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# Methodology for the determination of water vapor transport across plastic films

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There are numerous criteria to be considered in the development of plastics for the packaging of pharmaceuticals. These criteria should include barrier properties, sterilization qualities, clarity, weight, cost of production, inertness, flexibility and biologic safety. Barrier properties are particularly important criteria in the development of plastic packaging systems for parenteral solutions. In theory, removal of sufficient water from an aqueous parenteral drug formulation via water vapor transport across its plastic packaging system may have several detrimental effects. For example, (1) the drug concentration may exceed allowable limits during storage; (2) solubility problems may be encountered; and/or (3) degradation rates may be highly dependent upon drug concentration. There is a need therefore, for methodology which rapidly assesses the water vapor barrier properties of plastics. Such a methodology would serve as an aid to polymer chemists and plastic engineers in developing plastic packaging systems for not only parenteral solutions but pharmaceuticals in general. There are several methodologies currently available for measuring water vapor transport across plastics. In general, these methods utilize a cell in which a source of water vapor is separated from a detector of water vapor by the plastic of interest. Most of these methods differ in the design of the cell and by the type of detector used. Methods of detection used for monitoring water vapor permeability across various barriers have included gas chromatography with thermal conductivity detection (Lomax, 1980); measuring changes in vapor pressure as a function of time with a McLeod gauge (Michaels and Binder, 1961); infrared detection (Wood, 1970); by weight gain or loss (Nemphos et al., 1976; Lomax, 1980; Woodruff et al., 1972); electrochemical detection following reaction with phosphorus pentoxide (Hamilton, 1967); and the use of tritiated water and subsequent detection by scintillation spectrometry (Matsui, 1970; Dyer et al., 1975; Rabinow et al., 1986). Most of these reported methods have disadvantages attributable to (1) sensitivity limitations, (2) being time-consuming, (3) cost and/or (4) not able to measure water vapor permeability under precisely controlled conditions. This report describes a sensitive, precise and relatively inexpensive method of measuring water vapor transport rate (WVTR) across plastics under precisely

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controlled conditions. The method depends upon the transport of tritiated water across the barrier of interest, the subsequent uptake by a hygroscopic liquid and detection by scintillation spectrometry.

The experimental system consists of an all-glass diffusion cell (Crown Glass, Sommerville, NJ) in which two compartments, donor and receiver, are separated by the plastic film under investigation (Fig. 1). The cell is equipped with a water jacket in order to maintain the temperature at 25 °C with use of a temperature-controlled circulating water bath (MGW Lauda Brinkman RM20; Lauda, F.R.G.). The exposed plastic surface area is constant at 0.8 $cm^2$. Each plastic material was preconditioned by drying in a desiccator for at least 12 h prior to an experimental run. An aliquot of concentrated sulfuric acid (Fischer reagent A-300; Fair Lawn, NJ), 400 $\mu$l, was introduced into the well of the receiving compartment. The water vapor pressure in this compartment approaches zero during the course of an experiment, due to the hygroscopicity of concentrated sulfuric acid. A 400 $\mu$l aliquot of a saturated solution of KCl (Mallinckrodt, Paris, KY) was introduced into the well of the donor compartment. This solution was prepared with a quantity of tritiated water (1.0 mCi/g, New England Nuclear, Dupont, Boston, MA) of a known specific activity. A saturated aqueous solution of KCl generates a water vapor pressure of 20.5 mmHg at 25 °C (Rockland, 1960). At predetermined sampling intervals, a 10 $\mu$l aliquot of sulfuric acid is quickly removed from the cell and introduced into a vial to which scintillation cocktail (Beckman Ready-Solv, EP Liquid Scintillation Cocktail; Fullerton, CA) was added. Cumulative water transported at each sampling interval is then determined by utilizing a liquid scintillation spectrometer (LKB Instruments, Inc., 1219 Rackbeta, Gaithersburg, MD). In order to determine the solubility coefficient(s) of water for the plastic of interest, the test system was assembled as described. However, 10 $\mu$l aliquots of sulfuric acid were not removed from the receiving compartment at predetermined intervals. Instead, 24 h following assembly of the system, the cells were dismantled and the plastic was soaked in water until the tritiated water was completely removed. Preliminary experiments indicated that 24 h ensured that the system had reached steady state. The amount of water contained in the plastic at steady state when exposed to a water vapor pressure of 20.5 mm Hg was determined by measuring the recovered tritiated water by liquid scintillation spectrometry.

