DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(6), 643-652 (1993)

THE DETERMINATION OF LOW-LEVEL WATER IN TRANSDERMAL DOSAGE FORMS AS TYVEK LAMINATES WITH AN EVAPORATOR OVEN

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An assay of water in adhesive monolithic transdermal drug dosage forms ('patches'), using lamination to Tyvek, and gaseous extraction in an evaporator oven into a Karl Fischer titrator, is described. The method is simple, linear, accurate, specific and more sensitive than alternatives.

INTRODUCTION

The assay of water in the adhesive of monolithic transdermal drug dosage forms (those with penetration enhancers and/or drug in the adhesive) ('patches') presents special problems. The flexible, self-adhesive nature of the patches prevents easy manipulation or extraction, and the adhesive, enhancers, and sometimes the drug tend to clog titrator frits or contaminate chromatographic columns. A lamination and evaporation technique is described and discussed which affords accurate low-level water determination by Karl Fischer titration, without stringent anhydrous technique, and demonstrates its utility in a research simulation of typical 'patch' manufacturing variables (drying and curing times and temperatures).

MATERIALS AND METHODS

Apparatus An Aquastar C2000 Coulometric Karl Fischer titrator, with an attached EV-6 Solid Evaporator oven (EM Science, Gibbstown, NJ) was used for the water assays.

Materials Tyvek - The porous spun-bonded HDPE film Tyvek (TM Dupont) Style 1070D, was purchased from Dupont (Wilmington, DE).

Patches - Transdermal units containing nitroglycerin and a penetration enhancer were prepared as follows:

1. The polymer blend containing nitroglycerin and penetration enhancer was coated on a silicone-coated paper using knife over roll technique.

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2. The coated sheets were transferred to a convection oven and dried at 50, 60, 70 or 80°C for 15 minutes.

3. The dried sheets were removed and laminated to a facestock and stored in polyethylene bags.

4. 10 cm^2 circular units were punched and samples were submitted for moisture analysis at 0, 1, 2, 3, 7, 14 and 21 days (curing interval).

EXPERIMENTAL PROCEDURE

Preparation of the Tyvek: Disks of Tyvek, slightly larger than the transdermal units, were cut with scissors.

Preparation of the Apparatus: The K.F. titrator and evaporator oven (set at 80°C) were equilibrated at a nitrogen flow rate of 100 mL/min^{-1}, and the titrator function checked by injection of a known water standard. The titrator settings were as follows: judgement interval 90 seconds; titration start delay 1 minute, and readout in mg H_2O. The 'sample' mode of the titrator was then engaged (locking the background correction).

Sample Analysis: For each analysis, one Tyvek disk was held to the release-paper side of the patch. The release paper was peeled using forceps, and the exposed adhesive face laminated immediately to the Tyvek. (Finished dosage forms, laminated to PVC release liner, may be similarly manipulated.) The Tyvek/adhesive/facestock laminate was bent in two, Tyvek side in, and inserted into the sample boat. The boat was then heated at 80°C, 100 mL/min dry nitrogen flow. The entrained moisture passed by the bubbler tube into the K.F. titration chamber, and titration to completion ensued. Alternatively, when required by prolonged extraction time, the run was manually stopped by retracting the sample and temporarily setting the judgement interval to a minimum. After the run terminated and data were printed, the sample was removed, and the parameters reset. The apparatus was ready for the next run when it came to a steady-state moisture blanking rate, in ca. 5 minutes.

CALCULATIONS

The water titrated (Wt) data, automatically collected for up to 99 minutes, were the raw titrator output. The data (Wt) were seen to form an exponential approach to an asymptotic value:

$$W(t) = W\infty + A*10^{-kt} \qquad \text{(Equation 1)}$$

Where: $W\infty$ = the water assay of the transdermal unit

The measured water was found in these patches to be independent of the oven temperature (data not shown); this and the monoexponential kinetics indicated an extraction going to completion. If the rate constant of extraction was rapid ($k > 0.1$ min^{-1}), complete extraction occurred. However, to maximize analytical efficiency, for thick films ($>> 100$ μm) of some polymers which release their water very slowly ($k < 0.03$ min^{-1}), a curve-fitting program or graphical means may best be used to solve for $W\infty$. Thus, for a graphical solution, an asymptotic value ($W\infty$) was estimated and tested by plotting $\log_{10}$ ($W\infty$ - Wt) against time, where ($W\infty$-Wt) is the remaining water. (Truncation of long runs in this way prevents any slight undercompensation in the automatically corrected drift, which would accumulate linearly with run time, from causing the later time data points to perturb the obtained W∞ value.) For a properly chosen W∞, the major portion of this test plot (t ≥ 10 minutes) was linear. The kinetic water release rate constant, k (the slope of the test plot) may be used to compare different adhesives' drying behaviors, for films of identical thickness at the same extraction temperature. (The constant A in Equation 1 relates to initial onset of extraction and is of no particular interest.)

