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Water vapor diffusion in model tablet systems: II. Experiments with lactose anhydrous based tablets

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Summary

Investigations were conducted to study water vapor diffusion in lactose-based compacts of increasing compositional complexity, using a previously described diffusion apparatus. Diffusion parameters were found to be a function of a pore structure for a particular system. The pore structure was influenced by tablet composition and degree of densification. Results from mercury intrusion porosimetry suggest that a large percentage of the pore volume had pore diameters in which the diffusion process was transitional between viscous (ordinary) diffusion and free-molecular (Knudsen) diffusion. The diffusion process was modeled using Percolation Theory. Resulting estimates of percolation threshold (ϕ_c) and coordination number (z) suggested that the pore network in lactose compacts was highly connected.

Introduction

Mass transport in porous media is an area of considerable interest due to its many important applications. The utility of porous catalyst pellets with high internal surface area, the extraction of oil from porous geological structures and release of drug from a controlled release matrix tablet are just a few examples of mass transport in a porous matrix. Invariably, mass transport in a porous medium, whether it is a diffusion or bulk flow process, is a function of the pore geometry, topography, and volume. While pore volume, in many instances, can be readily measured, pore geometry and topography are difficult to assess. However, it is pore geometry and topography that are responsible for the large deviations observed from simple models describing transport in porous systems.

Mercury intrusion porosimetry is well suited for determining pore size distribution in porous samples, using the functional relationship between applied pressure (P), pore radius (r), surface tension of mercury (γ) and contact angle between the mercury and the sample (θ) (Washburn, 1921):

$$\Delta Pr = -2\gamma \cos \theta \qquad (1)$$

Mercury intrusion porosimetry has been used in pharmaceutical research since 1956, when

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Strickland et al. measured the apparent density of granules to calculate intra-granular porosity for powder systems. Reich and Gstirner (1968) used mercury intrusion porosimetry to investigate the pore structure of tablets. In general, they observed pore diameters in the range of 5–0.5 μm. Gucluyildiz et al. (1977) used mercury intrusion porosimetry to determine the porosity and pore size distribution of an aspirin formulations with varying level of colloidal silicon oxide. Subsequently, it was suggested that the stability of the formulations may be dependent upon the pore structure of the tablet.

In the preceding article, the design, qualification and utility of a apparatus constructed to investigate water vapor diffusion in model tablet systems was discussed (Jerzewski and Lordi, 1994). In that report, compacts (tablets) of HDPE resin were utilized as the ideal, inert porous matrix. Water vapor diffusion through that system was found to be consistent with Fickian diffusion. Subsequent analysis of the pore structure by mercury intrusion porosimetry revealed a uniform pore structure with median pore size on the order of 5.8–12.1 μm. While HDPE served as a useful reference material, it was recognized that pharmaceutical tablet systems are considerably more complex in the nature, both in regards to their composition and pore structure. The remainder of this paper will be concerned with water vapor diffusion in more complex systems and attempts to model the effect of matrix porosity on the effective diffusion coefficient. The ultimate objective was to assess whether tablet porosity can be used to 'control' diffusion of water vapor into the tablet.

Materials and Methods

Materials

Lactose anhydrous direct compression grade was obtained from Sheffield Products, Norwick, NY. Crospovidone (Polyplasdone XL10®) was purchased from G.A.F. Corp., Wayne, NJ. Magnesium stearate was obtained from Mallinckrodt Inc., St. Louis, MO.

Experimental

The experimental apparatus, procedure and data treatment for conducting water vapor diffusion experiments were described in the preceding article and were used to conduct the following investigations.

Effect of compact porosity

The effect of lactose compact porosity on diffusion parameters was evaluated over the following range, $\epsilon = 0.106$–0.211, corresponding to compaction pressures of 210.7–77.3 MPa, respectively. For all diffusion runs the following variables were held constant: compact weight (4.0413 g); surface area (5.0671 cm^2); temperature (25°C) and donor compartment water vapor concentration (15.4 μg/ml or 67% R.H.).

Effect of magnesium stearate

Lactose anhydrous was blended with magnesium stearate at levels of 0.625, 1.25, 1.875 and 2.5% (w/w). For all diffusion runs the following variables were held constant: compact weight (4.0413 g); surface area (5.0671 cm^2); compaction pressure (96.1 MPa); temperature (25°C) and the donor compartment water vapor concentration (15.4 μg/ml).

The effect of adsorptive filler

The experimental tablet formulation consisted of lactose anhydrous (95.75% w/w), Polyplasdone XL-10 (3% w/w) and magnesium stearate (1.25% w/w). Surface area was held constant at 1.2668 cm^2. Donor compartment water vapor concentration was 15.4 μg/ml. Temperature was 25°C. The samples had the following approximate physical properties: thickness, 0.3175 cm; weight, 0.505 g; porosity, 0.2. Samples comprised of lactose anhydrous (98.75% w/w) and magnesium stearate (1.25% w/w) were also run, as a control.

