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A comparison of test methods for determining *in vitro* drug release from transdermal delivery dosage forms

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Abstract: Three test methods for determining *in vitro* drug release rate from transdermal delivery dosage forms were tested for equivalency of results, ease of implementation and precision. The 'paddle-over-disk' (POD) method is under consideration by the USP as a standarized method for release-rate testing of all transdermal delivery dosage forms. The 'reciprocating disk' (RD) and 'diffusion cell' (DC) methods are both commonly employed throughout the pharmaceutical industry. The three methods were demonstrated to be equivalent in terms of release rate profile (curve shape) and total drug released over the lifetime of the dosage form tested (Transderm-Scop). The precision for the RD method as measured by the mean relative standard deviation over all time points was 4.6%; the precision of the POD method was 5.4% and that for the DC method was 6.7%. Steady-state flux values derived from the POD and RD methods were equivalent (~4 $\mu g\ cm^{-2}\ h^{-1}$) but were ~25% greater than the steady-state flux value derived from the DC method (~3 $\mu g\ cm^{-2}\ h^{-1}$). All three methods gave results which were within the specifications of the manufacturer (CIBA–GEIGY). The POD method was the easiest to use on a routine basis, required the least amount of specialized equipment and most resembled the current test methodology for dissolution testing of other dosage forms such as tablets or capsules.

Keywords: *Transdermal delivery dosage form; dissolution testing; paddle-over-disk method; reciprocating disk method; diffusion cell method; scopolamine.*

Introduction

The dissolution test, a product performance test, is routinely carried out in pharmaceutical laboratories for solid dosage forms such as tablets or capsules to determine compliance of a particular formulation with specifications for dissolution. Dissolution testing is rigorously standardized in terms of apparatus, methodology and reagents and is applied world-wide. The Pharmacopeias of Great Britain, Japan and the United States of America all list virtually identical apparatus and specifications for dissolution testing [1–3].

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Transdermal delivery dosage forms or transdermal delivery (TD) systems are rapidly gaining popularity for the administration of a wide variety of drugs [4, 5]. Because of their physical nature most TD systems are loosely classified as solid dosage forms, albeit novel ones, and are therefore subject to the same or a similar set of performance tests as are tablets and capsules. *In vitro* drug release testing (equivalent to dissolution testing for capsules and tablets) falls within the realm of such dosage form performance tests for TD systems.

Unfortunately, until recently none of the major Pharmacopeias has specified standardized dissolution test apparatus and/or methodology to be applied to transdermal delivery dosage forms; however, a recent Supplement to the French pharmacopoeia includes a description of a standardized test apparatus [6]. The Pharmaceutical Manufacturers' Association (PMA) (USA), working in conjunction with the US Pharmacopeial Convention, has recognized the need for a standard drug release ('dissolution') test for TD systems and has commissioned a study to compare a proposed standard method ('paddle-over-disk') with several of the more popular methods which have been evolved in development laboratories to satisfy the requirement for dissolution testing of TD systems. The present work in which the 'reciprocating disk' and 'diffusion cell' methods are compared with the 'paddle-over-disk' method is a part of this PMA study.

Experimental

Paddle-over-disk apparatus

The POD apparatus consisted of the USP Dissolution Apparatus 2 [1] into which was placed the dosage form attached to a cellulose-type dialysis membrane (Cuprophan Type 150 PM, Catalog #0914, Life Med, Inc., Compton, CA, USA) that was used to anchor the TD system to a 25.5-cm^2 stainless steel disk by means of a rubber 0-ring (Fig. 1). The disk assembly was situated at the bottom of the test vessel 25 ± 2 mm from the stirring paddle. The stirring rate was 50 rpm. The solvent medium was 500 ml of HPLC-grade water maintained at 32°C. The test vessel was covered throughout the test procedure to minimize evaporation. Samples of 2 ml were taken at specified time intervals with sample volume replacement.

Reciprocating disk apparatus

The RD apparatus consisted of a vessel containing 500 ml of HPLC-grade water maintained at 32°C in which a vertical reciprocating arm oscillated the continuously submerged TD system with an amplitude of ~5 cm and a frequency of ~0.5 Hz. The TD system was attached to a Teflon disk on the reciprocating arm by means of the Cuprophan membrane and an 0-ring as with the POD method (Fig. 2). The test vessel was covered to minimize evaporation. Samples of 2 ml were taken at specified time intervals with sample volume replacement.

