ELSEVIER

International Journal of Pharmaceutics 133 (1996) 59–63

international journal of pharmaceutics

'The insertion cell': a novel approach to monitor drug release from semi-solid dosage forms

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Received 3 November 1995; accepted 4 December 1995

Abstract

The flow-through cell for use in dissolution rate testing of solid dosage forms has recently become an additional compendial method in both the British Pharmacopoeia (Apparatus 3) and in the United States Pharmacopeia (Apparatus 4). Although none of the official dissolution methods have been specified for use with semi-solid dosage forms, their utility for assessing release rates of drugs from semi-solid dosage forms has become a topic of considerable interest. A custom-made insertion cell was constructed such that its dimensions permitted this cell to be used with the compendial flow-through cell. The release of acyclovir from two semi-solid dosage forms was monitored using this 'insertion cell' and the rank order of release was found to be in total agreement with previous data on the identical semi-solid dosage forms using previously described diffusion cells (Chattaraj et al., 1995; Chattaraj and Kanfer, 1995). The variability in the replicate data was, however, slightly greater when the %RSD values were compared to those previously obtained. These values, nevertheless, compare favourably with the results obtained using Franz diffusion cells. The 'insertion cell' offers distinct advantages compared to the Franz cells in that it is easier to use and readily adaptable for use with the compendial flow-through apparatus and does not suffer from the problem of having to remove air bubbles at the membrane/liquid interface, which commonly occurs when using Franz cells.

Keywords: Insertion cell; B.P. Dissolution Apparatus 3; USP Dissolution Apparatus 4; Flow-through cell; Drug release; Semi-solid dosage forms; Acyclovir

Dissolution testing of solid dosage forms is now well-established as a standard technique to assess drug release from such dosage forms. It is currently considered as the single most useful in vitro method for assuring batch-to-batch uniformity (Shah et al., 1989). It has become an extremely valuable quality control procedure for comparing release profiles of different lots of finished product. In addition, it has great utility as a pre-formulation tool (Shah et al., 1993; Martin et al., 1989) and has even been suggested as a useful surrogate measure to predict bioavailability for extended-release oral dosage forms using pre-established in vitro–in vivo correlations (US Subcommittee on Biopharmaceutics, 1988; Leeson et al., 1985).

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SSDI 0378-5173(95)04410-C

Currently, several different apparatuses for dissolution testing have been included in the British Pharmacopoeia (British Pharmacopoeia, 1993) and in the United States Pharmacopeia (US Pharmacopeia, 1995). The former compendium makes provision only for the dissolution testing of tablets and capsules, specifying and describing the basket apparatus (Apparatus 1), the paddle apparatus (Apparatus 2) and the flow-through cell (Apparatus 3) whilst the USP includes the above and, in addition, specifies and describes apparatuses for extended-release articles (Apparatus 3; and Apparatus 4, flow-through cell identical to the B.P. Apparatus 3) as well as methods and equipment for transdermal delivery systems such as the paddle over disk (Apparatus 5), cylinder (Apparatus 6) and the reciprocating disk (Apparatus 7).

To date, no official methods have been specified for suppositories or semi-solid dosage forms, although the basket method has been used to determine the release of drug from suppositories (Palmieri, 1982; Kiss, 1989; Suleiman and Najib, 1990; Asakura et al., 1993), whilst in a recent report, Sanghvi and Collins (1993) utilized the paddle method to determine the release of hydrocortisone from an emollient ointment mounted in their enhancer cell.

The present study was undertaken to investigate the possibility of using the compendial flow-through apparatus in conjunction with a custom-made insertion cell to monitor the release of acyclovir from two different semi-solid formulations.

