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A study on water permeation through rubber closures of injection vials

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Summary

Freeze-dried products are highly hygroscopic. Because of their reactivity with water, they must be adequately protected against the uptake of moisture. In the vial presentation, the rubber closure forms the critical barrier. Water absorption and desorption profiles indicate that the rate-controlling water diffusion coefficient is concentration dependent. From these curves the diffusion coefficients can be estimated. Real time penetration experiments were compared with the absorption curves. From this it can be concluded that rubbers with a low permeability are often able to take up significant amounts of water. The rate at which saturation is achieved is an indication of the diffusion coefficient. Therefore, this reveals an elegant way of discriminating between the quality of rubbers. On the basis of the experimental results, it is possible to evaluate the water protection capacity of rubber closures. Quantitative permeation through the rubbers is, however, highly unpredictable because of the concentration dependency of the diffusion coefficient.

Introduction

Like all pharmaceutical dosage forms, injection preparations must meet certain stability criteria. Stability of a dissolved drug is often very limited. In such cases, freeze-drying offers a possibility to increase shelf-life considerably. However, the dry product obtained is hygroscopic and must be protected against exposure to moisture. For a vial presentation, the rubber stopper forms the critical barrier. Protection of the product against moisture or, e.g. oxygen, is totally dependent upon the quality and functioning of this barrier. In this respect, it is known that rubber is not only a barrier against moisture, but can also be a source of water (Van Amerongen, 1964).

This report discusses the speed of water uptake, the saturation and finally the permeability of different types of rubber closures. The aim of the investigation was to obtain an understanding of the fundamental mechanisms which determine the barrier quality. In addition, an easy method of discriminating between different rubbers is proposed.

Theory

Diffusion must be distinguished in a concentration independent and a concentration dependent type.

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Concentration-independent diffusion coefficient

Steady-state diffusion Steady-state diffusion is described by Fick's first law;

$$A = -D\frac{\mathrm{d}c}{\mathrm{d}x} \qquad (1)$$

where A is the amount of diffusing substance passing a section of surface area per unit time, D represents the diffusion coefficient, C is concentration and x denotes distance.

This equation implies that under steady-state flow, the concentration of the penetrant changes linearly over the thickness of the membrane.

When dealing with gases, the gas concentration in the rubber is in equilibrium with the gas pressure p, expressed by Henry's law

$$C = Sp \qquad (2)$$

where S is the solubility coefficient.

From Eqns 1 and 2, the permeability P can be derived as (Van Amerongen, 1964):

$$P = DS \qquad (3)$$

Transient-state permeation If one face of the membrane is brought into contact with the penetrant, it will take some time before the penetrant has crossed the membrane and even longer before steady-state flow is established. Here, Fick's second law applies, where the concentration gradient over the membrane changes in time:

$$\frac{\mathrm{d}c}{\mathrm{d}t} = \frac{\mathrm{d}}{\mathrm{d}x}\left(D\frac{\mathrm{d}c}{\mathrm{d}x}\right) \qquad (4)$$

The lag time L is given by

$$L = x^2/6D \qquad (5)$$

Concentration-dependent diffusion

Here, the concentration of penetrant does not change linearly over the thickness of the membrane. Fig. 1 shows the concentration gradient of water in a rubber membrane during stationary permeation. The concentration gradient deviates strongly from linearity.

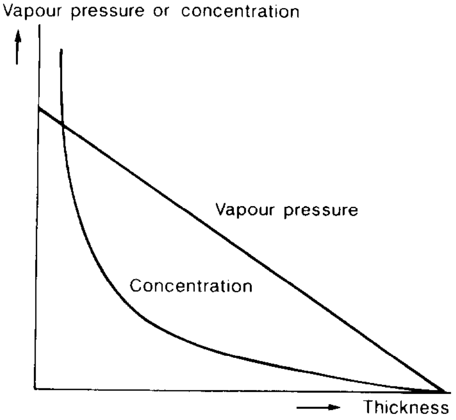

Fig. 1. Water vapour pressure and concentration gradients during steady-state permeation through natural rubber (Van Amerongen, 1964).

