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Water vapor diffusion in model tablet systems: I. Design of a diffusion apparatus

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Summary

A diffusion apparatus was constructed to investigate the diffusion of water vapor through model tablet systems. The apparatus consisted of three main components; a humidification system; a flow-through diffusion cell; and a modified gas chromatographic system which served as the detector. The system was qualified using compressed high density polyethylene powder as an ideal non-reactive porous barrier. Results from preliminary investigations suggested that the donor and receptor compartments of the diffusion cell were well mixed. Results from studies examining the effect of surface area, compact thickness, water vapor concentration in the donor compartment and particle size of the HDPE powder were consistent with a model of Fickian Diffusion through a porous barrier. Subsequently, the pore structure of the HDPE samples was determined using mercury intrusion porosimetry. The pore size distribution of the samples was in the range where normal gaseous diffusion was expected. Thus, the apparent diffusivity of water vapor through the HDPE samples was controlled exclusively by sample porosity and was independent of pore size.

Introduction

Compressed tablets are exposed to water vapor throughout their shelf-life. This exposure may have a profound impact on the physical and chemical stability of the dosage form. Aspirin is a classical example of water vapor effecting chemical stability. Numerous investigators have reported on the sensitivity of various aspirin/excipient formulations with respect to elevated temperatures and humidity (Lee et al., 1965; Patel et al., 1988). There are also reports in the literature describing the softening of tablets upon exposure to water vapor (Sangekar et al., 1972; Chowhan, 1980). Such softening is often dependent upon the composition of the formulation and its method of preparation. Obviously the detrimental effects of moisture can be overcome by limiting the exposure of dosage forms to atmospheric water vapor. This can be accomplished by film coating of the tablets, and by the judicious selection of packaging.

Investigators have reported on factors effecting water vapor permeation through protective film coatings. Banker and co-workers (1966) found

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that water vapor diffusion through polymer films was dependent upon the vapor pressure gradient across the film, which was consistent with Fickian diffusion. Swarbrick and co-workers (1972) reported that water vapor diffusion across certain polymer films was independent of the method of film preparation, either casting or spraying. From these reports and others, it can be concluded that film coatings applied to tablets behave as a continuous barrier. Thus, film coatings can substantially impede the diffusion of water vapor into tablets, thereby providing short-term protection from moisture.

For long term, tablets can also be 'protected' from water vapor by external packaging systems. There are reports in the literature concerned with the protective characteristics of packaging. Veillard et al. (1979) investigated water vapor diffusion through polyvinyl chloride blisters and its effect on tablet properties. Nakabayashi et al. (1980) used package permeation experiments to develop predictive models for long-term stability of solid dosage forms for several packages and storage conditions.

In general, most of the available literature describes the direct interaction between moisture and tablets under quasi-equilibrium conditions. The reasons for this are two-fold. First, such experiments are easy to conduct. Second, the information generated from such investigations clearly defines the humidity at which product failure will occur. Such experiments, however, do not take into consideration the kinetic aspect of the water vapor/tablet interaction.

The kinetics of the interaction are also affected by the mass transfer of water vapor from the surface to the innermost reaches of the tablet, presumably, via the tablet pore network. The porous nature of a tablet has been demonstrated by mercury intrusion porosimetry (Reich and Gstirner, 1968). Reports in the literature suggest that the pore size in tablets are typically one micron or less (Gucluyildiz et al., 1977).

In the case where the tablet is considered an inert, porous matrix, the mass transport of water vapor would occur in the interstitial void spaces between particles. Thus, if diffusion experiments were conducted utilizing a compact as the resistive barrier, the mass transport of water vapor should be a function of compact porosity. The remainder of this report will detail the fabrication and qualification of a diffusion apparatus designed for investigating water vapor diffusion in model tablet systems.

Materials and Methods

Materials

The material used for in the experiments was high density polyethylene (HDPE) resin. The HDPE resin was obtained from Newark Chemical Co., Gillette, NJ, as a powder grade (0–200 μm) and a scatter-coat grade (200–400 μm). These materials were prescreened, to supply a no. 100/140 mesh cut and a no. 50/60 mesh cut, respectively. These two mesh cuts were used for experimental purposes.