1. Cell Design and construction

The insertion cell was constructed in our laboratory and each cell consisted of three basic components. Fig. 1a depicts the relevant components in an unassembled form whilst Fig. 1c shows the assembled insertion cell placed inside the large flow-through tablet cell used in the compendial flow-through apparatus (Sotax Tablet Dissolution Cell, internal diameter = 22.6 mm, Sotax AG, Basel, Switzerland). The upper section (Fig. 1a) consisted of an oblong block of plexiglass (1.5 mm thickness) and dimensions such that it fitted into the large flow-through compendial tablet cell. A small circle of 9 mm was cut out of this block. The middle section (3.0 mm thickness) consisted of a matching oblong block of plexiglass into which a similar circle of 9 mm was cut out and acted as the sample holder. The lower component was a solid block of plexiglass (1.5 mm thickness) of compatible dimensions and all three sections were screwed together with the aid of two bolts on either side of the three components. The membrane was placed between the upper and sample holder sections prior to assembly. A stainless steel spring support (Fig. 1b) was constructed to act as a holder for the insertion cell when used in the 'turbulent flow' mode, whilst a layer of glass beads (1 mm diameter) placed into the conical section of the flow-through cell (Fig. 1c) acted as a support for the insertion cell when used in the 'laminar flow' mode. The insertion cell was positioned at a distance of 10 mm from the conical section of the flow-through cell when used with the spring support.

2. Drug release measurements

Prior to assembly, each semi-solid preparation was accurately weighed (165 mg) and placed into the centre of the sample holder which had been positioned onto the lower block. The membrane (cellulose acetate 0.45 μm, CA 502500, 150 μm thickness; Lida Manufacturing Corporation, USA) was then placed on top of the sample holder and all three sections firmly bolted together. In view of the fact that two different oriented positions of the insertion cell were possible, i.e. top of insertion cell facing down with direct impact of flow or insertion cell facing up avoiding direct flow impact, both orientations were assessed. Furthermore, the influence of flow-type, i.e. laminar or turbulent, was also investigated. When the glass beads were used to support the insertion cell, laminar flow was assumed due to the even spreading of flow by the beads across the cross-section of the flow-through cell. Using the stainless steel holder without glass beads was assumed to have resulted in a turbulent flow