In contrast, it is the vapour pressure, regarded as being at equilibrium with the concentration at a given place, that exhibits a linear gradient. This is further demonstrated in Fig. 2, where equilibrium absorption of water in rubber is plotted as a function of the relative vapour pressure. From this, it is clear that especially at high vapour pressure considerable deviation from Henry's law occurs, i.e. there is no proportionality between pressure and solubility.

At lower vapour pressure, however, water uptake behaves roughly in accordance with Henry's law. This means that for rubber materials, one can distinguish two situations; at low vapour pressures, Fick's and Henry's laws hold, while at high vapour pressure this is not the case. For the first situation calculations concerning permeation and lag time can be carried out using Eqns 1, 3 and 5. In another procedure (Van Amerongen, 1964), D is calculated from the absorption vs time profile, according to:

$$D = \frac{1}{16}\pi(F^2X^2/t) \qquad (6)$$

$$A/A_{\max} = F$$

where F is the amount of water absorbed (A) as a fraction of the ultimate absorption ($A_{\max}$). Here

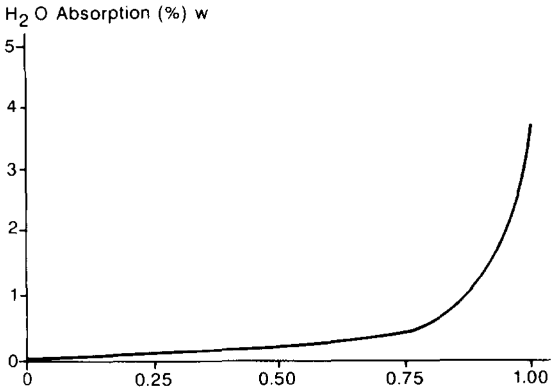

Fig. 2. Solubility (equilibrium absorption) of water in natural rubber as a function of relative vapour pressure (Van Amerongen, 1964).

F is mostly plotted vs $\sqrt{t}$ yielding initially straight lines.

When Fick's and Henry's laws apply, the absorption and desorption curves coincide. This is not true for concentration-dependent diffusion coefficients. In such cases, it is proposed that D should be estimated by taking the mean value of the absorption and desorption curves (Long and Thompson, 1955; Van Amerongen, 1964). Since permeability increases strongly at higher vapour pressures (Figs 1 and 2), the present study employed severe stress conditions to discriminate between the performance of the rubbers.

Materials and Methods

Experiments were performed with freeze-drying closures. 13 mm diameter closures of the same dimensions were used. Six different types of rubber were compared. Suppliers were Helvoet (FM 157 (grey) and FM 257 (grey)), Pharma Gummi (PH 701/45 (red), PH 21/50 (red) and PH 4104/40 (grey)) and the West Company (W888 (grey)). All rubbers were of the bromobutyl rubber type, with the exception of W888, which consists of a halobutyl/polyisoprene blend.

After drying at 110°C for 24 h in a hot-air oven, water absorption was followed by weighing. The conditions applied were 30°C-75% relative humidity (RH) and 40°C-95% RH using Hereaus humidity test chambers. After absorption of water, the closures were dried above phosphorus pentoxide at 30 and 40°C, yielding the desorption curves.

Water uptake and release were assessed by weighing approx. 50 stoppers.

Permeation was estimated by measuring the increase in water content of a freeze-dried formulation in 10 ml vials, stored under fixed conditions. Water in the product was determined using an automated Karl Fischer method (Mitsubishi moisture meter, model CA-05).