Results and Discussion

Experiments with lactose anhydrous

Lactose anhydrous, a disaccharide, is a commonly used tablet diluent that is obtained from

TABLE 1

Physical characteristics of excipients

Material	Surface area (m^2/g)	Particle size (μm)	True density (g/ml)
Lactose anhydrous	0.38	116.2 (H) 108.8 (W) 92.8 (B)	1.57
Polyplasdone	1.08	6.2 (H) 6.0 (W) 5.1 (B)	1.22
Magnesium stearate	8.37	3.8 (H) 3.5 (W) 3.0 (B)	1.08

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

cows' milk whey (Goodhart et al., 1986). Anhydrous lactose normally contains $< 1\%$ water, which makes it compatible with many moisture sensitive drugs. Since it is relatively non-hygroscopic, tablets prepared from lactose anhydrous exhibit good physical stability when exposed to humidities below 70% R.H. (Sangekar et al., 1972). Under pressure, lactose anhydrous exhibits brittle fracture behavior during the tablet formation process (Marshal and Rudnic, 1990). For these reasons, lactose anhydrous was chosen for the progressive development of model tablet systems used in the diffusion experiments. Some relevant physical characteristics of the lactose used in following experiments are given in Table 1.

Diffusion experiments were conducted with neat lactose compacts as described in the experimental section and the results are given in Table 2. The results of these experiments were contrasted to those obtained for neat HDPE compacts at an equivalent porosity (Table 3). The difference in parameter means for HDPE and lactose compacts was statistically significant ($p < 0.05$) using a Student's t-test. In general, the results suggest that the diffusion process is substantially reduced in the lactose compacts when compared to HDPE compacts. Furthermore, reduction in porosity for lactose compacts directly effects the diffusion parameters, J, D_{app}, T_{lag} and T_{bk}.

Maxwell's model for diffusion (Maxwell, 1873) in a porous matrix was applied to the lactose

TABLE 2

Diffusion parameters for lactose-porosity experiment

Pressure (MPa)	Porosity	J ($\mu g/cm^2$ per s)	D_{app} (cm^2/s)	T_{lag} (min)	T_{bk} (min)
77.3	0.2110	0.165	0.0373	21.0	10
93.1	0.2059	0.174	0.0395	52.0	10
94.8	0.2023	0.126	0.0316	53.9	10
96.6	0.2018	0.174	0.0394	32.2	10
96.9	0.2012	0.164	0.0371	39.8	7
99.2	0.2005	0.157	0.0355	28.6	7
105.3	0.1842	0.128	0.0338	48.0	16
114.1	0.1758	0.114	0.0306	43.6	19
127.2	0.1580	0.071	0.0191	61.5	19
131.4	0.1553	0.054	0.0145	52.9	19
133.4	0.1513	0.055	0.0149	72.5	22
138.7	0.1470	0.047	0.0130	85.1	22
144.8	0.1442	0.050	0.0143	76.7	22
171.2	0.1250	0.029	0.0091	106.9	35
188.7	0.1190	0.026	0.0086	127.8	40
208.9	0.1116	0.021	0.0071	146.2	50
208.9	0.1085	0.013	0.0045	134.0	50
210.1	0.1074	0.014	0.0050	136.5	50
210.7	0.1062	0.012	0.0042	155.2	60

TABLE 3

Comparison of HDPE and lactose diffusion parameters in compacts with equivalent porosity ($\epsilon = 0.2$)

Sample	J µg/ cm^2 per s)	D_{app} (cm^2/s)	T_{lag} (min)	T_{bk} (min)
HDPE	0.204	0.045	6.16	< 1
	(0.011)	(0.003)	(1.56)	
Lactose	0.159	0.037	41.3	8.8
	(0.020)	(0.003)	(11.4)	(1.6)

(S.D., $n = 5$)

porosity data for preliminary data treatment with poor results. This finding, coupled with the significant differences between the HDPE and lactose data for equivalent porosity, suggest differences in the diffusion path between the two substrates. To elucidate these differences, mercury intrusion porosimetry was conducted. The results given in Table 4 clearly indicate a fine pore structure that exists in the lactose compacts. Moreover, as depicted in Fig. 1 there was a first order relationship between median and mean pore radii ($p < 0.001$, $R^2 = 0.89$ and $p < 0.001$, $R^2 = 0.96$) and compaction pressure.