Surface area

The surface area of the HDPE resin was determined by multipoint B.E.T. adsorption using a commercially available instrument (Autosorb-1, Quantochrome, Syosset, NY).

Particle size by optical microscopy

The determination of sample particle size was performed by optical microscopy (Nikon Microphot-FX) coupled with image analysis (Model 3000, Image Tech. Corp., Manville, NJ). Sample particles were dusted onto a microscope slide and finely dispersed. A minimum of 200–300 individual particles were scanned for measurement of particle size.

Mercury intrusion porosimetry

Measurements of pore size and distribution for compact samples from the diffusion experiments were determined by mercury intrusion porosimetry. The porosimeter, a model Autoscan 60 with a data acquisition/analysis system, was commercially available from Quantachrome, Syosset, NY.

True density

The true density of materials was obtained using a commercially available helium pycnometer (Quantachrome). A sample of known weight was added to a sample cell with known volume. Pressure equilibrium between the sample cell and a reference cell allowed calculation of the samples true density (g/ml).

Diffusion apparatus

The experimental diffusion apparatus is shown in Fig. 1. To simplify further description, the system can be broken down into three main components. The first component was the humidification system which supplied the donor compartment with a constant flow of air at the specified water vapor concentration. The humidification system consists of two parts, a saturator and a condenser. Both saturator and condenser were situated in separate temperature controlled (−20 to 100°C) water baths. The saturator consisted of a series (2) of stainless-steel filter housings (Cole-Palmer, Chicago, IL) which contained distilled water. All connections in the system were made using 1/8 inch copper tubing with appropriate fittings (Swaglok Co., Solon, OH). Air from a gas cylinder was introduced to the bottom of the filter housings via medium porosity sparge tubes (Corning Glass, Corning, NY). The humidified air stream then traveled to a copper condenser situated in the second water bath. The condenser was a U-shaped piece of 3/4 inch copper tubing having a volume of 171 ml. The concentration of water vapor in the donor compartment was dependent upon the temperature of the condenser bath. From the condenser, the humidified air stream was transported via heated 1/8 inch copper tubing to a circulating hot air oven that housed the diffusion cell.

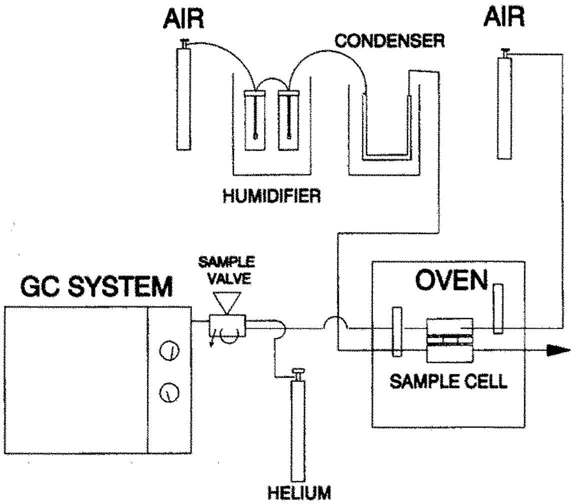

Fig. 1. Diagram of the experimental diffusion apparatus with GC detection system.

The second component of the system is the diffusion cell. The diffusion cell consisted of two half cells, between which resided a sample holder. The half cells were constructed of aluminum at a width of 5.25 inch and a thickness of 1.25 inch. A 1.25 inch diameter by 0.75 inch thick chamber, with a volume of 15.1 ml was center drilled in both compartments. To promote mixing, a baffle with dimensions of 1.25 inch diameter, 0.25 inch thickness and 0.5 inch height, was placed normal to the gas flow in each of the compartments. The final available volume in the compartments was 12.54 ml. Two, 1/8 inch holes were drilled in each compartment to accommodate flow of the appropriate gas. Sample holders were constructed from stainless steel, in several thicknesses (0.1, 0.2 and 0.4 inch) and sample diameters (0.5, 0.75, and 1 inch). The entire cell was held together by vertical steel rodding. An airtight seal between the half cell/sample holder interface was accomplished by utilizing recessed viton O-rings (Goodyear Rubber Products, Newark, NJ). The diffusion cell was situated in a hot air oven (Precision Science Group, Chicago, IL) to maintain the desired experimental temperature. Both humidified air for the donor compartment and dry air, less than 3 ppm water, were brought to the experimental temperature by first passing through heat exchangers, constructed from 3/4 inch copper tubing finned with aluminum for efficient heat transfer. Flow of the respective compartments was adjusted using inline precision needle valves (Cole-Palmer). To prevent bulk flow, the pressure differential between the donor/receptor compartments was balanced using a magnehelic gauge (Dwyer Instruments, Michigan City, IN) which bridged the exit line of the respective compartments.