Results and Discussion

In Fig. 3, the absorption curves of the closures at 30°C-75% RH and 40°C-95% RH are given, while Fig. 4 shows the desorption curves at 30 and 40°C. As can be seen, a considerably prolonged time is required to achieve saturation. This is a direct consequence of the properties of the rubber, as demonstrated in Figs 1 and 2. The driving force for the water transport in the rubber is the relative humidity. Approaching saturation, a small difference in vapour pressure results in a strong increase in water content (Fig. 2). The reverse process (Fig. 4), where the wet rubbers are kept at 0% RH, can be considerably faster (Van Amerongen, 1964). Therefore, it was expected from a theoretical point of view that large differences between rate of absorption and speed of desorption would exist (see Introduction). However, only a small difference was found.

In Fig. 3, saturation ($A_{\max}$) was not reached. To estimate the value of $A_{\max}$, curve fitting was performed using the formula

$$A = A_{\max}(1 - e^{-k\sqrt{t}}) \qquad (7)$$

This provided the values for both $A_{\max}$ and the rate constant k, as listed in Table 1.

Using these data, Fig. 5 was constructed by plotting $A/A_{\max}$ ($=F$) vs $\sqrt{t}$ (Eqn 6) for the 40°C/95% RH condition. Comparing Fig. 5 with

Fig. 3, it is obvious that the sequence of the curves has reversed. For example, the rubber which took up considerable amounts of water, e.g. PH 4104, exhibits a low speed of saturation whereas a rubber which absorbed less water reaches its saturation sooner. This is reflected in the k values.

Permeation

As indicated in Theory (Eqn 6), k^2 can be considered as an estimate of the diffusion coefficient D. Apparently, the rubbers which are capable of taking up significant amounts of water have a relatively low diffusion coefficient. Absorption curves yield a slightly lower value than the des-