As described in the previous article, pore size data from mercury intrusion porosimetry can be used to determine the predominant diffusion mechanism, viscous (ordinary) diffusion or free-molecular (Knudsen) diffusion. Applying the mean free path estimate of 0.0763 µm previously obtained, the pore volume distribution for the lactose samples was calculated, and is given in Table 4. The results suggest that a significant portion of the larger pores are effectively removed as compaction pressure increases, and that the majority of the pore volume is in the transition region.

The reduction in diffusivity of the lactose compacts was greater than could be accounted for using Maxwell's model. This has been observed for many other systems and has prompted investigators to develop other models for mass transport in porous media. Alternative models include the random pore model (Reyes and Jensen, 1985), the dusty gas model (Mason et al., 1967), and

TABLE 4

Pore size and distribution in lactose samples

Porosity	Pore radii (µm)		Volume distribution (%)		
	Mean	Median	Viscous [a]	Transition [b]	Hindered [c]
0.2110	0.427	0.627	38.4	61.4	0.2
0.2059	0.272	0.550	33.1	65.8	1.1
0.2023	0.274	0.520	28.6	70.2	1.2
0.2018	0.272	0.531	27.6	71.1	1.3
0.2012	0.276	0.541	25.1	73.6	1.3
0.2005	0.261	0.536	24.0	74.6	1.3
0.1842	0.251	0.468	2.5	95.9	1.6
0.1758	0.248	0.420	0.7	97.4	1.9
0.1580	0.240	0.360	0.4	97.6	2.0
0.1553	0.241	0.360	0.3	97.7	2.0
0.1513	–	–	–	–	–
0.1470	0.220	0.336	0.7	97.2	2.1
0.1442	–	–	–	–	–
0.1250	0.188	0.267	0.0	97.6	2.4
0.1190	0.169	0.238	0.0	97.2	2.8
0.1116	0.150	0.209	0.0	96.6	3.4
0.1085	0.150	0.209	0.0	96.7	3.3
0.1074	0.147	0.200	0.4	96.3	3.3
0.1062	0.146	0.198	0.7	95.8	3.5

[a] Pore radius > 0.763 µm; [b] pore radius < 0.763µm, > 0.025 µm; [c] pore radius < 0.025 µm.

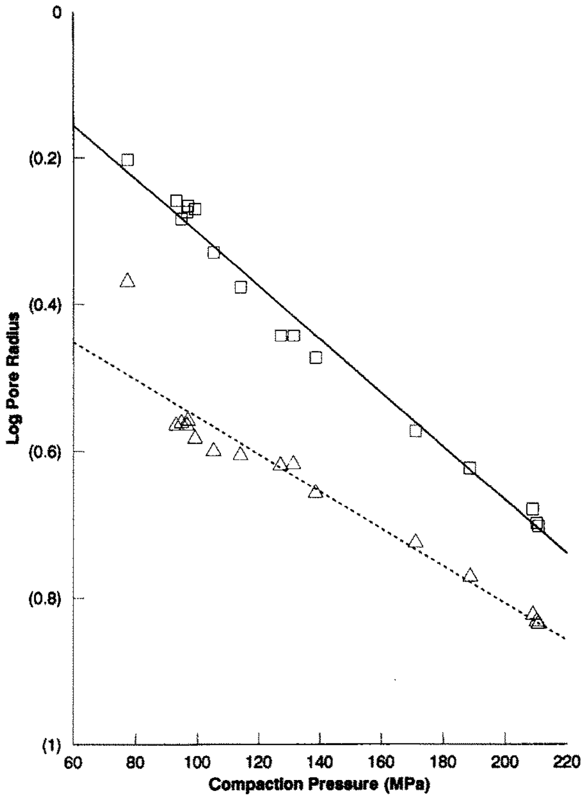

Fig. 1. The effect of compaction pressure on median pore radius (□) and mean pore radius (△) of lactose anhydrous compacts.

percolation theory (Broadbent and Hammersly (1957).

Percolation theory uses geometrical and probablistic concepts to predict the behavior of composite systems. Percolation theory was derived for infinite periodic lattices that can be subdivided into sites or alternately, bonds. These sites (bonds) can be occupied or unoccupied, with probabilities of P and $1-P$, respectively. Several models have been developed utilizing the site (bond) concept. In percolation theory it is the probability of how the sites (bonds) are linked together into clusters that influences the behavior of the lattice. Clusters may be infinite (continuous) if they span one dimension of the lattice or finite (discontinuous) when they do not span the lattice.

For a given system or lattice, the percolation probability (P) or the fraction of occupied sites or formed bonds, is a primary discripter of the lattice state. At $P=1$ all sites are occupied or all possible bonds are formed. When percolation theory is applied to real or finite systems, some characteristic or behavior of that system is a function of the percolation probability (P). At a particular probability called the percolation threshold (ϕ_c), one observes a dramatic change in the measured characteristic. Ideally, the characteristic should approach zero or infinity at ϕ_c.

