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A simple diffusion cell to monitor drug release from semi-solid dosage forms

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Abstract

A simple plexiglass cell was constructed and the in vitro release of acyclovir and diclofenac from semi-solid dosage forms was monitored using nylon and cellulose acetate membranes. The release of acyclovir was also monitored using Franz diffusion cells. Comparison of the data indicated that the rank order of release of acyclovir was the same using either the plexiglass or the Franz cells. However, data from the plexiglass cells indicated that better precision was obtained using this system as reflected by the much lower degree of variability between replicate experiments compared to the results obtained using the Franz cells. The results clearly indicate that the plexiglass cells provide a simple, precise and reliable system to monitor in vitro drug release from semi-solid dosage forms and do not suffer from the problem of having to remove air bubbles at the membrane/liquid interface which often occurs when using the Franz cells.

Keywords: Diffusion cell; Semi-solid dosage form; Drug release; In vitro release; Acyclovir; Diclofenac; Nylon membrane ; Cellulose acetate membrane

The use of in vitro methods to assess the release of active ingredient(s) from semi-solid dosage forms is gaining increasing attention from both the pharmaceutical industry and regulatory authorities (Skelly et al., 1987; Martin et al., 1989; Shah et al., 1989, 1991; Kundu et al., 1993).

Satisfactory release of active ingredients from dosage forms is a prerequisite for therapeutic efficacy. Although determination of dissolution characteristics has become one of several standard techniques routinely used to assess release from solid oral dosage forms a universally acceptable drug release test and associated conditions for semi-solid formulations has yet to be established.

Currently, no compendial method exists for determining the in vitro release of a drug from topical products such as gels, creams and ointments. Many reports describing various equipment and methodologies have appeared in the literature over the past two decades (Poulsen et al., 1968; Ayres and Laskar, 1974; Bottari et al., 1974, 1975, 1977; Chowhan and Pritchard, 1975;

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Behme et al., 1982; Weng and Parrot, 1983; Velissaratou and Papaioannou, 1989; Shah et al., 1991, 1993; Rolland et al., 1992; Corbo et al., 1993; Sanghvi and Collins, 1993).

The Franz diffusion cell has become a popular method of studying the diffusion of drug from transdermal delivery systems and has recently also been used to assess drug release from semi-solid dosage forms (Shah et al., 1989, 1991, 1992, 1993; Wu et al., 1992; Corbo et al., 1993; Kundu et al., 1993; Sanghvi and Collins, 1993).

Although Shah et al. (1991) claim that the Franz diffusion cell can be routinely used to characterise the release of drugs from topical dosage forms, a serious drawback is the difficulty in removing air bubbles at the membrane/liquid interface. Failure to remove these air bubbles results in poor precision of the data. Since it is