The final component of the experimental apparatus was the detector, which in this case was a modified gas chromatographic system with thermal conductivity detector (Perkin Elmer model Sigma 2, Norwalk, CT). The gas stream from the receptor compartment was carried to a six port GC switching valve (Supelco Inc., Bellefonte, PA). Thus, the effluent stream was continuously purging a 0.25 ml loop, the contents of which were introduced into the GC gas phase, by simple valve actuation. The column used to separate water vapor from air was a 30 m megabore column containing GSQ support (J&W Scientific, Folsom, CA). Data were acquired by an in-house laboratory computer system (Hewlett Packard model HP1000, Cupertino, CA).

Diffusion experiments

Diffusion samples of HDPE were prepared on a 30 ton Carver press. Compacts were compressed within the stainless-steel sample holder. The diffusion cell with sample was returned to the oven where dry air was allowed to pass through both compartments until the water peak was below the limit of detection (< 0.003 μg/ml). At time zero humidified air was introduced to the donor compartment to start an experimental run. The receptor gas stream was analyzed at a minimum frequency of 3 min over the course of the run to determine the water vapor concentration. The actual water vapor concentrations were determined using a standard response curve of peak area and water mass. The minimum quantifiable level was 0.01 μg/ml. The standard response curve was obtained by spiking acetonitrile with known amounts of water and injecting the solutions on the GC system to obtain peak areas.

At the end of each run, a cumulative mass vs time plot was generated. As depicted in Fig. 2, steady-state flux was obtained from the linear portion of the plot and lag time (t_{lag}) from the intercept using relationships reported for a zero-order diffusion process in a porous system (Flynn et al., 1974). Linearity of the slope was confirmed by residuals testing for independence and randomness and lack of a significant quadratic term ($p < 0.05$) indicative of curvature. The apparent diffusivity (D_{app}) was obtained from the steady-state flux and physical measurement of the sample (thickness, porosity). The breakthrough time (t_{bk}) was taken as the time when the area of the water peak was greater than the minimum quantifiable level (0.01 μg/ml).

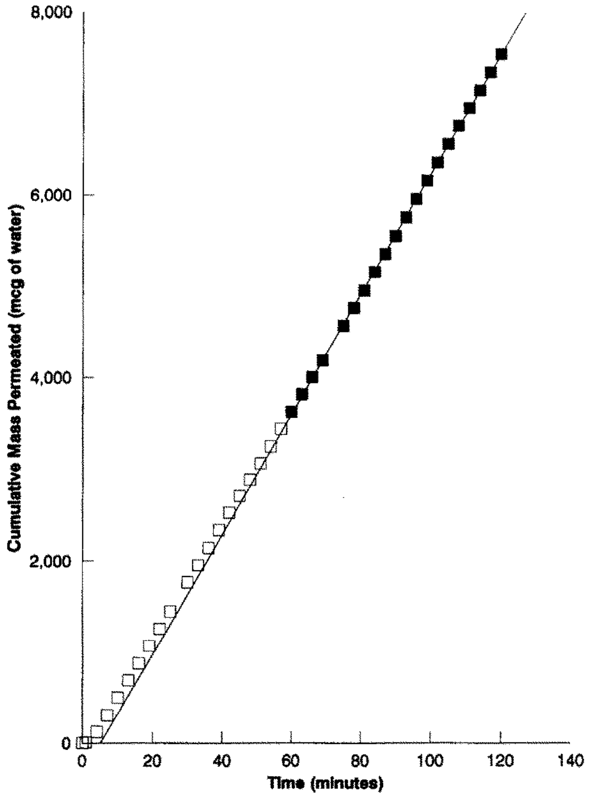

Fig. 2. A plot of cumulative mass of water permeated vs time for a typical HDPE compact diffusion experiment with data points used in linear regression analysis (■).