Independent of the percolation model used, the porous matrix can be characterized in terms of its geometrical properties. One measure of a porous system is the total volume fraction (ϕ_i) of the pore phase. This can be divided into accessible and inaccessible fractions. The accessible fraction can be further divided into backbone and deadend fractions. The backbone fraction is the pore volume, through which transport (diffusion, conduction, etc.) occurs. The deadend fraction which branches off the backbone fraction does not contribute to steady-state transport.

Near the percolation threshold the following relationship between mass transport and porosity is observed:

$$\phi_i^E = m(\phi_i - \phi_c)^c \tag{2}$$

where ϕ_i^E represents normalized transport (diffusivity, etc.) and m is a scaling constant. The relative magnitude of the exponential term is $c > 1$ (Reyes and Jensen, 1985). For 3-D lattices, the value of c ranges from 1.6 to 2.0 depending upon the lattice type. Topology of the lattice can be described using the concept of 'connectedness' of the lattice subparts or sites. The connectedness or coordination number (z) of the lattice refers to the maximum number of bonds that can be connected at one site. In a porous lattice there is a direct correlation between increased connectedness and increased flux.

Percolation theory, in conjunction with several physical models, has been used to describe conduction phenomena in composite media. Kirpatrick (1973) investigated the utility of a network model of cubic tessellations in predicting conduction behavior. Winterfeld (1981), used Voronoi tessellations to simulate conduction in 2- and

3-dimensional disordered composite media. Bethe lattices (Cayley trees) have also been used to model conduction behavior (Larson and Davis, 1982).

A Bethe lattice is a perpetual branching network that lacks any reconnections. Thus, the network can be characterized by a coordination number (z) that refers to the number of bonds exiting a node. Fisher and Essam (1961) derived the following equation to estimate the coordination number from prior knowledge of the percolation threshold:

$$Z = 1/(\phi_c - 1) \tag{3}$$

The Bethe lattice model has been used to effectively predict transport phenomena in porous media. Heiba et al. (1985) utilized the Bethe lattice to model flow through porous reservoir rock. Mohanty et al. (1982) used the Bethe lattice to simulate polymerization propagation of polymers.

A physical representation of a Bethe lattice bond-percolation transport problem is depicted in Fig. 2. In Fig. 2a the bond which connects nodes of the lattice is conducting, while in Fig. 2b the bond is non-conducting. This may be representative of the pore structure of a tablet given that tablets are composed of particles. It is reasonable to assume the existence of a pore (conducting bond) at the interface between two particles. During the compaction process, a fraction of the pores are lost as bonding between particles occurs. There still remains an interface between the two particles, however, the dimension of this interface is such that the pore can be assumed non-conducting.

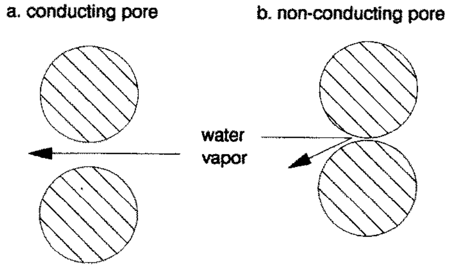

Fig. 2. A physical model of a Bethe lattice bond-percolation conduction model: (a) conducting pore, (b) non-conducting pore.

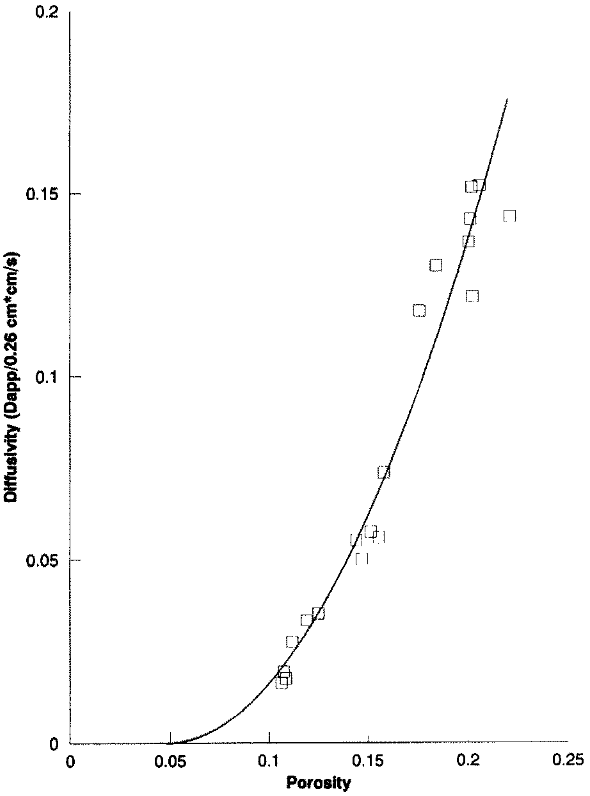

Fig. 3. The effect of porosity on water vapor diffusivity in lactose anhydrous compacts: experimental data (□) and percolation model (———).