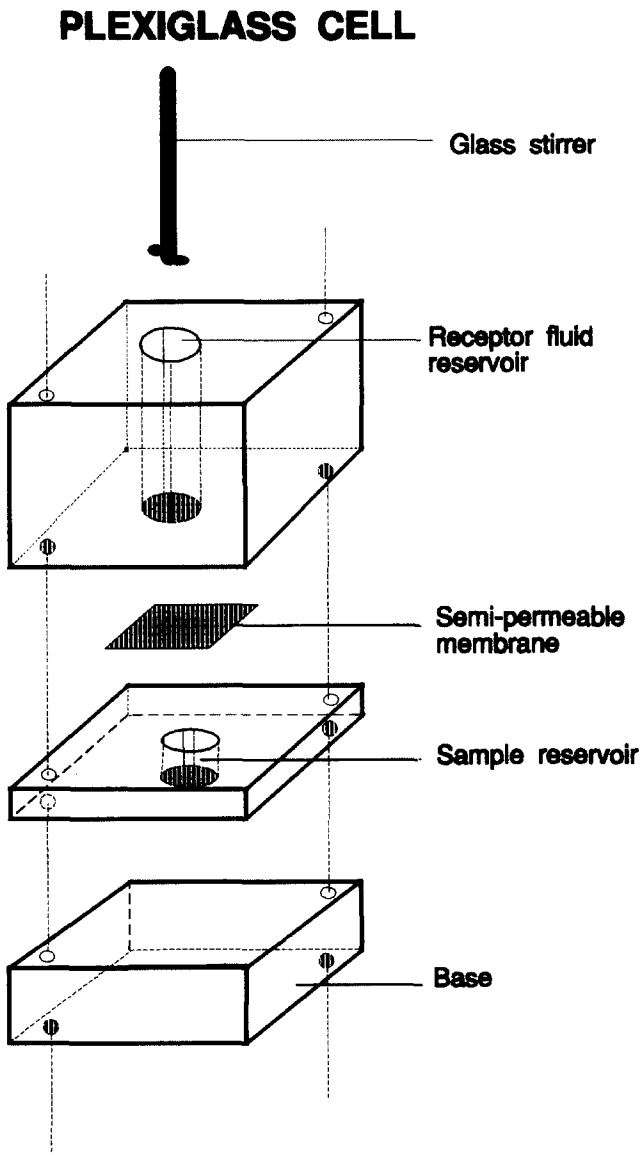

Fig. 1. Plexiglass cell.

often extremely difficult to observe these bubbles, evidence of their presence is usually only realised at the termination of the experiment, resulting in a reduction of the number of replicates whose data can be used.

The plexiglass cell does not suffer from the abovementioned drawbacks of the Franz cell and is simple to use. It requires a minimal quantity of the semi-solid dosage form (less than 1 g) for each evaluation and variables such as temperature, stirring rate, sample withdrawal and re-introduction are readily controlled. In addition, the semi-solid dosage form is mounted underneath the membrane as opposed to the Franz cell where the dosage form is placed on top of the membrane.

In light of the above, this study was undertaken to evaluate a simple plexiglass cell, which we have routinely used in our laboratories and to compare the results obtained with those using the Franz diffusion cell. This format prevents discontinuity occurring between the membrane and liquid interface thereby preventing the formation of air bubbles at the membrane/liquid interface.

Plexiglass cells were constructed in our laboratories and each cell consisted of three basic components (Fig. 1). Each component consisted of a 5 cm × 5 cm square block of plexiglass. The thickness of the base component was 1.2 cm, a sample reservoir block of 0.3 cm thickness into which a circle of 1 cm diameter was cut and the receptor fluid component (thickness of 2.4 cm) containing a similar 1 cm diameter hole which formed a cylindrical void and constituted the fluid reservoir. The thickness of the receptor fluid reservoir and sample reservoir could be varied by using thinner or thicker plexiglass blocks or by mounting additional reservoir blocks on either of these two components when required. The membrane is placed on top of the sample reservoir and the cell assembled as depicted in Fig. 1. Four holes were bored in each block to accommodate four bolts to secure the integrity of the cell.

Prior to assembly, the semi-solid preparation was accurately weighed directly onto the membrane and placed over the hole in the sample reservoir. After firmly bolting all the components together, the whole assembly was placed into a six-spindle dissolution apparatus (Pharmatest PTW-S, Germany). The cell was lowered into the water bath such that the water level was kept to a level of 1 cm below the surface of the receptor fluid reservoir component. Six cells were used and the temperature of the water bath was maintained at 32 ± 0.5°C. A small glass stirrer was fitted into each of the stirring stations and the drive unit lowered and lifted electrically. A stirring speed of 150 rpm was used for all studies. Degassed saline solution (0.09% w/v) was used as the receptor phase and 1.75 ml filled into the reservoir above the membrane. Samples (1.0 ml) were withdrawn at 15 min intervals over a period of 6 h. Both cellulose (CA 502500, 150 μm thickness) and nylon membranes (NY 502500, 150 μm thickness) 0.45 μm pore size (Lida Manufacturing Corp., USA) were used in separate experiments. The membranes were conditioned by immersing in receptor fluid for a period of 30 min and blot-dried prior to use.