Diffusion cell method

A diagram of the DC apparatus is shown in Fig. 3. The TD system was placed so that the delivery side faced the interior of the cell on the lip of the main cell body. A glass cap and 0-ring assembly was used to secure the TD system in place for the duration of the test. An external bath was used to circulate heating water through the water jacket of the cell to maintain the temperature at 32°C. The medium (receptor phase) was 15.00 ml of

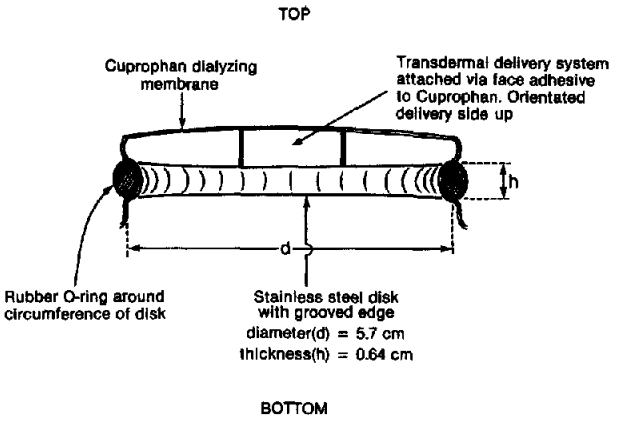

Figure 1
Diagram of the paddle-over-disk assembly.

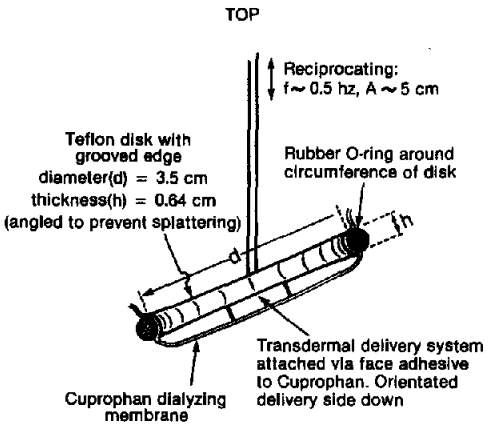

Figure 2
Diagram of the reciprocating disk assembly.

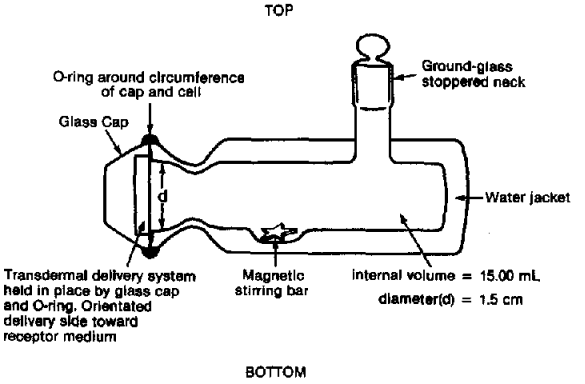

Figure 3
Diagram of the diffusion cell assembly.

HPLC-grade water. Stirring was accomplished by a magnetic star-headed stirring bar (10 × 8 mm) within the cell. The speed of stirring was approximately 800 rpm. Samples of 1 ml were taken at specified time intervals with sample volume replacement. Unlike the POD or RD methods, the DC method does not expose the entire delivery surface or sides of the TD system to the receptor phase. The cells exposed 1.77 cm^2 of the delivery surface of the TD system.

Test transdermal delivery system

In order to make a meaningful comparison of the test methods, it was decided to use a marketed transdermal delivery dosage form rather than an experimental system. It was reasoned that a marketed TD system should be better characterized than one under development and therefore would behave in a well-defined and predictable manner throughout the test. 'Transderm Scop' (CIBA-GEIGY Corporation, Summit, NJ, USA), a transdermal delivery dosage form designed to delivery scopolamine (hyoscine) over three days, was used for this test. This system contains a drug reservoir, a rate-controlling membrane and a drug-loaded face adhesive constructed in a multi-layer arrangement [7]. The area of delivery of the patch is 2.5 cm^2. Each 'Transderm Scop' patch is claimed to contain 1.5 mg of scopolamine.