Results and Discussion

Diffusion in a porous matrix is a special case of Fickian diffusion which requires modification of Fick's general equations to account for pore volume and diffusion path length. This increase in diffusion path length can be accounted for by introduction of the empirical tortuosity factor (τ) which, along with volume fraction of the pore phase (ϵ), results in the following equation for diffusion in a porous medium (Flynn et al., 1974):

$$J = -D \cdot (\epsilon/\tau) \cdot (\mathrm{d}C/\mathrm{d}x) \qquad (1)$$

Tortuosity values of 2–10 are commonly reported in the literature (Cussler, 1984). In many experimental systems, the calculated diffusion coefficient (D_{eff}) is actually a composite term of the true diffusion coefficient and tortuosity, D/τ (Aris, 1975).

Investigations with HDPE compacts

High-density polyethylene (HDPE) samples were used for preliminary diffusion experiments for several reasons. First, due to its hydrophobic chemical nature there is negligible interaction between water vapor and HDPE (Lynch, 1975). Thus, the diffusion process through the sample would be uninfluenced by the solid phase. Second, HDPE powder was found to deform elastically under the compaction conditions that were used in this investigation. Thus, the pore structure in the compact would not be subject to particle fragmentation or deformation effects. Third, the particle size of HDPE and its approximate spherical shape (Table 2) would be conducive for formation of a uniform pore structure, in terms of geometry and topology, in the sample compacts. For these reasons, HDPE compacts behave as the ideal, non-reactive porous barrier. Thus, the diffusion process in HDPE compacts should approach Maxwell's model for diffusion in a porous matrix (Maxwell, 1892). In his treatment, Maxwell utilized a model of periodically spaced spheres dispersed in a continuous phase to solve for D_{eff}. Thus, for this model there is no break in the diffusion process. The general solution can be reduced for the special case where diffusion is limited to the continuous phase:

$$(D_{eff}/D) = [2(1-\phi_d)]/(2+\phi_d) \qquad (2)$$

where ϕ_{d} is the volume fraction of the dispersed phase.

Effect of receptor compartment flow rate

Diffusion of volatile solutes in gas is quite rapid, on the order of 0.1 cm^2/s, and is several orders of magnitude larger than diffusion in a liquid (Cussler). Thus, one would not expect to see stagnant layer boundary effects in a well designed flow-through diffusion cell where diffusion takes place in the gaseous phase. To confirm this supposition, a qualification of the diffusion cell was performed.

The first qualification experiment of the diffusion apparatus, was to determine the effect of receptor compartment flow rate on concentration of water vapor in the receptor compartment. These experiments were conducted using HDPE 50/60 mesh compacts formed under 149 MPa of pressure, having a surface area of 1.266 cm^2, a thickness of 0.63 cm, and an approximate porosity of $\epsilon = 0.2$. Water vapor concentration in the donor compartment was 15.4 μg/ml and the temperature was 25°C. Flow rate in the receptor compartment was varied from approx. 11 to 22 ml/min. Results from the study confirm a significant inverse linear effect ($R^2 = 0.99$, $p < 0.001$) of receptor compartment flow rate on water vapor concentration when concentration was plotted against reciprocal flow rate. The linear effect suggests that water vapor flux into the receptor compartment was unaffected by flow rate, which confirms that the receptor compartment was well-mixed over the range of flow rates examined.

Effect of donor compartment flow rate

In a second qualification investigation, the effect of donor compartment flow rate was investigated. The experimental conditions used in this study were identical to those described in the prior experiment. The flow rate in the donor compartment was varied from approx. 10 to 31 ml/min, with concentration in the receptor compartment being the dependent variable. Concentration values were obtained by making several injections of the receptor compartment effluent at each of the flow rates. Subsequently, when the data was modeled, the only significant term was a constant concentration value ($p < 0.001$). In addition, ANOVA of the mean concentrations suggested that there was no difference between the means at each level ($p = 0.65$). These results suggest that the donor compartment flow rate, over the range examined, does not effect the mass transfer of water vapor into the receptor compartment. The overall results of both qualification studies suggest well-mixed donor and receptor compartments.