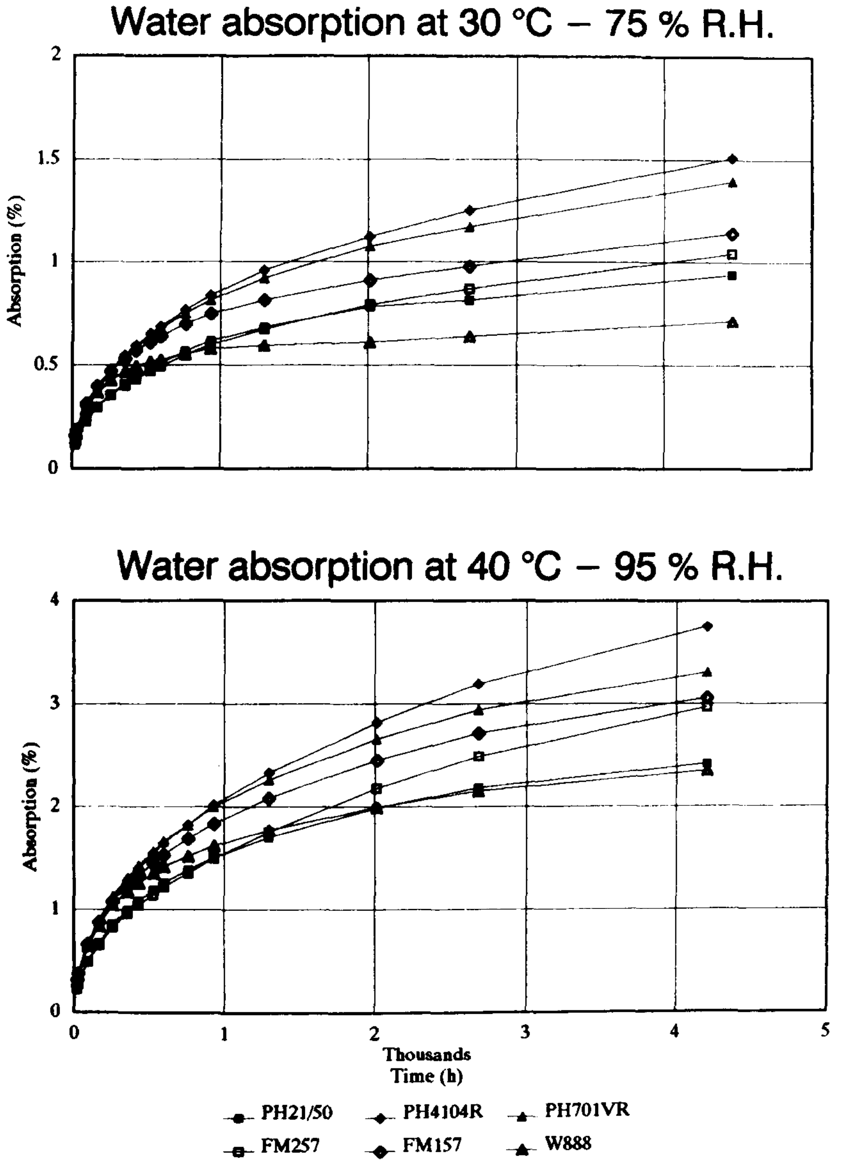

Fig. 3. Water uptake of rubber closures at 30°C-75% RH and 40°C-95% RH as a function of time.

orption curves. In practice, absorption is more important than desorption, assuming that rubbers are dried properly before use. Here, it is not the amount of water absorbed, but rather, the amount permeated that is of importance. The relevant characteristics are: (a) the lag time (i.e. the time after which leakage starts), and (b) the subsequent water flux (i.e. permeation). To assess these properties, 10 ml vials containing a freeze-dried formulation were stoppered with the different closures, which were dried before use at 110 °C for 24 h. The samples were stored at 40°C-95% RH. This condition was chosen since rapid discrimination is only possible under severe conditions. From the earlier discussion (Figs 1 and 2) it follows that *D* increases with increasing RH. In