Using Eqn 2, experimental data of normalized diffusivity ($D_{app}/0.260\ cm^2\ s^{-1}$) can be plotted against porosity of a tablet composition and values of m and ϕ_c can be calculated by nonlinear regression analysis. The coordination number (z) can be estimated using the percolation threshold (ϕ_c) and Eqn 3. Once obtained, the values of ϕ_c and z can be used to comment on the topological properties of that tablet system. A plot of the lactose data fit with the percolation model is given in Fig. 3 ($R^2 = 0.96$). The percolation threshold (ϕ_c) was estimated to be 0.0479 with a standard error of 0.0078. The scaling factor (m) was estimated to be 5.923 with a standard error of 0.680. A coordination number (z) of 22 was obtained by applying Eqn 3.

The calculated percolation threshold is significantly lower than reported values for tessellations (Winterfeld, 1981). The low ϕ_c is indicative of a system with a high degree of connectedness. The degree of connectedness for a system is also described by the coordination number, which for the simple lactose system was calculated to be $z = 22$. There may be several explanations for the observed differences between the experimental results and theoretical simulations for conducting systems. First, implicit with percolation models for conducting systems, is the assumption that conductivity is restricted to the conducting fraction. While this may hold true for conduction of current, deviations may occur with respect to diffusion. There are innumerable reports of diffusion in solid barriers that are considered non-porous, where the diffusion process is occurring at the molecular level. Similarly, diffusion in porous systems may occur both in the pore phase and the solid phase. More importantly, in systems where diffusion can occur in both phases, the diffusion process does not stop at the terminal point of a dead-end pore. Rather, the diffusion mechanism would change to molecular diffusion until another pore in the diffusion path is breached. Hastedt and Wright (1990) reported on the release of drug from a porous matrix system at porosities above the percolation threshold. For their experimental system, the authors calculated a percolation threshold of 0.08 and a coordination number 37. The authors suggested that diffusion through the polyvinyl stearate polymer may have contributed to the their experimental results.

Second, the compaction of irregular-shaped pharmaceutical powders represents a real, finite system compared to infinite models constructed using uniform tessellations. During tablet formation, non-uniform distribution of force in the compact results in significant variability in density as a function of position. The non-uniformity of compression force and density was reported by Train (1956). The density profile in the compact will change as a function of the compression force. One can assume that there is a functional relationship between density in a given region and the pore structure. Thus, a single tablet may be represented by several finite 'systems' of pore structure which would necessarily complicate modeling of the diffusion process and may result in the observed connectivity values.

Experiments with lactose / magnesium stearate

One of the necessary excipients included in a tablet formulation is the lubricant. A lubricant is necessary to reduce the coefficient of friction at the interface between tablet constituents and the die wall. The mechanism through which the lubricant functions is known as boundary lubrication. In general, boundary lubricants all exhibit the characteristic of spreading when subjected to shear pressure (Hardy, 1936). Thus, it is the transport of the lubricant from the region of shear pressure (powder bed) to the adjacent boundary where pressure is reduced (interface between tablet and die wall) that imparts a lubricants functionality.

Magnesium stearate is a lubricant commonly used in pharmaceutical tablet formulations. Some physical characteristics of magnesium stearate include a fine particle size, with high surface area and low bulk density (Han et al., 1986). Reports in the literature suggest that magnesium stearate can impact on tablet properties such as hardness (Sheikh-Salem and Fell, 1981), water permeability (Ganderton, 1969), disintegration (Bolhuis et al., 1981) and dissolution (Levy and Gumtow, 1963).

Many of the observed effects of magnesium stearate on tablet properties may be due, in part, to the formation of a film on particle surfaces. Therefore, when powders containing magnesium stearate are compressed, it is reasonable to assume that magnesium stearate would be located at the solid:gas interface of the tablet pore structure. For this reason, experiments investigating the effect of magnesium stearate level on water vapor diffusion parameters were conducted. The simple lactose anhydrous/magnesium stearate system is a further evolution of a model tablet system.

Before discussing the effect of magnesium stearate on the diffusion parameters, it is appropriate to first discuss changes in the pore structure as determined by mercury intrusion porosimetry.