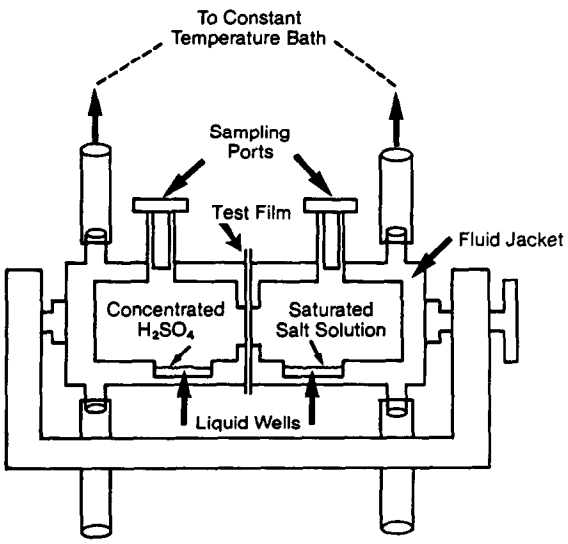


Fig. 1. Diffusion cell schematic.

Percent recovery determinations were performed in order to ensure system closure with respect to moisture loss during a typical run. Tritium was recovered from the receiver, donor compartments, and plastic film under investigation by soaking in water following an experimental run. Preliminary experiments established that 48 h were necessary to leach the tritiated water from the plastic of interest. Recovered tritium was determined by liquid scintillation spectrometry and then compared to amount of tritium introduced to the system to compute percent recovery. In order to establish whether test plastics retain their transport properties during the course of a typical experimental run, WVTR was established for the same polyvinylchloride film in three successive runs. The plastic film was dried prior to each run.

Table 1 indicates that by mass balance, essentially all of the tritiated water introduced into the system is accountable at the end of the experi-

TABLE 1

*Percent recoveries*

| Plastic | Percent $^3H_2O$ recovered |
|---|---|
| Polyvinylchloride | 99.0 (2.60), $n = 3$ |
| Polypropylene–ethylene copolymer | 100.8 (2.00), $n = 3$ |
| High-density polyethylene | 93.1 (3.08), $n = 3$ |

Values are means (S.E.M.).

ment. This observation implies good system closure with respect to moisture loss. Therefore, the water vapor pressure in the donor compartment of the diffusion cell is maintained over the course of an experiment. Moreover, the source of tritiated water being sorbed by the concentrated sulfuric acid in the receiver compartment of the cell must be from the donor compartment via transport across the test plastic.

WVTR across polyvinylchloride is shown graphically in Fig. 2. The shape of the profile is representative of profiles obtained for other types of plastics as well. That is, in general, WVTR profiles are characterized by a non-linear followed by a linear segment. The linear segment is consistent with steady-state transport of water vapor as described by Ficks law,

$$WVTR = \frac{P}{l}(\rho_2 - \rho_1) \qquad (1)$$

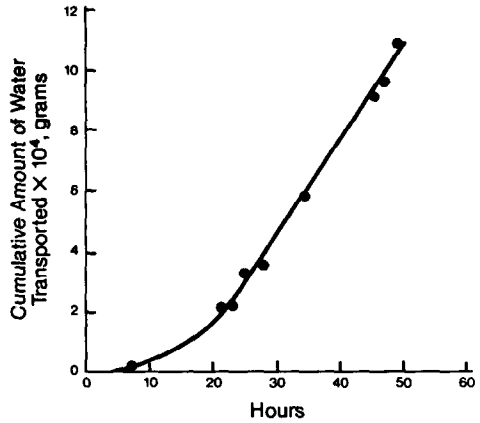


Fig. 2. Cumulative amount of water transported across polyvinylchloride as a function of time.

where WVTR is the amount of water being transferred across plastic of unit cross sectional area per unit time; $l$ is the thickness of the plastic; $(\rho_2 - \rho_1)$ is the water vapor pressure gradient across the plastic. $P$ is the permeability coefficient of water vapor for the plastic of interest and is defined as the following:

$$P = D \cdot S \qquad (2)$$

where D is the diffusion coefficient of water vapor within the plastic; S is the solubility coefficient of water within the plastic.