Some various types of titrations possible with this technique are illustrated in Table 1 and Figures 1 - 4. Figure 1 shows a normal, rapid release; Figure 2, a release initially limited by the titrator maximum operating current ("rate limited"); Figure 3, a release through a PVC release liner and facestock (<u>not</u> Tyvek-laminated), slow but well-behaved; and Figure 4, a release at 25°C, which takes 20 minutes to attain its final exponential release kinetics.

For a patch with much water, the initial higher permeability of the adhesive might be expected to lead to a curvature of the test plot data, but the limited titration rate (~1200 μg/min) yields linear titration data at low t and obscures this region as in Figure 2. This region, and the initial region of Figure 4, would need to be discarded before applying curve-fitting software.

RESULTS OF THE STUDY

The effect of the convection oven drying temperature on the water contents of the initial (non-cured) patches is shown, Table 2 (zero days curing time). Final water content was a rough function of drying temperature; fifteen minutes drying at 80°C reproducibly reduced the adhesive moisture content to ≤0.5%.

Table 2 also displays the effect of the room temperature curing stage duration (a further, milder, drying procedure) on patch water, for patches of each oven-dried temperature. Figure 5 displays the time course of water loss from the patches during the curing stage. The data and the regression fits for exponential approach to 0.40% moisture level are redisplayed as the test plots in Figure 6. These show a more rapid equilibration of the 60°C and 70°C patches, most likely due merely to the finite water vapor transmission rate of the polyethylene storage bag. Thus, the equilibrium water content, hot and cold drying kinetics, and information on possible in-process storage conditions, are obtained from the data.

DISCUSSION OF THE METHOD

Competitive methods for water assay in monolithic drug-adhesive transdermal drug dosage units ('patches') suffer from drawbacks. One common film analysis technique, infra-red oven/balance gravimetry, failed to distinguish between water and other volatiles including here both the drug and the transdermal penetration enhancer (Table 3).

When measuring water content in single patches, extraction techniques (as into anhydrous methanol) are conceptually simple, but not sufficiently sensitive. Extraction into 20 mL methanol of a single 10 cm^2 patch, with 150 mg adhesive at 0.5% water, (750 μg water) yields 38 μg/mL (0.004%) in the extract, versus a typical >30 μg/mL blank. Large test aliquot volumes afford more precision, but limit the titrant lifetime by dilution. Variable exposure times of the methanol and patch in preparation

TABLE 1

Types of Extraction Kinetics

Type	Extraction Temperature (°C)	Water Assay W_∞ (μg)	Release Rate Constant k (min^{-1})
Normal	80	118	0.32
Rate Limited	80	3695	0.28
Prolonged	80	2300	0.0075
Slope Change	25	3230	0.019

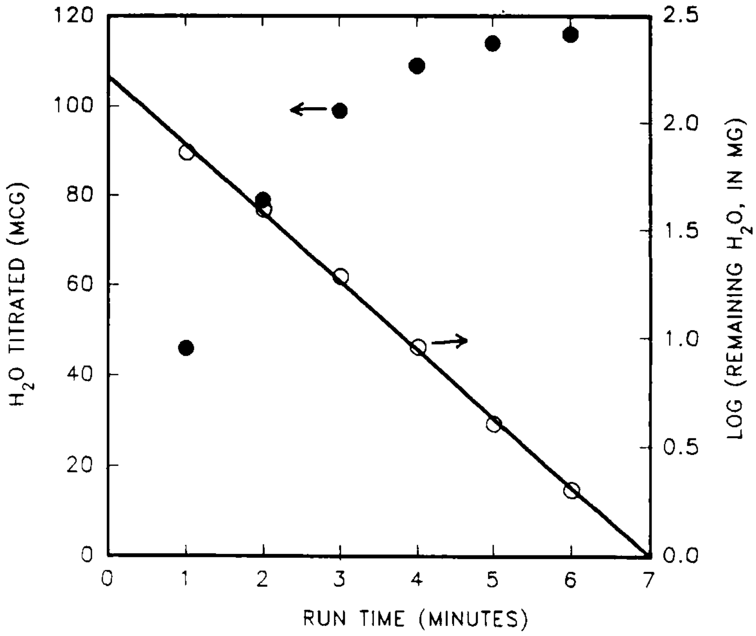

FIGURE 1

Water release kinetics in a normal extraction.
● - Release data ○ - Kinetics plot data