TABLE 5

Effect of magnesium stearate level on mean and median pore radii in lactose anhydrous compacts as determined by mercury intrusion porosimetry

Magnesium stearate (%)	Mean pore radii (μm)	Median pore radii (μm)
0.000	0.2713 (0.0072)	0.5228 (0.0101)
0.625	0.2168 (0.0019)	0.4320 (0.0033)
1.250	0.2020 (0.0081)	0.3848 (0.0049)
1.875	0.1880 (0.0063)	0.3488 (0.0012)
2.500	0.1733 (0.0067)	0.3148 (0.0060)

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

Results for the effect of magnesium stearate level on the mean and median pore radius are given in Table 5. Increasing magnesium stearate level also causes a slight decrease in total porosity (Table 6). However, when the experimental porosity is divided into contributions of free, transition and hindered volume, one can see the marked impact of magnesium stearate on the compact pore structure. These findings suggest that magnesium stearate preferentially fills the larger pores in the compact. One would expect that the larger pores represent a volume of 'lower pressure' to which the magnesium stearate would spontaneously flow to, when the compact is being formed.

TABLE 6

Pore size distribution in lactose:magnesium stearate compacts

Magnesium stearate (%)	Volume distribution (%)			
	Porosity	Viscous [a]	Transition [b]	Hindered [c]
0.000	0.2059	33.1	65.8	1.1
	0.2023	28.6	70.2	1.2
	0.2018	27.6	71.1	1.3
	0.2012	25.1	73.6	1.3
0.625	0.1882	7.8	89.1	3.1
	0.1907	6.7	89.7	3.6
	0.1924	5.5	90.9	3.6
	0.1921	6.2	90.2	3.6
1.250	0.1840	2.0	93.7	4.3
	0.1845	2.2	93.0	4.8
	0.1872	3.1	92.6	4.3
	0.1880	2.2	94.2	3.6
1.875	0.1810	1.7	93.5	4.8
	0.1794	1.0	94.4	4.6
	0.1806	0.7	94.4	4.9
	0.1825	0.8	94.3	4.9
2.500	0.1760	1.4	93.5	5.1
	0.1748	1.1	93.7	5.2
	0.1765	0.7	93.5	5.8
	0.1809	0.4	94.6	5.0

[a] Pore radius > 0.763 μm; [b] pore radius < 0.763 μm, > 0.025 μm; [c] pore radius < 0.025 μm.

TABLE 7

Effect of magnesium stearate level on water vapor diffusion parameters in lactose anhydrous compacts

Magnesium stearate (%)	ϵ	J (μg/cm² per s)	D_{app} (cm²/s)	T_{lag} (min)	T_{bk} (min)
0.0	0.2023	0.159	0.037	41.3	8.8
	(0.0021)	(0.020)	(0.003)	(11.4)	(1.6)
0.625	0.1915	0.141	0.032	43.5	13.0
	(0.0022)	(0.004)	(0.008)	(5.9)	(0.9)
1.250	0.1859	0.124	0.028	56.6	16.6
	(0.0017)	(0.007)	(0.002)	(1.2)	(0.6)
1.875	0.1814	0.096	0.022	58.4	16.6
	(0.0016)	(0.006)	(0.001)	(5.2)	(0.6)
2.500	0.1778	0.080	0.018	57.3	16.6
	(0.0029)	(0.007)	(0.002)	(5.5)	(1.1)

(S.D., $n = 5$)

Diffusion parameters for lactose:magnesium stearate compacts are given in Table 7. The percolation model described previously was also used to analyze the diffusivity of the lactose:magnesium stearate compacts. A plot of the experimental data and the fitted percolation model is depicted in Fig. 4. The percolation threshold was estimated to be 0.109 with a standard error of 0.011 ($R^2 = 0.70$). The scaling factor (m) was estimated to be 16.6, with a standard error of 4.6. A coordination number of $z = 9$ was obtained using Eqn 3.

Similar to the results obtained for compacts of pure lactose, the calculated percolation threshold was lower than reported values for simple tessellations. However, the coordination number for the lactose:magnesium stearate compacts was less than that obtained for pure lactose compacts. This suggests that the addition of magnesium stearate has reduced the connectedness of the pore network. This can be rationalized by the following argument. If system connectedness is