TABLE 2

*Water vapor transport rates across various plastics*

| Plastic | Thickness (mils) | WVTR ($g \cdot s^{-1} \cdot cm^{-2}$) | $(\rho_1 - \rho_2)$ (cm Hg) | D $cm^2/s$ | S ($g \cdot cm^{-3} \cdot cm\ Hg^{-1}$) | P ($g \cdot cm\ Hg^{-1} \cdot s^{-1} \cdot cm^{-1}$) | P *** ($g \cdot cm\ Hg^{-1} \cdot s^{-1} \cdot cm^{-1}$) |
|---|---|---|---|---|---|---|---|
| Polyvinylchloride * | 14.2 | $8.61 \times 10^{-9}$ ($1.93 \times 10^{-10}$) | 2.05 | $6.88 \times 10^{-8}$ | $2.21 \times 10^{-3}$ ($3.24 \times 10^{-4}$) | $1.52 \times 10^{-10}$ | $1.33 \times 10^{-10}$ (Lorant, 1967) |
| Polypropylene – ethylene copolymer ** | 4.0 | $2.50 \times 10^{-9}$ ($2.38 \times 10^{-10}$) | 2.05 | n.d. | n.d. | $1.24 \times 10^{-11}$ | n.r. |
| High density polyethylene * | 10.0 | $9.73 \times 10^{-10}$ ($7.66 \times 10^{-11}$) | 2.05 | $1.09 \times 10^{-7}$ | $1.10 \times 10^{-4}$ ($8.65 \times 10^{-6}$) | $1.2 \times 10^{-11}$ | $0.96 \times 10^{-11}$ (Schrenk, 1969) |

The donor compartment contained a saturated KCl solution having a water vapor pressure of 20.5 mm Hg at 25 °C. Numbers in parentheses are S.E.M.; n.d. = not determined; n.r. = not reported.

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*** Literature values.

TABLE 3

*Intra- and intervariation of water vapor transport rates across polyvinylchloride films*

| Plastic film | Water vapor transport rate ($g \cdot s^{-1} \cdot cm^{-2}$) |
|---|---|
| Polyvinylchloride (each determination performed on same film) | $8.61 \times 10^{-9}$ ($1.93 \times 10^{-10}$) * $n = 3$ |
| Polyvinylchloride (each determination performed on different film) | $8.46 \times 10^{-9}$ ($2.37 \times 10^{-10}$) * $n = 3$ |

Numbers in parentheses are standard errors of the mean.
* No significant difference (t-test, $p = 0.05$).

Steady state WVTR across the plastics was achieved within 24 h at 25 ° C for all of the plastics studied. WVTR and associated standard error were computed from the slope of the linear segment and are shown in Table 2. These data indicate that the described methodology is precise and can be used on a relative basis, for comparing water vapor transport rates. Also included in Table II are the various parameters of Eqs. (1) and (2) for each of the plastics studied.

Table 3 indicates that a representative test plastic retains its transport properties during the course of a typical experiment. There is no significant difference in the water vapor transport rate of a plastic which had been tested repeatedly compared to the WVTR obtained when measurements were made on a fresh sample each time. That the plastic retains its transport properties over the course of an experiment is also apparent from the observed linearity of the steady state portions of the WVTR profiles. If the transport properties were not being retained, one would expect to observe deviations from linearity.