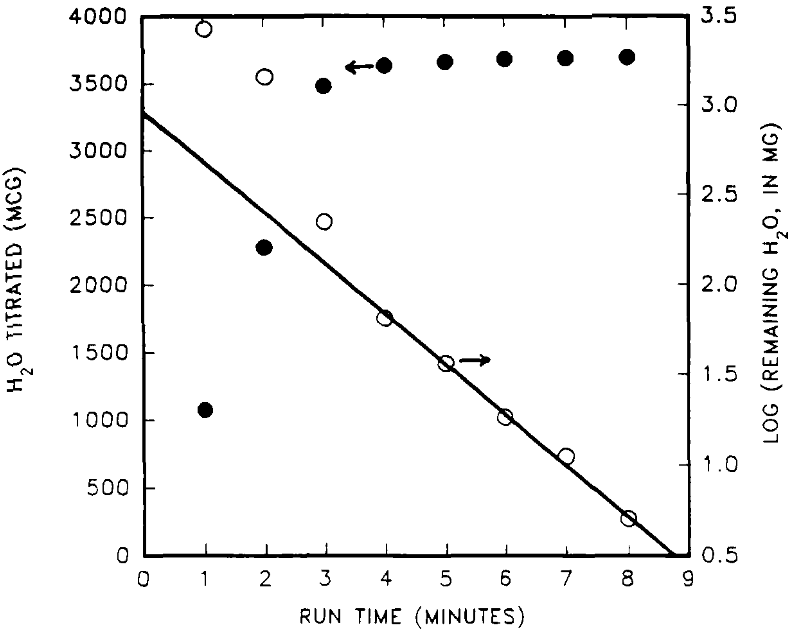

FIGURE 2

Water release kinetics in a rate-limited extraction.
● - Release data ○ - Kinetics plot data

contribute to imprecision. Thus, even with special methanol preparation and assay care, signal/noise considerations preclude precise measurement in this range. Additionally, adhesive polymers may gum up the glass frit present on some titrator apparatus.

40 μg/mL in extract is also below the analysis levels reported for alternative techniques such as flow-injection analysis into a KF reagent stream with spectrophotometric detection (1). Alternatively, an extraction into predried benzene has been described, with marginally adequate GLC/TCD sensitivity and an appreciable blank correction (2). A third quantitation alternative, conversion of the water to acetone, followed by GLC/FID, was reported only at higher water ranges (3). For both the latter methods, the soluble adhesive presents a messy matrix. Alternatively, headspace GC, with a thermal conductivity detector, might be possible. However, this is usually performed with an internal standard, and method development would be complicated by matrix effects. Multiple headspace extraction (4) (as often used for residual solvent analysis), is a possibility (with an external standard), but semi-volatile enhancers or drugs would tend to contaminate the column, and sample manipulation would still be a problem.

Gaseous extraction suffers from none of these drawbacks, and was therefore utilized. Although bare patches can be precisely rolled to expose their adhesive on the 'inside' for a gaseous extraction, this is tedious. Therefore, lamination to Tyvek was

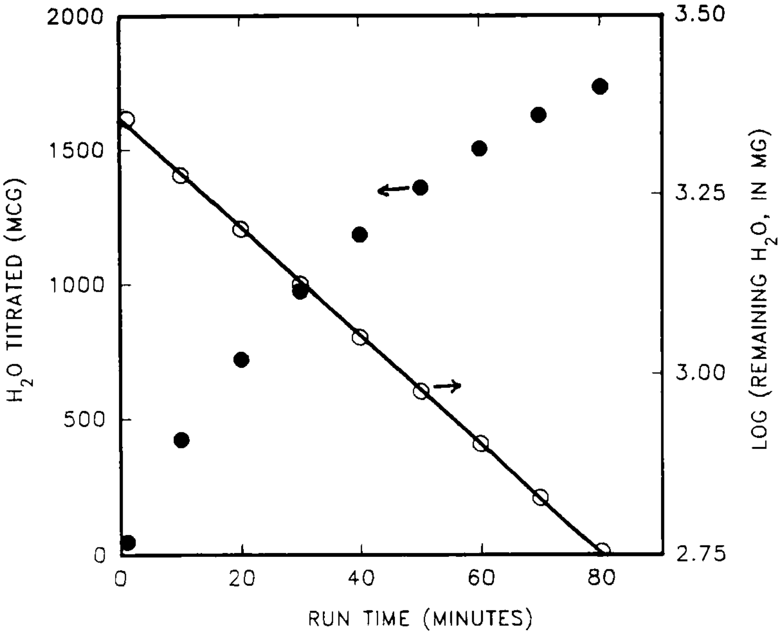

FIGURE 3
Water release kinetics in an impeded extraction.
● - Release data ○ - Kinetics plot data

