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Application of radiotracer method for precise determination of water vapor transmission characteristics of unit dose packaging systems

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The selection of packaging materials for unit dose, oral and solid drugs requires specific knowledge of their water vapor transmission properties (Am. Soc. Hosp. Pharm., 1977; Gupta et al., 1980, Reamer and Grady, 1978; Reamer et al., 1977; Kentala et al., 1982). Typically, water vapor transmission rates (WVTRs) are determined by weight gain of packages that contain a desiccant and that have been incubated in a humid atmosphere (Reamer and Grady, 1978; Kentala et al., 1982; Single-unit containers, 1980). Identical containers of equivalent weight, containing no desiccant, are analyzed as blanks to distinguish between water permeation and water absorbed by the packaging materials. Weight gain methods exhibit limited sensitivity and a long time period is often required to obtain measurable moisture data. Recently, a novel radiotracer method has been developed for sensitive and precise measurement of moisture ingress for bulk tablet packaging systems (Rabinow et al., 1986). This technique is not only more sensitive than the weight gain methods, but it is also specific for moisture permeation, eliminating the need for blanks. This communication describes an additional application of this methodology for unit dose container systems.

Three different unit dose packaging systems described below were selected for WVTR determination.

Package A: Blister pack, Pentapharm 170, 7.5 mil PVC heat sealed to PHAR 9010 paper/adhesive/1 mil foil/vinyl heat seal coating (from Alcoa).

Package B: Blister pack, 0.200 mm Pentapharm PVC/0.025 mm polyethylene/0.040 mm PVDC (from Klockner-Pentaplast) heat sealed to PHAR 9010 paper/adhesive/1 mil foil/vinyl heat seal coating (from Alcoa).

Package C: Strip pack, K195 HB23 (coated cellophane)/no. 10 white polyethylene/0.7 mil aluminum foil/no. 22 low density polyethylene from Wraps, Inc., heat sealed to the same.

These packaging materials were assembled containing desiccant tablets composed of 68 mg $CaCl_2$, 65 mg microcrystalline cellulose and 3 mg talcum. Desiccant tablets were prepared by

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pressing pellets in the same dies used for product tabletting. After packaging in the candidate package systems, they were incubated in a closed container having a radiolabelled, 75% relative humidity (RH) atmosphere.

Chambers were prepared for incubation of test samples in a constant, radiolabelled, 75% relative humidity (RH) atmosphere. These chambers contained a saturated sodium chloride salt slush to maintain a constant 75% RH. In addition, the water used to prepare the saturated salt solutions was spiked with a known amount of tritium-labelled water ($\approx 1\ \mu$Ci/ml). This creates a convenient tracer for observing water vapor transmission into the test samples. The incubation chambers included a small 3 V electric fan to provide some circulation within the chamber. Test containers were supported on a wire mesh platform to avoid obstructing airflow. At appropriate intervals, packages were removed, and the desiccant tablets were analyzed for radioactivity. From these data, and the known activity of the humid atmosphere, the WVTR for each package type was calculated.

Extraction of the radiolabelled water from these tablets was performed by removing 40 tablets from each package type. The 40 tablet sample was crushed finely using an agate mortar and pestle, and then transferred to a centrifuge tube. Ten ml of unlabelled water was added. The tube was capped and vortexed vigorously before being spun in a small laboratory centrifuge. The supernatant was decanted into a separate test tube. Three separate aliquots (2 ml each) were transferred to scintillator vials and combined with 20 ml of Beckman Ready-Solv MP scintillation cocktail. Sample vials were counted using a Beckman Model LS 9800 liquid scintillation detector along with water blanks, and standards having an activity similar to that of the samples. Instrument calibration was performed using a sealed, unquenched standard containing a β-emitter, ^{14}C source with an activity of 43.2 nCi. The linearity of detector response was confirmed using standards having activities ranging from 0.48 to 4.8 nCi.

The accuracy of this method was demonstrated by performing a recovery study for the spiked samples of desiccant tablets. Forty tablets were placed in each of 9 screw cap bottles. A calibrated pipettor was used to deposit 50 and 100 μl aliquots of 20 nCi/ml, radiolabelled water directly onto the desiccant tablets. The bottles were capped immediately to allow the $CaCl_2$ to become hydrated with the water. After 20 min, the tablets were processed as described above to recover the radioactive water. This procedure exhibited the results shown in Table 1. These data indicate that the extraction of radioactivity from desiccant tablets yields quantitative results. The average recovery for 7 samples spiked at two levels of activity was 94.8% with a relative standard deviation of 4.5%.

The WVTR for each of the 3 package systems was calculated on the basis of water migration for an individual unit container in terms of mg $H_2O \cdot day^{-1} \cdot unit^{-1}$. The tablets, initially containing no radioactivity, were monitored for increases in radioactivity over a 44 day period. The amount of water migration was calculated using the following equation.

$$\text{mg } H_2O/\text{unit} = \frac{\text{activity of 40 tablet sample (Ci)}}{\text{specific activity of salt slush } \left(\frac{\text{Ci}}{\text{mg}}\right) \times 40 \text{ tablets}} \quad (1)$$

A plot of mg H_2O/unit vs elapsed time is shown in Fig. 1. The slopes of the resulting lines represent the WVTRs. Linear regression analysis

TABLE 1

RECOVERY OF RADIOACTIVE WATER FROM SPIKED DESICCANT TABLETS

Sample	Spiked activity (nCi)	% Recovery
A	1.0	97.9
B	1.0	101.5
C	1.0	97.4
D	2.0	93.5
E	2.0	92.8
F	2.0	91.0
G	2.0	89.4
		Average = 94.8%
		C.V. = 4.5%

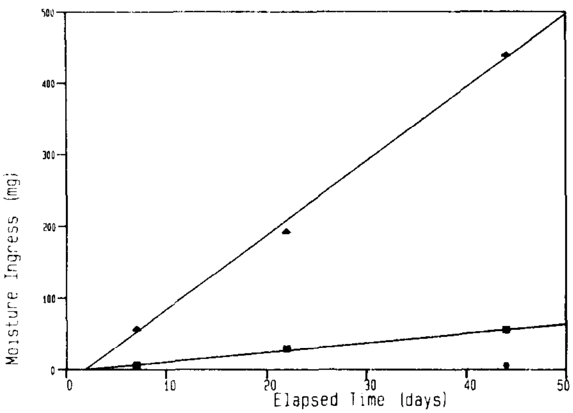

Fig. 1. Rate of moisture pickup of unit dose package systems. ▲, package A; ■, package B; ●, package C.

yields the following:

Test package	WVTR ($mg \cdot d^{-1} \cdot unit^{-1}$)
A	10.2
B	1.3
C	< 0.3

Calculation of WVTR for a single blister using published permeability data (Kirk-Othmer, 1978) for PVC sheet material was determined to be 2.02 mg/day. It is not surprising that this calculated value is 5 times smaller than the actual rate. The process of making a blister in PVC sheet material causes some regions to become stretched. Inspection of the blisters revealed some thin areas in the plastic film after forming. These areas would have significantly greater water permeation rates since the WVTR is inversely proportional to thickness.

It is clear that this method has the necessary sensitivity for measuring the WVTR for most unit dose packaging systems. Containers with the low permeation may be characterized by increasing the radioactivity of the salt slush. The radiotracer method is sensitive enough that a single tablet yields a significant response after incubation over the period of this experiment. A possible application of this sensitive method might be identification of non-uniformity in multi-unit dies used to form the blisters. Because of the sensitivity of the assay, accurate WVTR information was available in the first 14 days of incubation.

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