Of particular interest with the present methodology is whether $^3H_2O$ is a real indicator of $H_2O$ movement through the plastics. The use of radiotracers as an analytical tool in transport studies is widely accepted. In fact, radiotracers have been utilized (Crank and Park, 1968) in order to obtain molecular diffusivity in the absence of any overall gradient of chemical composition by using a gradient of concentration of a labelled compound where the total amount of that compound is constant. Of perhaps greater concern than possible differences in the diffusion coefficient between $H_2O$ and $^3H_2O$ is the possibility of tritium exchange or equilibrium isotope effects during transport across the plastic. There is evidence that $^3H_2O$ has a higher specifity for some substrates such as glass filters relative to $H_2O$ (Bryan, 1983). Similarly, enhanced absorption of deuterium ions, as compared to protons onto glass surfaces in contact with solutions of $D_2O$ or $H_2O$ in $CCl_4$ has been shown (Glasoe and Bush, 1972). There is also a possibility that rapid proton exchange processes may operate in hydroxyl-rich regions of some polymer systems (Rabinow et al., 1986). However, given the relatively inert chemical composition of the plastics examined in the present studies, this latter possibility may not be important. In fact, Matsui (1970) compared the measurement of WVTR across an alkyd film using a radiotracer method with a gravimetric method and showed equivalence between the two methods. Rabinow et al. (1986) showed that water vapor transport rates through pharmaceutical tablet containers made of high density polyethylene agreed within 20% when measured either by radiotracer or gravimetric methods. Finally, as shown in Table II, permeability coefficients for polyvinylchloride and high density polyethylene are in agreement with permeability coefficients reported in the literature for similar polymer systems in which non-labelled $H_2O$ was used as the permeant (Lorant, 1967; Schrenk and Alfrey, 1969). A permeability coefficient for polypropylene–ethylene copolymer at 25 ° C using non-radiotracer methodology has not been reported. In addition, the diffusion coefficients for water vapor in polyvinylchloride and polyethylene as reported in Table II are of the same orders of magnitude as those reported in the literature (Crank, 1968). The similarity of permeability coefficients and water vapor transport rates measured using either radiotracer or non-radiotracer methodology appears to substantiate that $^3H_2O$ may indeed be a reasonable indicator of $H_2O$ transport through plastics. Nevertheless, one should exercise some caution in interpreting data in which less inert polymer systems are used as the test article.

The described methodology has several advantages over previously reported methods for measuring water vapor transport across plastics. The sensitivity of gravimetric methods is limited because of the inherent limitations of measurements made using an analytical balance. Therefore, inordinate periods of time are often required before steady state water vapor transport rates can be determined. The sensitivity of the present method is limited only by the specific activity of the tritiated water. Therefore, relative to other methodologies, water vapor transport rates can be obtained rapidly, particularly for strong water vapor barriers such as high-density polyethylene. Previously reported methods using radiotracers for analytical detection of water utilized anhydrous solids as water scavengers which necessitated extraction of $^3H_2O$ from the solid material prior to scintillation counting (Rabinow et al., 1986). The use of a hygroscopic liquid in the present method therefore reduces the total analytical time. An inherent weakness in many of the previously reported methods was inadequate control of critical variables which influence the rate of water vapor transport. However, the present method allows the control of temperature, surface area of plastic exposed to water vapor as well as water vapor pressure gradient across the plastic during the course of an experiment. This in turn allows determination of the permeability coefficient and therefore an absolute comparison of the barrier properties of one plastic to another can be performed. Finally, the scintillation spectrometer is not a component dedicated to the described method and therefore can be used in the detection of radioisotopes in other unrelated experiments at the same time. This is unlike the method described by Wood (1970) in which an infrared spectrometer is used to detect water and is a component dedicated to that particular method. If the scintillation spectrometer is already available to the analyst, the described method is extremely inexpensive.

In conclusion, a sensitive, simple, precise and relatively inexpensive method has been developed as an alternative for measuring water vapor transport across plastics. The plastic materials tested by this method are currently being used or have potential to be used as packaging systems for large volume parenteral solutions. However, this method could be used to assess the barrier properties of other types of materials as well. Moreover, this method has potential to serve as a tool for understanding mechanisms of water vapor transport across plastics.

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