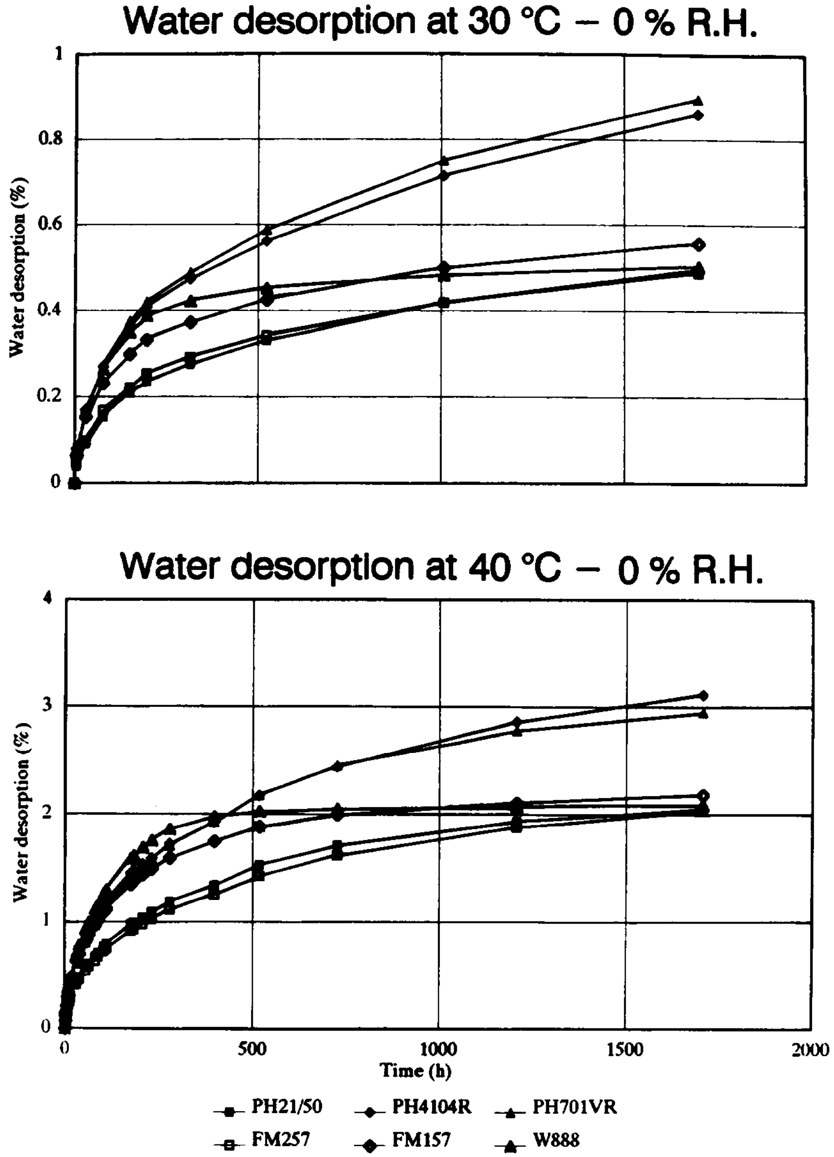

Fig. 4. Drying curves of the rubber closures, used for Fig. 3, at 30 and 40°C.

practice, only at 40°C-95% RH do measurable amounts of water penetrate all the vials within the period of investigation.

The increase in water contents of the products is demonstrated in Fig. 6 for the different closures. As can be observed, no water was released from the closures themselves. Obviously, heating for 24 h at 110°C results in sufficient drying. From Fig. 6, the lag time and the permeation were estimated and the values are listed in Table 2.

The results demonstrate that the barrier quality of the rubbers follows the order: W888 $\ll$ PH 701 = FM 157 < PH 21/50 $\ll$ FM 257 = PH 4104. The lag time L can be considered as the time period needed for the diffusion front to cross the