Effect of surface area

The effect of surface area on the diffusion process was investigated at three levels: 1.2664, 2.850 and 5.0671 cm^2 using HDPE compacts with a porosity of approx. 0.20 and a thickness of 0.635 cm. The average particle size of the HDPE particles was 350 μm (50/60 mesh). The water vapor concentration in the donor compartment was 15.4 μg/ml, and the temperature was 25°C. Four replicates were run at each surface area level.

The results for these experiments are given in Table 1. A typical plot of cumulative mass vs time for HDPE compacts is shown in Fig. 2. Water vapor flux (μg/s) was observed to be a linear function of surface area (Fig. 3). The slope was highly significant ($R^2 = 0.96$, $p < 0.001$). However, parameter means for D_{app} and T_{lag} were found to be independent of surface area ($p > 0.05$). These findings are consistent with Fickian Diffusion in that the amount diffusing is a direct function of the surface area available for diffusion. Other diffusion parameters, D_{app} and T_{lag}, are dependent upon the diffusion path, which is unaffected by surface area.

TABLE 1

Effect of experimental variables on water vapor diffusion parameters in high density polyethylene compacts

Variable	J (μg/cm^2 per s)	D_{app} (cm^2/s)	T_{lag} (min)
Surface area (cm^2)			
1.27	0.192 (0.014)	0.045 (0.003)	5.45 (0.44)
2.85	0.185 (0.010)	0.042 (0.002)	5.40 (0.85)
5.07	0.204 (0.011)	0.045 (0.003)	6.16 (1.56)
Thickness (cm)			
0.318	0.386 (0.009)	0.044 (0.001)	1.81 (0.38)
0.635	0.185 (0.010)	0.042 (0.002)	5.40 (0.85)
0.953	0.126 (0.004)	0.043 (0.001)	11.70 (0.59)
Concentration gradient (μg/ml)			
4.5	0.061 (0.002)	0.043 (0.001)	6.16 (0.51)
9.5	0.132 (0.004)	0.044 (0.002)	6.43 (0.70)
14.0	0.204 (0.011)	0.045 (0.003)	6.16 (1.58)
Particle size (μm)			
114	0.194 (0.016)	0.042 (0.002)	5.62 (1.77)
350	0.204 (0.011)	0.045 (0.003)	6.16 (1.56)

(S.D., $n = 4$)

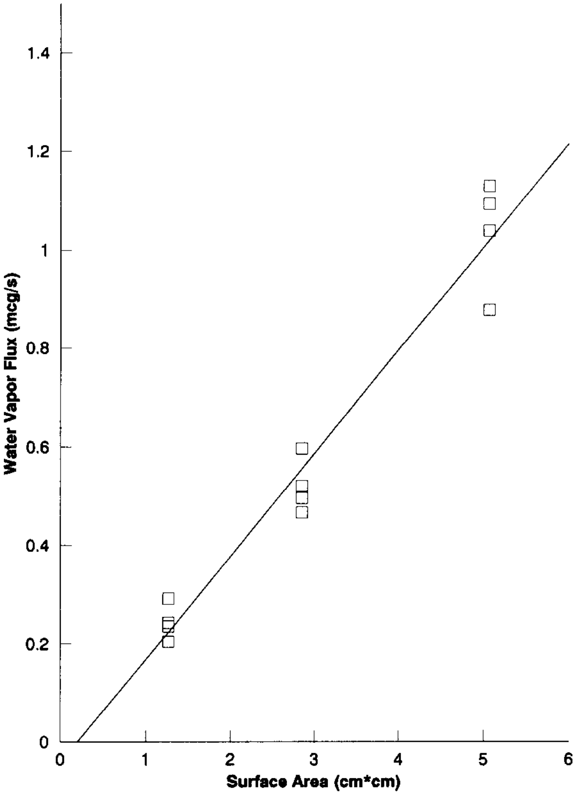

Fig. 3. The effect of compact surface area on water vapor flux through HDPE compacts prepared from 50/60 mesh cut HDPE powder.