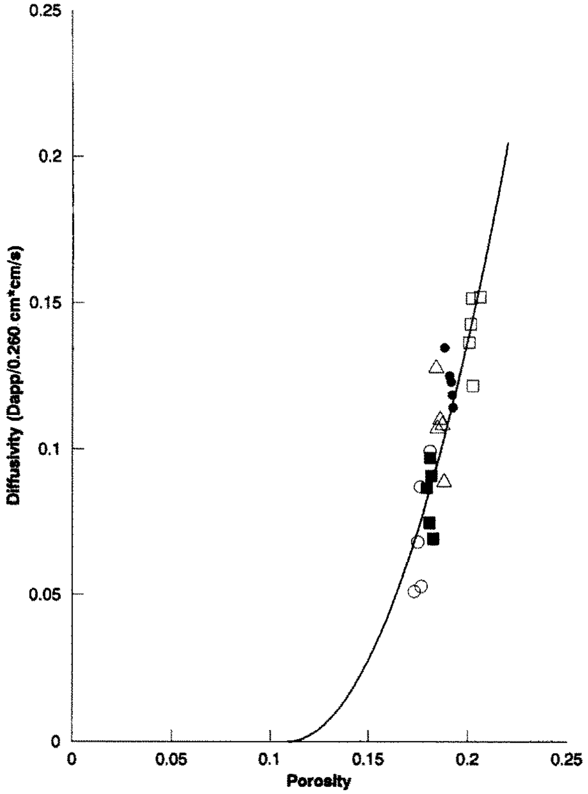

Fig. 4. The effect of porosity on water vapor diffusivity in lactose anhydrous compacts with varying amounts of magnesium stearate: 0% (□), 0.625% (●), 1.25% (△), 1.875% (■), 2.5% (○) and percolation model (———).

equated to the number of diffusion paths emanating from a node, then the addition of magnesium stearate results in a decrease in the diffusion paths. Given the fluid nature of lubricants under pressure, one would expect that a fraction of the diffusion paths would be occluded by lubricant intrusion.

The effect of porosity on T_{lag} and T_{bk} is illustrated in Fig. 5. In this plot, data from both lactose:pressure experiments and lactose:magnesium stearate experiments are shown. The fact that the data overlaps, suggests that it is the reduction in pore size, or pore topology, that is responsible for observed changes in T_{lag} and T_{bk}. Thus, constrictions in the pore, regardless if caused by pressure or magnesium stearate, have the same effect on retarding water vapor diffusion.

Experiments with tablets containing a disintegrant

In addition to filler (lactose anhydrous) and lubricant (magnesium stearate), tablets usually contain a disintegrant. Disintegrants are agents which aid in the physical break-up of the tablet into particles. Disintegrants, regardless of chemical structure, are typified by a high affinity for moisture. Therefore, one would expect that disintegrant particles in a tablet matrix to act as sorptive fillers which would affect the water vapor diffusion process (Flynn et al., 1974).

To investigate the effect of disintegrant (sorptive filler) on the diffusion process, cross-linked polyvinylpyrrolidone (Polyplasdone XL-10®, G.A.F. Corp.) was added to the lactose anhydrous/magnesium stearate blend. Polyplasdone XL-10 was selected as the disintegrant for several reasons (G.A.F. Corp., 1990). First, it exhibits

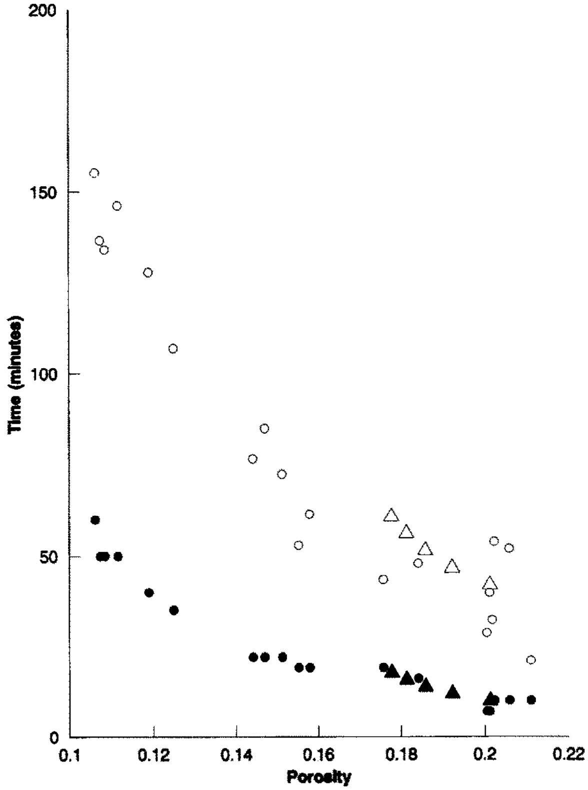

Fig. 5. The effect of porosity on T_{lag} in lactose anhydrous compacts, neat (○) and with magnesium stearate (△) and on T_{bk} in lactose anhydrous compacts, neat (●) and with magnesium stearate (△).