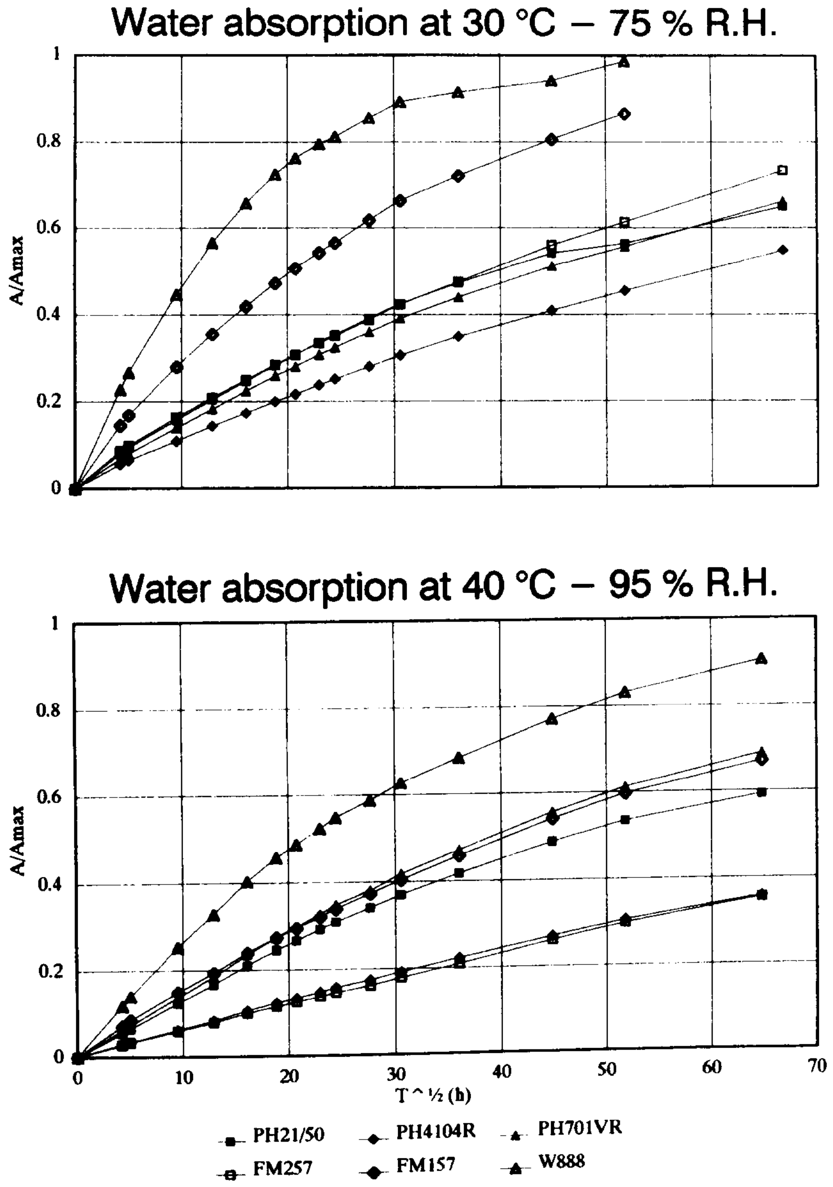

Fig. 5. Saturation ($A/A_{\max}$) as a function of $\sqrt{t}$ (Eqns 6 and 7) of closures stored at 30°C-75% RH and 40°C-95% RH.

TABLE 1

Maximum water uptake A_{max} and rate constant k (Eqn 7) of rubber closures stored at 40°C-95% RH and 30°C-75% RH

	A_{max} (%)	k (h^{-1})	k^2
40°C/95% RH			
W 888	2.59	0.032	1.02×10^{-3}
FM 157	4.55	0.017	0.29×10^{-3}
PM 701	4.80	0.018	0.32×10^{-3}
PM 21/50	4.08	0.015	0.23×10^{-3}
FM 257	8.39	0.007	0.049×10^{-3}
PH 4104	10.46	0.007	0.049×10^{-3}
30°C/75% RH			
W 888	0.65	0.066	4.36×10^{-3}
FM 157	1.13	0.035	1.23×10^{-3}
PH 701	2.10	0.016	0.26×10^{-3}
PM 21/50	1.45	0.018	0.32×10^{-3}
FM 257	1.42	0.018	0.32×10^{-3}
PH 4104	2.75	0.012	0.14×10^{-3}

TABLE 2

Lag time and permeation derived from Fig. 6

	Lag time (weeks)	Permeation (μg/week)
W 888	2	80
FM 157	6	25
PH 701	6	21
PH 21/50	10	16
FM 257	10	7.5
PH 4104	10	7.2

whole barrier. In the case where Fick's law applies, L is given by Eqn 5. Using k^2 as an estimate for D and bearing in mind that $X^2/6$ is constant for all closures, L can be calculated as $1/k^2$ (Table 3). A low degree of correlation is