Analysis

The mean of six values (n = 6) was calculated at each time point for each of the methods. All sample solutions from the various test methods as well as standard solutions were stored at 5°C protected from light until assay. An HPLC method was used for the determination of scopolamine. An endcapped 5-μm C_8 column (150 mm × 4.6 mm i.d.) (IBM Instruments, Danbury, CT, USA) and a mobile phase of acetonitrile–water–0.1% (m/v) hexylamine adjusted to pH 3 with phosphoric acid (30:40:30, v/v) were used to effect separation. The flow rate was 2.0 ml/min and the column was at ambient laboratory temperature. Detection was by UV absorbance at 210 nm. Under these conditions the capacity factor (k') for scopolamine was ~2.5. Comparison of the peak area of scopolamine in each sample with a standard curve for scopolamine yielded the sample concentration. This method was shown to give a linear response over a concentration range of 0.5–40 μg/ml and to be specific for scopolamine. Scopolamine hydrochloride reference standard was obtained from the United States Pharmacopeia standard collection (U.S.P.C., Inc., Rockville, MD, USA).

Results and Discussion

A drug release profile for the test patches was obtained for each method by plotting the mean total amount of scopolamine released at a given point versus time. Figs 4, 5 and 6 represent the dissolution profiles obtained by the three methods. Superimposition of the three curves indicates that the methods provide similar profiles (curve shape) for the test patches with the 'burst' or 'dose dump' of scopolamine completed after ~8 h, a value which corresponds well with the duration previously reported for 'dose dumping' by other workers [8]. All three methods show a similar amount of scopolamine released after 72 h (~500 μg cm^{-2}) and whereas the amount released per unit time is virtually equivalent for the RD and DC methods it is apparent that the POD method shows a slower initial release rate. Table 1 summarizes the mean cumulative total amount of scopolamine released per unit area over the three 24-h periods for each method.

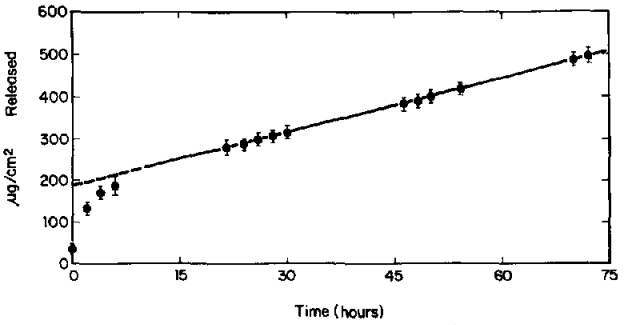

Figure 4
Drug release testing of 'Transderm Scop' patch: paddle-over-disk method. Cumulative amount released/unit area against time. $n = 6$ for each point. Vertical bars represent ± standard deviation. Results of linear regression analysis for points $t = 10$ h and greater: $y = 4.276x + 186.9$; $r = 0.9998$.

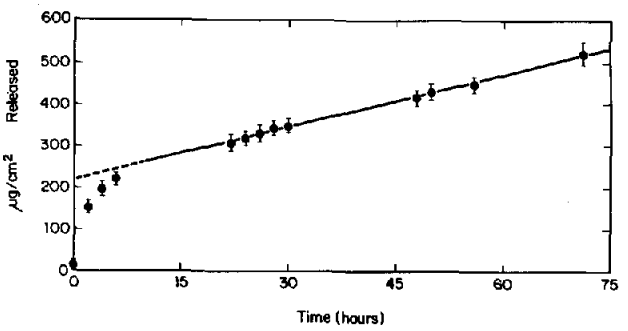

Figure 5
Drug release testing of 'Transderm Scop' patch: reciprocating disk method. Cumulative amount released/unit area against time. $n = 6$ for each point. Vertical bars represent ± standard deviation. Results of linear regression analysis for points $t = 10$ h and greater: $y = 4.160x + 220.3$; $r = 0.9980$.

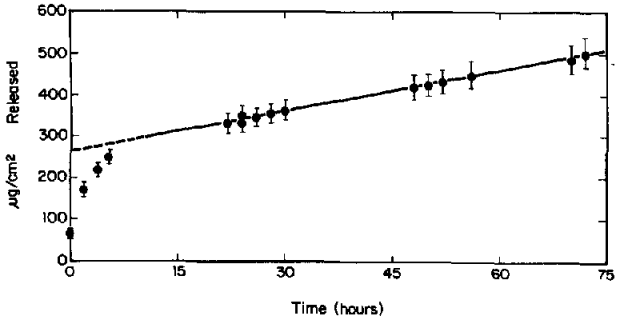

Figure 6
Drug release testing of 'Transderm Scop' patch: diffusion cell method. Cumulative amount released/unit area against time. $n = 6$ for each point. Vertical bars represent ± standard deviation. Results of linear regression analysis for points $t = 10$ h and greater: $y = 3.290x + 263.2$; $r = 0.9971$.

