 cm of internal diameter), and a disintegration apparatus HZ-41D specially modified to fit the dissolution chamber (Miyamoto Riken Ind. Co., Ltd., Osaka, Japan; www.miyamotoriken.co.jp). The agitator is hung by the arm of a disintegration apparatus and moves up and down. The attached weight and a closure do not touch the bottom of the reservoir during the experiment. The dialysis tube is suspended in a beaker containing 1 L of 50 mM phosphate buffer (pH 7.0) at 37.0 ± 0.1 or 38.0 ± 0.1 °C. The top of the disintegration apparatus is equipped with a plastic cover to reduce evaporation of the dissolution medium. The arm of the disintegration apparatus moves up and down automatically at a constant speed (40 rpm).

Prior to in vitro release testing, residual fluid in the dialysis tube was removed manually by pulling the dialysis tube through a film squeegee (King®, Asanuma & Co., Japan) that pinched the dialysis tube. The dialysis tube (length 17 cm) was soaked in purified water and was rinsed before being used. After one end of the dialysis tube was closed