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Design and use of an apparatus for measuring diffusion through glycerogelatin films

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Abstract

The diffusion of ethanol into and through soft gelatin films analogous to capsule shell formulations during the drying process has been investigated using a specially designed diffusion cell. Using microcomputer-controlled sampling, it was possible to monitor the diffusion through films at regular intervals for periods of 24 h and longer. Films having moisture contents in the range 4.5–42% w/w were investigated. The moisture content of the glycerogelatin soft gelatin capsule shell formulations has an important influence on the diffusion process; the higher the moisture content, the more rapid the diffusion of ethanol.

Keywords: Glycerogelatin; Ethanol diffusion; Moisture content; Soft gelatin film

1. Introduction

1.1. Diffusion in soft gelatin capsules

Whilst investigating the release of drugs from soft gelatin capsules, Armstrong et al. (1980, 1984a) noted differences between the release from filled soft gel capsules compared to that from unencapsulated solutions for a variety of model compounds. This was shown to be due to the diffusion of the model drugs into the capsule shell. The transfer was governed principally by the partition coefficient of the solute between the capsule fill and capsule shell (Armstrong et al., 1982). The transfer to the shell began as soon as the capsules were formed and reached final equilibrium during tray-drying (Armstrong et al., 1984b).

Armstrong et al. (1986) investigated the diffusion process using glycerogelatin columns having an analogous composition to freshly formed capsules. The viscosity of the fluid in the interstices of the gel matrix was the most important factor influencing the diffusion process (Gebre-Mariam et al., 1989).

There are certain limitations to this work. In the first place all the model compounds studied had molecular weights greater than 100 and are solids at room temperature. Secondly the method used by Armstrong et al. (1986) and Gebre-Mariam et al. (1989) was limited to the investigation of diffusion in glycerogelatin gels having

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moisture contents very similar to freshly filled soft gelatin capsules (approx. 40% w/w).

Whilst it has been shown by Armstrong et al. (1984b) that the transfer process starts as soon as the capsules are filled, it is also known that the transfer process continues during the subsequent drying of the finished capsules during which time the water content of the capsule shells falls to 8–10% w/w. This present report describes studies on migration in more rigid dried films, analogous to finished capsule shells.

2. Materials, equipment and methods

2.1. Materials

All materials were used as received from the indicated sources: Limed bone 150 Bloom Gelatin (Sanofi Bio-Industries via Messrs R.P. Scherer Ltd, having been shown to be representative of a typical batch of gelatin used in the manufacture of soft gelatin capsules), glycerol B.P. (Macarthy Medical Ltd and Evans Medical Ltd), methyl 4-hydroxybenzoate G.P.R. (BDH), absolute ethanol A.R. quality, SIN 1170 (Hayman Ltd), lithium chloride G.P.R. (BDH), magnesium chloride hexahydrate G.P.R. (BDH), sodium dichromate G.P.R. (BDH) and sodium chloride Analar (BDH).

Distilled water was employed throughout the studies reported here and was used freshly distilled.

2.2. Design of the apparatus

Soft gelatin capsules produced by the rotary die method consist of a glycerogelatin shell enclosing a liquid fill. The filled capsules are dried on trays in a stream of air. In order to simulate more closely the dynamics of a filled capsule, diffusion through a glycerogelatin film was selected for this investigation. The choice of carrier solvent is important in the formulation of soft gel capsule products. In general, solutions are more easily processed and filled than are suspensions, and there may be advantages of efficacy and speed of onset of action of a drug when formulated as a water miscible solution (Serajuddin et al., 1986; Patel et al., 1989a,b). Currently, the choice of carrier solvent for use in soft gelatin capsule filling is restricted. Partly, these restrictions concern potential toxicity, but some pharmaceutically acceptable solvents diffuse out of the capsules during drying and subsequent storage.

Ethanol was selected as the model solvent since, apart from water, it has the lowest molecular weight of the pharmaceutically acceptable solvents. It is also known to diffuse readily and if a method could be found of inhibiting ethanol migration it could be of relevance to other solvents. Having chosen ethanol as the model diffusant, an analytical method was required that would measure ethanol concentrations at frequent intervals over long periods (e.g., 24 h). The equipment selected was the Lion Alcolmeter AE-D3 (Lion Laboratories Ltd, UK). This equipment is based on fuel-cell technology and may be operated in conventional 'Breathalyser' mode as used in the studies reported here, and also for headspace analysis using an alternative sampling head.