Table 1
Mean* total amount of scopolamine per unit area by cumulative 24-h periods

t (h)	Paddle-over-disk mean ± SD ($\mu g/cm^2$)	Reciprocating-disk mean ± SD ($\mu g/cm^2$)	Diffusion cell mean ± SD ($\mu g/cm^2$)
24	288 ± 13	318 ± 10	366 ± 22
48	391 ± 14	415 ± 17	420 ± 30
72	496 ± 18	520 ± 25†	505 ± 37

*$n = 6$.
†$t = 71.25$ h.

Precision as indicated by the mean relative standard deviation over all points was 4.6, 5.4 and 6.7% for the RD, POD and DC methods, respectively.

The slope of the linear portion of the curve resulting from a plot of average cumulative amount of drug released per unit area versus time is defined as the steady-state flux [9]. For the curves in Figs 4, 5 and 6 data points collected after $t = 10$ h were considered part of the linear portion of the curve and were included for linear regression analysis. The steady-state fluxes as determined from the three methods all fall within the product specification (D. Hunt, ALZA Pharmaceutical, Palo Alto, CA, USA, personal communication). Steady-state flux values were 4.3, 4.2 and 3.3 $\mu g\ cm^{-2}\ h^{-1}$ for the POD, RD and DC methods, respectively. One plausible explanation for the apparent difference of ~25% between steady-state flux values for the POD and RD methods and the DC method is the potential formation of an unstirred boundary layer at the TD system–receptor phase interface. Although the diffusion cells used in this study have been validated for efficient mixing using another compound, it is possible that the diffusion of scopolamine is more sensitive to the existence and/or size of an unstirred boundary layer.

In terms of ease of implementation, the POD method is the most desirable since it employs the methodology and apparatus which is most like that specified in the USP for dissolution testing of tablets and capsules. Both the POD and RD methods, however, have two potentially serious drawbacks which may preclude their general use as methods for determination of the release rate of drugs from TD systems. First, both the RD and POD methods employ a dialysing membrane (Cuprophan) as a means of securing the TD system to the disk surface. Although the effects of Cuprophan as a diffusion barrier or diffusion enhancer for scopolamine were not specifically determined, such effects are possible with compounds of different chemical and/or physical properties. It will be necessary to study the effects of this membrane on a wide variety of compounds and, if the membrane is shown to modify the release rate, alternate membrane choices will have to be provided to enable either of these methods to be applied universally. Second, both the POD and RD methods prescribe complete immersion of the TD system; thus if that TD system is constructed so as to be free of edge sealing (as in some multilayer laminate configurations), the potential exists for uncontrolled diffusion of the active ingredient from the side edges. 'Transderm Scop' does not have sealed edges. Modification of the TD system or release rate test system would have to be considered to overcome this potential problem.

The DC method does not suffer from either of the potential problems of interference from a dialysis-type membrane or edge leakage. It is more prone, however, to the formation of a diffusion boundary layer because of inefficient stirring of the receptor phase.

The methodologies described provide the added benefit of permitting an approximation of *in vivo* delivery characteristics of TD systems containing a rate controlling membrane (e.g. Transderm Scop). It should be noted that for the class of TD systems which relies on the human skin for rate control, it is not feasible to correlate *in vitro* release and *in vivo* performance owing to the lack of rate control (i.e. absence of human skin) afforded by the test methods. The inability of the methods to approximate *in vivo* performance for all types of TD systems is only a minor disadvantage, however, since the primary function of a dissolution test is to serve as a quality control tool to define and maintain *in vitro* performance characteristics of the product. For this purpose, the POD, RD and DC tests all function equally well.

The viability of application of these tests to transdermal devices containing hydrophilic constituents and/or water-soluble components other than the active ingredient (e.g. erodible matrix TD systems) has not been addressed in the present work but is recognized as an area for further study.

Conclusion

Three test methods with defined apparatus were determined to to be equivalent when applied to the testing of drug release from transdermal delivery dosage forms. The TD system used as a model contained a rate controlling membrane but these tests are expected to perform equivalently when applied as dissolution tests for other types of TD systems including those which rely upon the human skin for rate control. The paddle-over-disk method is the most easily implemented for use in drug release (dissolution) test laboratories. Any of the three methods seems to be acceptable for *in vitro* drug release testing for quality control of the performance of TD systems.

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