Effect of sample thickness

The effect of diffusion path length on diffusion parameters was investigated at three thickness levels, 0.3175, 0.635 and 0.9525 cm. For these experiments, the surface area (2.8503 cm^2), porosity ($\epsilon \simeq 0.20$), temperature (25°C), and water vapor concentration in the donor compartment (15.4 μg/ml) were held constant. Four experiments were conducted at each thickness level.

A plot of moisture flux vs reciprocal sample thickness is shown in Fig. 4. Analysis of the data indicates a significant inverse linear effect of thickness (h) on moisture flux ($R^2 = 0.98$, $p <$

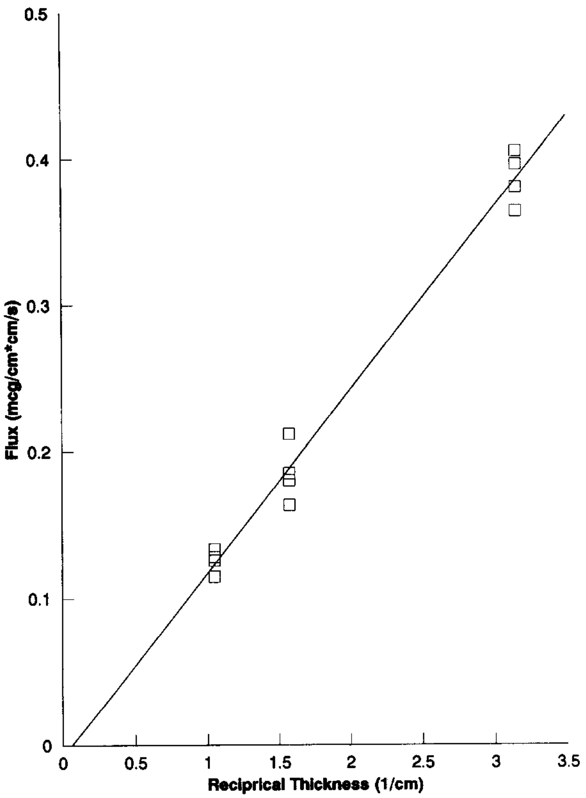

Fig. 4. The effect of sample thickness on water vapor flux across HDPE compacts prepared from 50/60 mesh cut HDPE powder.

0.001). The dependence of diffusion on sample thickness is fundamental to the Fickian diffusion process. However, D_{app} was found to be unaffected by sample thickness ($p > 0.05$).

Effect of water vapor concentration gradient

The effect of water vapor concentration gradient on diffusion parameters was investigated at levels of 4.5, 9.5 and 14.0 μg/ml. These values correspond to relative humidities of 19.6, 41.3 and 60.9% at the experimental temperature of 25°C. The compacts used in this study had constant surface area (5.07 cm^2), thickness (0.635 cm) and porosity ($\epsilon \simeq 0.20$). Four replicates were obtained at each level (Table 1).

In Fig. 5, the linear dependence of water vapor flux on concentration in the donor compartment is clearly significant ($R^2 = 0.95$, $p < 0.001$). This result confirms that concentration gradient is the driving force behind the diffusion process. However, parameters D_{app} and T_{lag} are independent of the concentration gradient. Experimental results for these parameters (Table 1) were found to be unaffected by the concentration gradient ($p > 0.05$).

Effect of HDPE particle size

In the last experiment, the effect of HDPE resin particle size on diffusion parameters was investigated. All previous experiments utilized HDPE resin from a 50/60 mesh cut with a mean particle size of 350 μm (Table 2). A second, finer grade of HDPE resin was obtained from a 100/120 mesh cut, which yielded a mean particle size of 114 μm.