The principle of operation is similar for both sensor heads. A sample is drawn over the fuel cell element by means of a spring-loaded bellows which is released when the 'READ' button is pressed. The sensor head is reset by pressing the 'SET' button. The action of pressing the SET button collapses the bellows and there is a mechanical latch to hold the bellows in the 'cocked' position until released by pressing the READ button again. This mechanical reset mechanism influenced the design of the automatic sampling interface and computer program.

An important consideration in the use of a fuel cell detector for repetitive sampling is the time taken for the fuel cell output to return to zero; the higher the concentration the longer the regeneration time. The minimum sampling interval for automatic sampling with this equipment was 10 min. It was anticipated that samples would be taken every 10 min over several hours. Because of the mechanical reset and latch system used in the Breathalyser sensor head a solenoid system interfaced via the parallel USER port to a BBC Model B Microcomputer was used. A sim-

ple pivoted lever device was used to convert the solenoid 'pull' action into a push. The final design and construction of the lever system were carried out by the Engineering Department, R.P. Scherer Ltd. A return spring was included in the SET mechanism to ensure the push-rod did not interfere with the correct operation of the bellows during sampling. A rubber tip was added to the SET push-rod to reduce the mechanical shock and prevent damage to the sensor head. Full details of the control apparatus, interfacing and associated computer program are given elsewhere (Moreton, 1992). All results were recorded on a printer and chart recorder and eventually stored on computer disc.

The Alcolmeter, when used in the Breathalyser configuration, has an effective analytical range of approx. 1–150 μg % w/v (μg per 100 ml), preferably 10–100 μg % w/v. The choice of diffusional cross-sectional area and air flow rate, and the analytical range of the detector are all interrelated. Based on preliminary studies using a Franz diffusion cell it was determined that a cross-sectional area of at least 10 cm^2 would be necessary using air flow rates from 10 to 400 ml min^{-1}.

The donor compartment was placed on top of the film with a stainless-steel support mesh to support the weight of the film and the donor phase. A PTFE washer was also included to accommodate the thickness of the support mesh. Reliable sealing of the cell was achieved using high vacuum silicone grease between the glass flanges, PTFE washer and glycerogelatin film. A schematic diagram of the diffusion cell is presented in Fig. 1.

All parts of the diffusion cell are constructed from either glass or stainless steel (either grade 316 or grade 321). An exception to this was the sampling tube for the Breathalyser sensor head supplied by Lion Laboratories and constructed from some form of polymeric material. The two parts of the cell are clamped together and the cell held in a frame constructed from aluminium sheet. The whole assembly is mounted in an insulated cabinet fitted with a heat exchange coil containing water at 22.5° C. Stirring of the receiver compartment is by means of a glass-coated

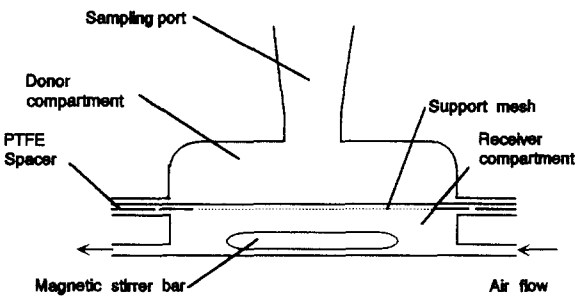

Fig. 1. Schematic diagram of the diffusion cell.

magnetic follower, with a thin smear of high vacuum silicone grease (Dow Corning) applied to the base of the compartment to allow the follower to move freely. This stirring had been shown to be effective by visualising an ammonium chloride aerosol.

Temperature was constantly monitored by using a temperature probe attached to a GP353 pH meter (EDT Instruments Ltd). The fluctuation over a 24 h period was found to be a maximum of ± 0.2° C which was considered acceptable.

Air was conditioned by blowing it over the surface of a saturated electrolyte solution. (It was not possible to bubble the air through the solution because of crystallization and blocking of the dip-tube.) The air flow rate was controlled using a constant differential gas flow controller (Porter Model VCD 1000, Jones Chromatography Ltd). In addition, and as a visual aid to flow rate adjustment, flowmeters were also used (Porter F150 series with different tubes and floats depending on the range required, Jones Chromatography Ltd). Flow rates were confirmed using a soap-bubble flowmeter.

2.3. Preparation of the films

Small scale batches (1 kg nominal batch size) of gel were prepared using a Micromelter apparatus developed and supplied by Messrs. R.P. Scherer Ltd, Swindon, UK. The formulation used in these studies was based on a limed ossein gelatin: gelatin 150 limed bone, 433.6 g; glycerol B.P., 200.1 g; distilled water, 366.3 g; total, 1000 g.

The small quantity of preservative included in some of the batches was added extra to the nominal batch total.