Commercially available Zovirax cream (acyclovir 5% cream, cream B, Wellcome, Pty

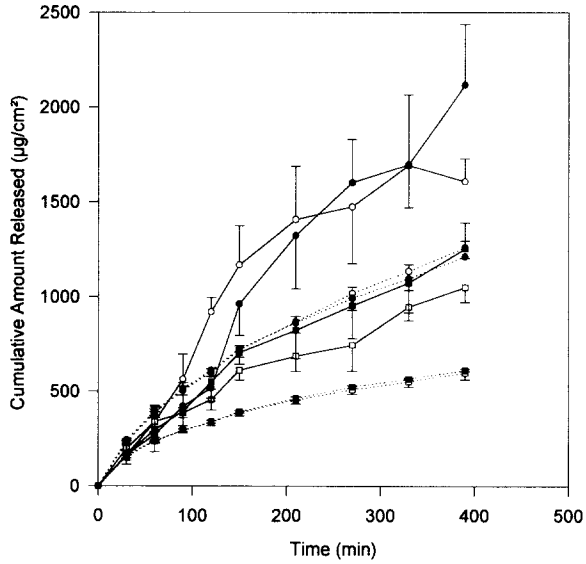

Fig. 2. Cumulative amount of acyclovir released. (Solid line) Franz cells; (dotted line) Plexiglass cells; (○) cream A (cellulose acetate membrane), (●) cream A (nylon membrane), (□) cream B (cellulose acetate membrane), (■) cream B (nylon membrane). * Replicate of six experiments.

Ltd, South Africa) and an extemporaneously prepared cream (cream A) containing 5% acyclovir were assessed. In addition, four different formulations containing the equivalent of 1% diclofenac were also assessed. The dosage forms consisted of Voltaren Emulgel (Ciba-Geigy, GmbH, Germany) and test formulations, cream RU-1, gel RU-2 and gel RU-3. Approx. 300 mg of each of the acyclovir preparations was used and 225 mg of each of the diclofenac preparations.

Six replicate experiments using Franz cells (Crown Glass Co., Inc., USA) were carried out to compare with the results obtained from the acyclovir studies using the plexiglass cells. Nylon and cellulose acetate membranes were used and the

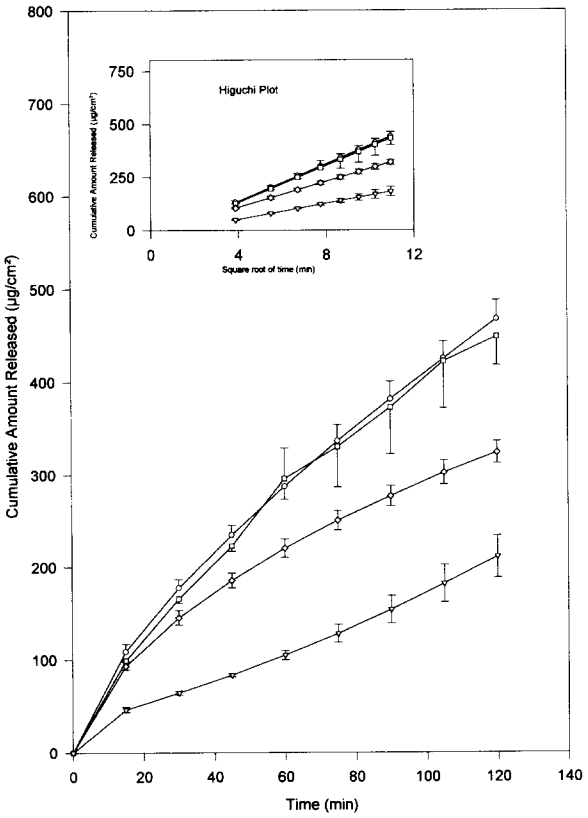

Fig. 3. Cumulative amount of diclofenac released using plexiglass cells. (▽) Gel RU-3 (Spectra/Pore 6 membrane), (○) Voltaren Emulgel (Spectra/Pore 6 membrane), (□) Gel RU-2 (Spectra/Pore 6 membrane), (◇) cream RU-1 (Spectra/Pore 6 membrane). * Replicate of three experiments.