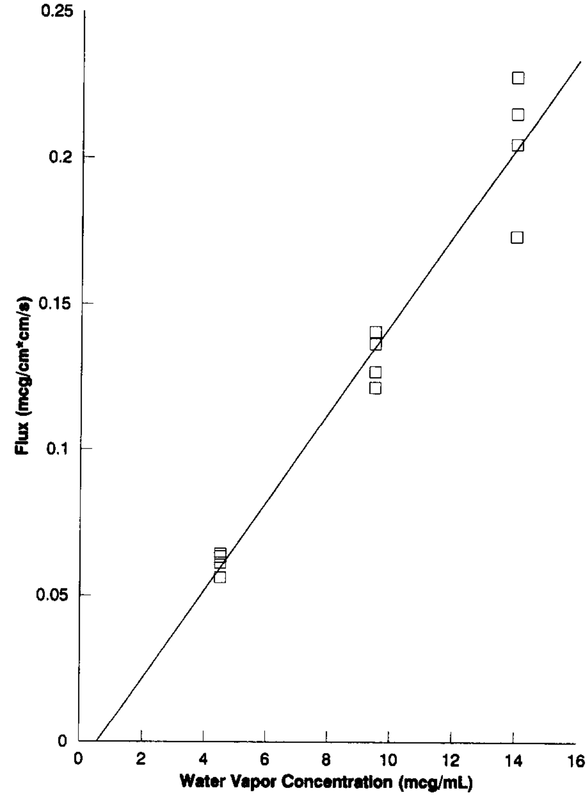

Fig. 5. The effect of water vapor concentration gradient on water vapor flux across HDPE compacts prepared from 50/60 mesh cut HDPE powder.

TABLE 2

Physical characteristics of high density polyethylene powder

Material	Surface area (m^2/g)	Particle size (μm)	True density (g/ml)
HDPE (50/60)	0.27	376.5 (H) 364.1 (W) 309.5 (B)	0.95
HDPE (100/140)	0.27	120.7 (H) 120.2 (W) 101.2 (B)	0.95

Height (H), width (W) and breadth (B) were estimated by image analysis using light microscopy.

One of the assumptions of Maxwell's model (Eqn 2) was that diffusion in a porous medium was only dependent on the dispersed phase volume of the sample. Thus, based on this assumption one would expect that the diffusion parameters between the two experimental groups should be the same. However, the Maxwell model does not distinguish between viscous (ordinary) diffusion and free-molecular (Knudsen) diffusion. In the former, the diffusion process is governed by the collisions between diffusing molecules. The mean free path of travel refers to the distance between molecular collisions and can be estimated using the following equation (Kennard, 1938):

$$\lambda = \frac{k_b T}{1.41\pi\sigma^2 P} \tag{3}$$

where λ is the mean free path, k_b denotes Boltzmann's constant, σ^2 is the collision diameter for diffusing species and P represents pressure. Viscous or 'unhindered' diffusion occurs when the diameter of the diffusion path is much larger than the mean free path of travel. However, when the diameter of the diffusion path approaches the mean free path, the collision frequency between the diffusing molecule and the boundary or 'wall' of the diffusion path becomes significant to the extent that diffusion is 'hindered'. This phenomena of hindered diffusion was reported by Knudsen (1909); a diffusion coefficient (D_k) can be estimated using the following formula (Sherwood et al., 1975):

$$D_k = \left(\frac{2r_e}{3}\right)\left(\frac{8RT}{\pi M}\right)^{1/2} \tag{4}$$

where R is the ideal gas constant, M denotes molecular weight and r_e is pore radius. The Knudsen equation indicates that the diffusion process is a direct function of the diffusion path diameter and is independent of pressure.

The change from viscous (ordinary) to Knudsen diffusion is not abrupt and it is suggested that there is a transition region where collisions with the boundary or other molecules have an equal probability (Ho and Roseman, 1979). The diffusion mechanism for a system can be estimated using the Knudsen number which is the ratio of mean free path to pore radius:

$$K_n = \frac{\lambda}{r_e} \tag{5}$$

where K_n is the Knudsen number. When the value of $K_n > 3$, Knudsen diffusion is the dominating mechanism; when $K_n < 0.1$, ordinary diffusion dominates. The so-called transition region occurs when $0.1 < K_n < 3$.

A porous matrix with a defined pore network is an ideal candidate for hindered diffusion. This was the primary reason for conducting the experiments with different particle sizes of HDPE. The experimental results for the effect of HDPE particle size are given in Table 1. In all instances the diffusion parameters (J, D_{app}, T_{lag}) were independent of pore size differences between the samples ($p > 0.05$). These results suggest that the pore size in both samples was sufficiently greater than the mean free path of travel for the diffusing species, so that normal (viscous) diffusion dominated the diffusion process.