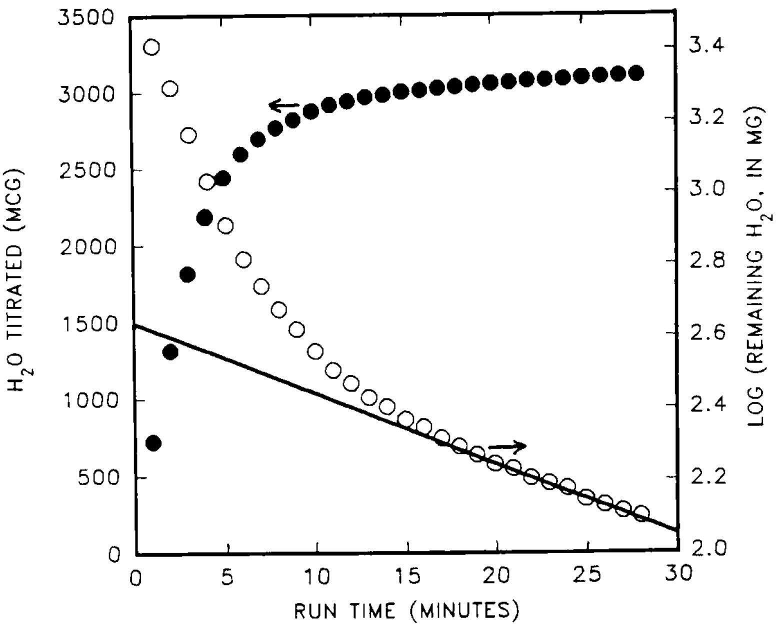

FIGURE 4
Water release kinetics in a sluggish extraction.
● - Release data ○ - Kinetics plot data

TABLE 2

Patch % Water Content During Room Temperature Curing

Curing Time (days)	% Moisture in Adhesive (duplicate samples)			
	Oven Drying Temperature			
	50°C	60°C	70°C	80°C
0	4.9, 11.5	3.2, 3.9	1.4, 7.4	0.55, 0.47
1	16.0, 14.0	1.1, 1.7	0.98, 3.2	0.57, 0.61
2	5.0, 9.4	0.81, 1.0	0.76, 0.59	0.50, 0.52
3	4.6, 7.2	0.62, 0.74	0.58, 0.63	0.43, 0.44
7	4.5, 5.0	0.88, 0.94	0.55, 0.61	0.39, 0.40
14	1.8, 3.0	0.75, 0.78	0.59, 0.61	0.35, 0.45
21	0.91, 0.92	0.59, 0.60	0.45, 0.52	0.44, 0.46

used. Any thermally stable, porous, non-hygroscopic, zero moisture content, flexible material would serve; Tyvek is low cost, easily cut, non-hazardous, and can be handled ungloved with usually insignificant moisture gain. Its limitations are its melting point of ~120°C, above which it shrinks and impedes water release, and its swellability (not observed in this study) by certain hydrocarbon solvents and low-molecular-weight adhesives.

The linearity of the method was briefly assessed (Table 4), on low-moisture unpunched sheet material cut to sample size 5-40 cm^2, and appears adequate. (The titrator linearity is adequate for liquid injected standards containing from 40 μg - 30 mg water, data not shown.) Method precision is difficult to assess as authentic moisture patch samples cannot be fabricated, but it appears $\leq$5% (see Table 3).

With sufficient experience on a single polymer, the short-time water release profile might be used to predict both water content and adhesive thickness, well before total water release occurs.

Three advantages accrue to using the above method to measure the water content in single patches. 1) Water content may vary along and across a roll of manufactured material. Specific areas can be sampled to measure this process variability. Likewise, specific suspect regions (or patches) can be easily sampled. 2) Research materials can be individually generated, if desired, in factorial or Plackett-Burman process protocols without the need for larger equipment required to generate multiple patches for extraction-based water assays. This encourages formulators to discover problems early in product development cycles. 3) Research and production equipment may sometimes be better characterized through single patch samples. For example, precisely even air flow in a convection drying oven is difficult to assure. This results in uneven drying (see Table II), best detectable through single-patch assays. If such an oven were filled with several sets of patches in such a study as described above, and multiple patches from various oven locations pooled as required to perform a methanol-extraction water assay, differences in samples might be attributed to a variable, e.g., drying time, which are partly, or totally, the result of oven zone variability.