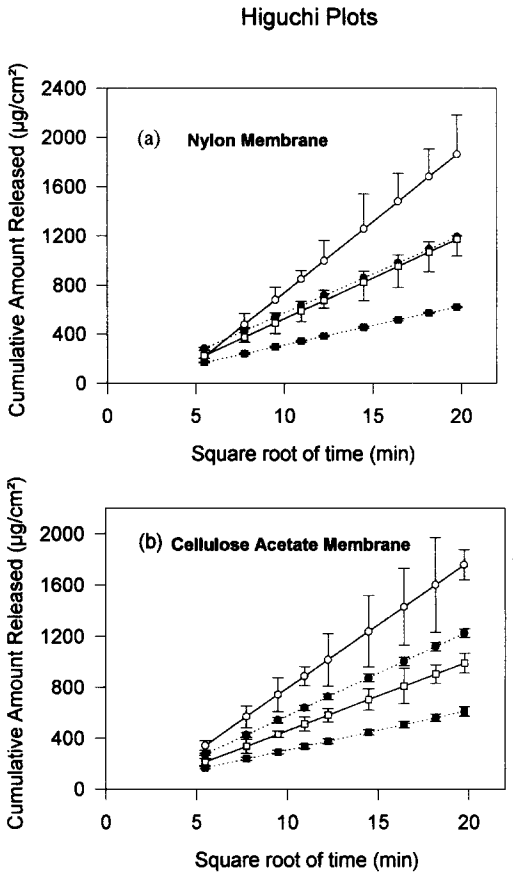

Fig. 4. Higuchi plots showing rates of release of acyclovir. (○) Cream A (Franz cell), (●) cream A (plexiglass cell), (□) cream B (Franz cell), (■) cream B (plexiglass cell). * Replicate of six experiments.

receptor fluid was the same as that used with the plexiglass cells. A stirring rate of 600 rpm was used employing the stirrer motor and stirring bars of the Franz cell manifold. Approx. 300 mg of each acyclovir formulation was used and the temperature of the system maintained at 32 ± 0.5°C. Samples (100 μl) were withdrawn at 30 min intervals and the concentrations of acyclovir released were determined by high-performance liquid chromatography (HPLC).

HPLC was used to determine the concentrations of drug released. The HPLC system consisted of a solvent delivery system (Beckman 114M, Beckman Instruments, USA), a UV variable-wavelength detector (Waters Lambda Max

Model 481, Waters Associates, USA), an automatic sample injector (WISP 710 B, Waters Associates, USA) and a recorder/integrator (Model 3390 A, Hewlett Packard, USA).

The columns consisted of a custom-packed 20 cm × 3.9 mm i.d stainless-steel column containing 10 μm C_{18} reversed-phase packing material (Techsil, HPLC Technology, UK). The mobile phase used for the acyclovir determination consisted of methanol/water (10:90), pumped at a flow rate of 1.0 ml/ min and the eluate monitored at a wavelength of 254 nm. Concentrations of diclofenac were measured using a mobile phase consisting of sodium acetate buffer (50 mM, pH 3) and acetonitrile (40:60) and pumped at a flow rate of 1.2 ml/min. The detector was set to a wavelength of 280 nm.

Fig. 2 depicts the cumulative amounts of acyclovir released over 6 h obtained using the plexiglass and Franz cells with cellulose acetate and nylon membranes, respectively. The results obtained for the diclofenac preparations using the plexiglass cells and cellulose membranes (Spectra/Por 6, Mol. Wt cut-off 1000, Spectrum Medical Industries, Inc., USA) are shown in Fig. 3.

All data were applied to the Higuchi equation (Higuchi, 1961) and the cumulative amount released plotted vs the square root of time (Fig. 3 inset and 4). Linear regression analyses of each line were performed and the respective rates of release determined from the slopes of the lines.

The rank order for the various acyclovir preparations was the same using either the plexiglass or Franz cells. However, inspection of these plots depicts that higher standard deviations were obtained using the Franz cells. Data from the plexiglass cells indicate that better precision was obtained as seen from the relatively small standard deviations. The data obtained from the Franz cells are clearly more variable resulting in a range of %RSD values between 10 and 30 whilst RSD values using the plexiglass cell were generally below 12.

From the data presented it is evident that the plexiglass cells provide a simple, precise and reliable system to monitor drug release from semisolid dosage forms.

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