TABLE 8

Diffusion parameters for compacts containing lactose / magnesium stearate / Polyplasdone XL-10

Sample	J (μg/cm^2 per s)	D_{app} (cm^2/s)	T_{lag} (min)	T_{bk} (min)
Without	0.239	0.0274	11.8	4.0
Polyplasdone	(0.019)	(0.003)	(2.2)	(0)
With	0.246	0.0283	36.2	11.7
Polyplasdone	(0.016)	(0.003)	(4.9)	(2.9)

(S.D., $n = 3$)

moderate swelling capacity (swelling factor 2.25–2.3) which should not significantly affect the tablet pore structure. Second, it has a very fine particle size (75–85% < 37 μm), which would allow a uniform dispersion in the tablet matrix even at low concentration levels. Third, it rapidly sorbs water.

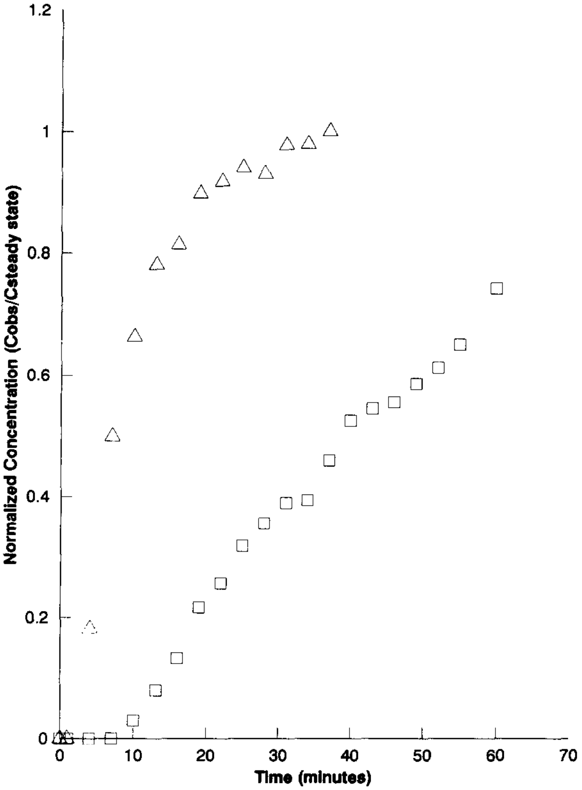

Fig. 6. The effect of compact composition on the nonsteady-state diffusion process in lactose anhydrous:magnesium stearate compacts with polyplasdone (□) and without polyplasdone (△).

The results from diffusion experiments suggest that the steady-state diffusion parameters remain unchanged with the addition of the sorptive filler (Table 8). This finding was expected, since steady-state diffusion would only be influenced by the geometrical and topological properties of the compact. However, there was a significant effect on the nonsteady-state diffusion process as demonstrated in Fig. 6. When a plot of normalized concentration ($C_{t=x}/C_{t=\infty}$) vs time is prepared for samples with and without the disintegrant, it is obvious that the initial diffusion process has slowed. This is due to the sorption of the diffusing water vapor molecules by the Polyplasdone XL-10. Therefore, steady-state diffusion was not achieved until the disintegrant has reached its equilibrium moisture content.

Conclusions

Investigations were conducted to study water vapor diffusion through lactose-based compacts of increasing compositional complexity, using a previously described diffusion apparatus. Diffusion parameters for neat lactose compacts were found to be a function of compact porosity. Results from mercury intrusion porosimetry suggest that a large percentage of the pore volume had pore diameters in which the diffusion process was transitional between viscous (ordinary) diffusion and free-molecular (Knudsen) diffusion. The diffusion process was modeled using Percolation Theory. Resulting estimates of percolation threshold (ϕ_c) and coordination number (z) suggested that the pore network in lactose compacts was highly connected.

Subsequent experiments in lactose : magnesium stearate compacts suggested that magnesium stearate modified the pore network. Resulting estimates of percolation threshold and coordination number suggested that tablets containing magnesium stearate were less connected then tablets comprised of lactose only. It was proposed that magnesium stearate flow, caused by compaction pressure, was responsible for filling pores, which effectively reduced the pore network connectedness.

Experiments with a sorptive filler (Polyplasdone XL-10) suggested that the nonsteady-state diffusion process modified due to the interaction between diffusing water vapor molecules and the filler. However, the steady-state diffusion parameters were unaffected by the sorptive filler.

From these studies it was concluded that the diffusion process in tablets is a function of the porosity and pore structure for a particular system. Both porosity and pore structure will be influenced by system composition and the degree of densification. The nonsteady-state diffusion process will be influenced by the sorptive nature of the system, however steady-state diffusion parameters should be a function of the porosity/pore structure only. In general, the diffusion process was rapid enough that water vapor would penetrate to the center of a normal tablet within several minutes of exposure to an external environment of high humidity. Therefore, making use of tablet porosity to 'control' diffusion of water vapor into the tablet does not seem plausible.

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