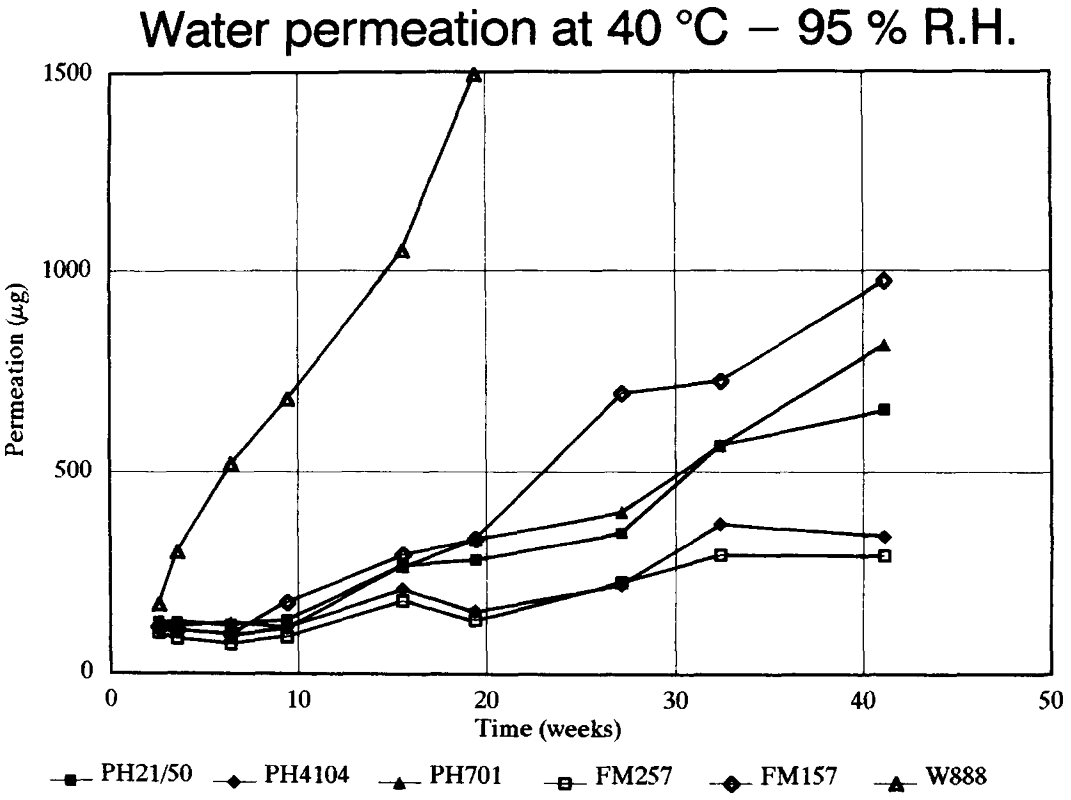

Fig. 6. Water permeation through rubber closures at 40°C-95% RH.

TABLE 3

Lag time (from Fig. 6), k values (from Table 1) and saturation at t = lag time (from Fig. 5) for permeation through rubber closures at 40°C-95% RH

	Lag time observed (weeks)	Relative	$1/k^2$	Relative	Saturation (%)	$1/k$	relative
W 888	2	1	980	1	49	31	1
FM 157	6	3	3 448	3.5	49	59	2
PH 701	6	3	3 125	3.2	49	56	2
PH 21/50	10	5	4 348	4.4	37	67	2
FM 257	10	5	20 408	20.8	34	143	5
PH 4104	10	5	20 408	20.8	34	143	5

evident, in line with expectation when Fick's law does not apply. Therefore, it is better to reconsider the absorption curves.

The point of saturation which is reached at a given lag time can be calculated (Table 3). It is remarkable that these saturation values are in the same order of magnitude. Hence, it is clearly possible to use the $A/A_{\max}$ vs $\sqrt{t}$ absorption plot as a means of discriminating between the different closures. In Table 3, $1/k$ values are also given. It can be seen that L is reasonably well correlated with $1/k$.

Regarding the permeation data in Table 2, it is proposed to apply Fick's first diffusion law, using k^2 as an estimate for D. Under storage conditions of 40°C-95% RH (i.e. constant Δc), and for equal size of the closures (i.e. constant Δx), only D varies. From Tables 1 and 2, one can see that a close correlation exists between water permeation and D under the conditions 40°C-95% RH. The best rubbers in this respect are FM 257 and PH 4104. Remarkably, these rubbers have the capacity to take up large amounts of water. Clearly, this does not negatively interfere with the barrier properties.

Conclusions

Permeation through the closures is highly unpredictable owing to the concentration dependency of the diffusion coefficient D. D increases strongly with increasing RH. New types of rubbers can be evaluated with respect to their barrier properties by means of the absorption profiles under stress conditions such as 40°C-95% RH. Thus, one does not require to make a selection on the basis of laborious permeation experiments. It has been shown that the capacity to take up a large amount of water is not necessarily an indication that the permeation is high. Here, the diffusion coefficient can be obtained from the absorption curve.

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