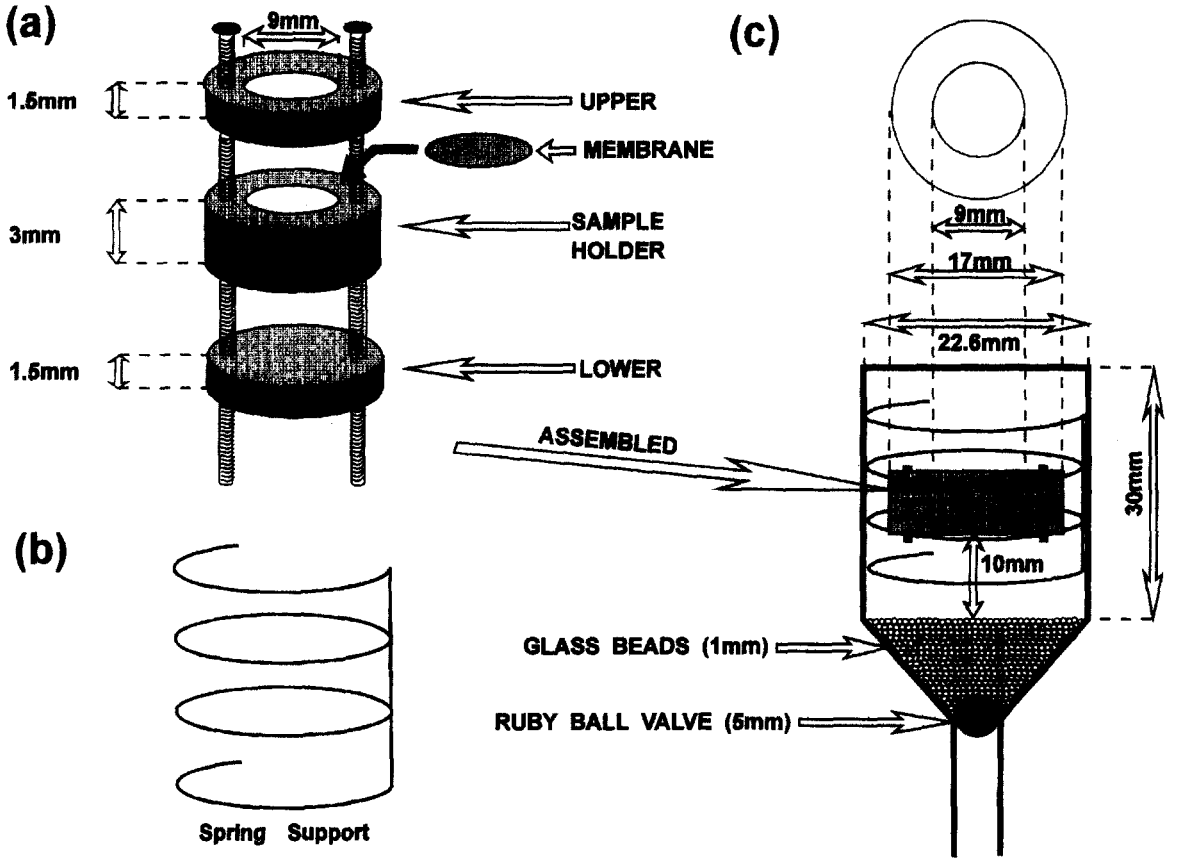

Fig. 1. Insertion cell in a compendial flow-through cell. (n.b. Glass beads without the spring support used during laminar flow studies.) (a) Insertion Cell. (b) Spring support used during turbulent flow studies. (c) Insertion cell inside compendial flow-through cell.

pattern due to the strong motion of fluid entering the flow-through cell.

The integrity of the cell was previously confirmed by filling the reservoir with a solution of phenol red and sealing the upper section with a solid piece of matching plexiglass.

All membranes were conditioned by immersing in receptor fluid (0.9% sodium chloride) for 30 min and blot-dried prior to use.

Commercially available Zovirax cream (Acyclovir 5% cream, Wellcome, Pty. Ltd., South Africa) and an extemporaneously prepared cream (Cream A) containing 5% acyclovir were assessed in both orientation modes using both laminar and turbulent flow in separate experiments.

Six replicate experiments were carried out using a Sotax Dissotest Flow-through Dissolution Apparatus (Sotax AG. Basel, Switzerland) and the insertion cell placed directly into the flow-through cell of the apparatus (Fig. 1). The dissolution medium flow rate was 6 ml/min at a constant temperature of 32°C ± 0.5°C and samples (60 ml) were collected in a Sotax C 615 fraction collector at 15 min. intervals. This was facilitated by the use of a Sotax MS 70(S) medium splitter which allowed for continuous reduction of dissolution medium to be collected over the specific collection intervals. The entire system was controlled by a Sotax CE 70 unit and PC. Samples were analyzed by a previously described HPLC method (Chattaraj et al., 1995).

Fig. 2 depicts the cumulative amount of acyclovir released from Zovirax cream and a Cream A using turbulent flow conditions and two differ-

ent orientations of the insertion cell. Plots of cumulative amount released versus the square root of time were found to be linear and the slopes of these plots were used to compare the release of acyclovir from the respective semi-solid dosage forms. These data indicated that the release of acyclovir from Cream A was greater than from Zovirax cream irrespective of the cell orientation. Better discrimination was, however, obtained when the insertion cell was used in a 'down' orientation. This mode of orientation made provision for direct impact of the flow of receptor fluid onto the surface of the membrane.