We anticipate that this method may find general use in analyzing moisture levels in items using water-based adhesives, for which residual water level may control adhesive properties and sometimes drug activity as well.

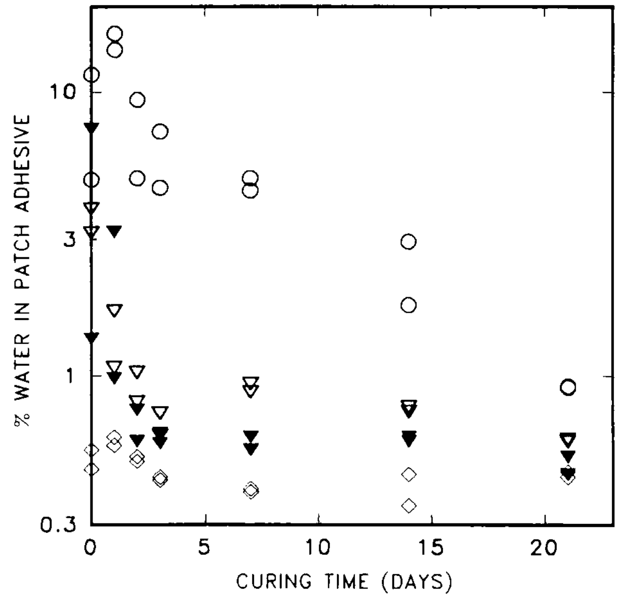

FIGURE 5

The effect of curing time on patch-adhesive water levels. Oven drying temperature key: ○ - 50°C ▽ - 60°C ▼ - 70°C ◇ - 80°C

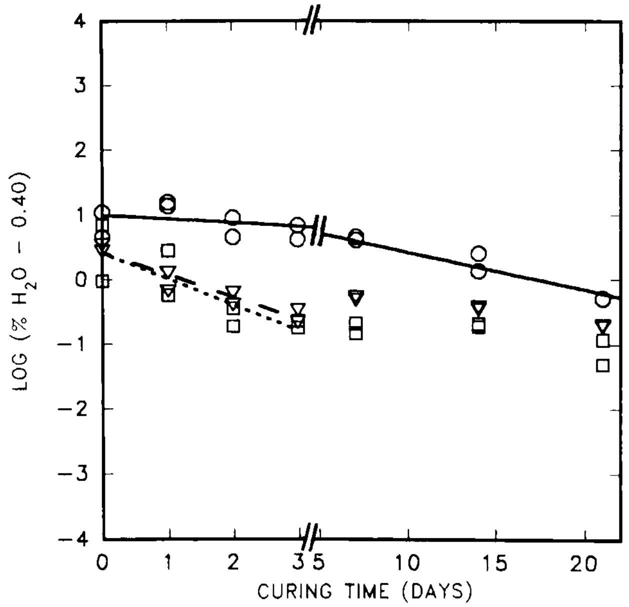

FIGURE 6

Kinetics test plot for loss of patch-adhesive water during curing stage. Oven drying temperature key:
○ - 50°C —— Regression, 0-20 days
▽ - 60°C — — Regression, 0-3 days
□ - 70°C ····· Regression, 0-3 days

TABLE 3

Water Assay
Comparison, IR-Oven Gravimetric and KF/Oven Titrimetric Methods

Sample Lot	IR Method Assay % H20	IR Method % CV	Present Method Assay % H20	Present Method % CV
1	4.43	57.6	1.76	18.8
2	5.08	29.7	1.76	2.4
3	5.17	22.2	2.79	3.1
4	3.91	23.7	0.32	5.0

All samples, n = 6 assays, each method. IR conditions = 30 minutes @ 80°C; KF conditions as described above.
All assays expressed as weight H_2O as a percent of adhesive weight.

TABLE 4

Linearity of H_2O Assay vs. Sample Size

Size (cm^2)	Coating Weight (g)	H_2O Found (µg)	% H_2O
40	0.5759	2787	0.48
20	0.3351	1473	0.44
10	0.1661	670	0.40
9	0.1362	627	0.46
9	0.1213	599	0.49
5	0.0862	460	0.53

Regression equation: H_2O found = -0.030 mg + 0.00478 x coating wt (mg),
$r^2 = 0.992$

ACKNOWLEDGEMENTS

The technical assistance of Susan Santos in manuscript preparation is gratefully acknowledged.

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