Subsequent to the diffusion experiments, the pore structure of the samples was determined using mercury intrusion porosimetry. The mean and median pore size for the compacts with different particle size are given in Table 3. The data suggest a gross pore network in the HDPE sam-

TABLE 3

Pore diameter of high density polyethylene compacts obtained by mercury intrusion porosimetry

Sample	Mean pore size (S.D.) (μm)	Median pore size (S.D.) (μm)
50/60 mesh	10.8 (0.3)	12.1 (0.2)
100/140 mesh	2.2 (0.1)	5.8 (0.1)

(S.D., $n = 4$)

ples. Using Eqn 3, the mean free path of travel for the experimental conditions was calculated to be 0.0763 μm. Inserting the mean pore size for the 100/140 mesh samples, and the mean free path of travel into Eqn 5, results in an estimated Knudsen number (K_n) of 0.072 which is clearly in the realm of viscous diffusion ($K_n < 0.1$). Therefore, the diffusion process in the HDPE compacts was governed by viscous diffusion, which supports the observed lack of particle size effect.

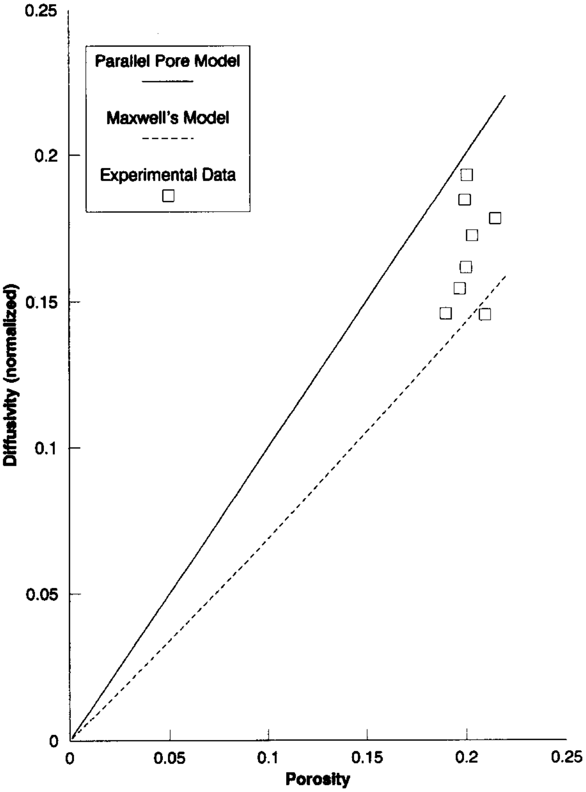

Fig. 6. A plot of normalized diffusivity ($D_{app}/0.26$ cm^2/s) vs HDPE compact porosity, in contrast to the parallel pore model and Maxwell's model for diffusion in porous medium.

The combined results of experiments conducted with HDPE compacts are clearly indicative of a diffusion process that is consistent with Fick's laws of diffusion. Furthermore, when the values for D_{app} are normalized by division with the reported diffusion coefficient for water vapor in air at 25°C (0.26 cm^2/s; Cussler, 1984) and plotted against porosity, the values cluster between the respective Parallel pore model and Maxwell's model for diffusion in a porous matrix (Fig. 6). This suggests that the diffusion path in the HDPE compacts exhibits minimal tortuosity effects.

Conclusions

A diffusion apparatus was constructed to investigate water vapor diffusion in model tablet systems. The apparatus was qualified by experimentally establishing that the donor and receptor compartments were well mixed and without the occurrence of stagnant boundary layer effects. Preliminary investigations were conducted using compacts comprised of HDPE resin, which served as the ideal, non-reactive porous barrier. Several experiments documenting the effects of surface area, thickness and concentration in the donor compartment suggest the water vapor diffusion is properly modeled as Fickian diffusion in a porous medium where diffusion only occurs in the continuous gas phase of the void space. The pore structure of the compacts, determined via mercury intrusion porosimetry, was in the size range which was substantially larger than the mean free path of the diffusing species. Thus diffusion of water vapor was viscous (ordinary) and unhindered by pore size.

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