Fig. 3 depicts the cumulative amount of acyclovir released from Zovirax cream and Cream A using laminar flow conditions (glass beads in flow-through cell) with two different orientations of the insertion cell. The rank order of release of acyclovir from the preparations studied was found to

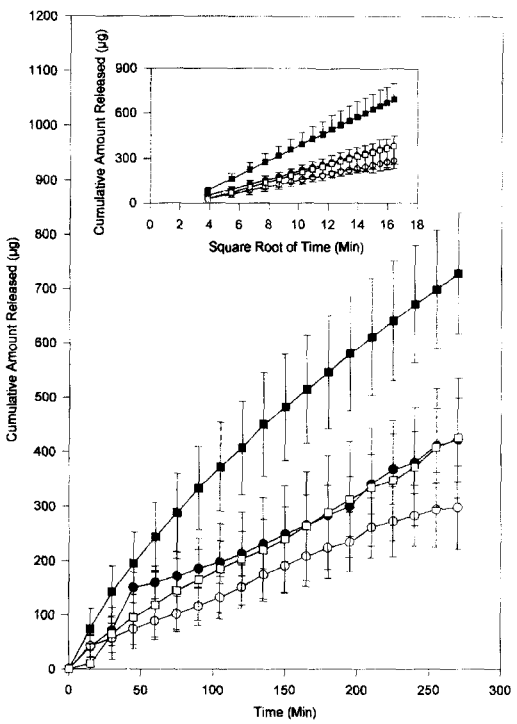

Fig. 2. Cumulative amount of acyclovir released using the insertion cell in a compendial flow-through apparatus. ● Cream A (turbulent flow-cell up). ○ Zovirax cream (turbulent flow-cell up). ■ Cream A (turbulent flow-cell down). □ Zovirax cream (turbulent flow-cell down).

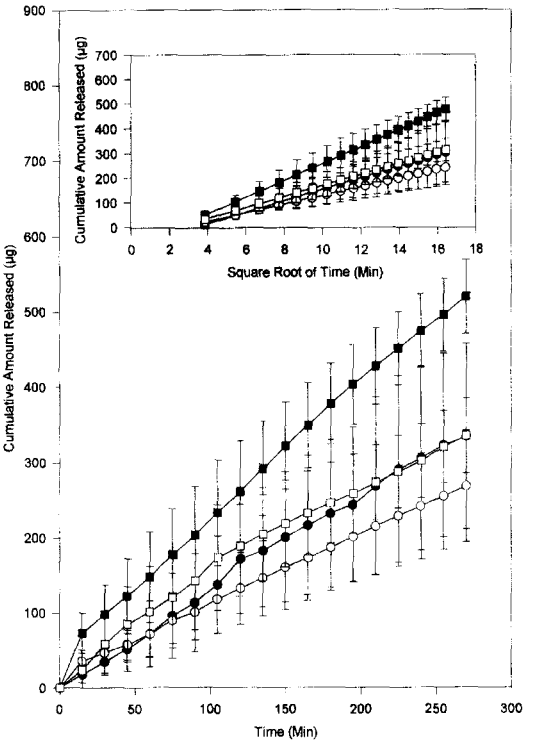

Fig. 3. Cumulative amount of acyclovir released using the insertion cell in a compendial flow-through apparatus. ● Cream A (laminar flow-cell up). ○ Zovirax cream (laminar flow-cell up). ■ Cream A (laminar flow-cell down). □ Zovirax cream (laminar flow-cell down).

be in total agreement with that found in our previous work on the identical semi-solid dosage forms using previously described diffusion cells (Chattaraj et al., 1995; Chattaraj and Kanfer, 1995). The variability in the replicate data was, however, slightly greater when the %RSD values were compared to those previously obtained (Chattaraj et al., 1995; Chattaraj and Kanfer, 1995). These values, nevertheless, compare favourably with the results obtained using Franz diffusion cells. However, the insertion cell overcomes the disadvantages of the Franz cell in that it is easier to use and readily adaptable for use with the compendial flow-through dissolution apparatus. Furthermore, it does not suffer from the problem of having to remove air bubbles at the membrane/liquid interface which commonly occurs when using Franz cells.

This report thus describes the potential application of the compendial flow-through dissolution apparatus for use in monitoring release of active ingredient(s) from semi-solid dosage forms for assuring batch-to-batch uniformity.

Acknowledgements

I.K. gratefully acknowledges financial support from the Foundation for Research Development of South Africa. A post-doctoral fellowship award from Rhodes University is acknowledged by S.C.

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