The basic method of preparation was developed by Messrs. R.P. Scherer Ltd. and is carried out in vacuo. The vessel was cooled to $< 18°$ C. The distilled water and glycerol were added to the vessel and degassed under full vacuum with stirring for 5–10 min. The gelatin was weighed, added to the vessel and hydrated whilst stirring under vacuum. Typically, the hydration process took 8–12 min. The temperature was raised to 99° C and maintained for 35 min, after which time the batch was deemed complete. During heating degassing was achieved by using vacuum. When complete, the gel was transferred to a hermetically sealed container which was sealed and allowed to cool and set at room temperature and then stored at $+4°$ C until needed.

Gel films were cast using a motorised plate spreader. A trough containing molten gel was passed over a glass plate. A gap to the rear of the trough governed film thickness which was also dependent on trough speed. For these studies a gap of 0.75 mm and a speed of 0.043 m s^{-1} were used throughout. The films were transferred to a humidity cabinet and conditioned above saturated electrolyte solutions (Nyqvist, 1983) for 5 days before transfer to storage desiccators containing the same saturated salt solutions until needed.

2.4. Diffusion experiments

After conditioning, the film was trimmed, its thickness measured and mounted in the diffusion cell. Air, humidified by passing over saturated electrolyte solutions as described above, was passed through the receiver compartment for 24 h prior to the start of an experiment.

Prior to the start of the diffusion experiment, the detector was calibrated using a MiniNALCO (Lion Laboratories Ltd) ethanol vapour standard at 35 μg per 100 ml. To start the experiment, 10 ml of 95% v/v ethanol were added to the donor compartment and sampling started simultaneously. The system was left running to sample continuously at 10-min intervals for a minimum of 24 h. At the end of the experiment the contents of the donor compartment were retrieved for subsequent moisture determination as were the trimmings from the film sample (prior to mounting of the sample in the cell) for subsequent moisture determination. Moisture analysis was carried out by Karl Fischer titration at 55° C using a Turbotitrator (Baird and Tatlock Ltd) and at room temperature in non-turbo mode for the receiver compartment samples.

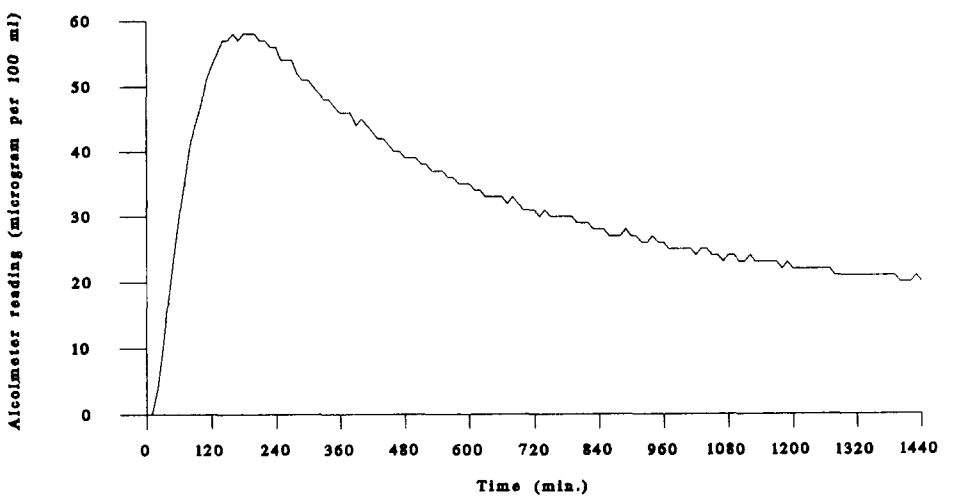

Fig. 2. Plot of Alcolmeter reading vs time for an experiment using a film conditioned above saturated NaCl solution.

2.5. Mathematical treatment of data

In the diffusion cell there is a known flow rate of air passing through the receiver compartment. The sampling interval was 10 min in all cases, and the output from the detector was calibrated to give the ethanol concentration in the air-stream in μg per 100 ml (μg % vol). Thus, the quantity of ethanol passing through the film in unit time can be calculated.

For diffusion through a film, the lag time equation of Daynes (1920) as developed by Barrer (1941) can be used to determine the diffusion coefficient. The lag time (L) is calculated by extrapolation of the steady-state portion of the flux vs time curve back to zero concentration. This can be calculated from the equation of the line of best fit for the steady-state portion of the curve. The equation developed by Daynes and Barrer is as follows:

$$L = \frac{l^2}{6D} \tag{1}$$

where L is the lag time, l dneotes the film thickness and D is the diffusion coefficient.

In 'classic' diffusion studies the contents of both the donor and receiver compartments are of the same phase, i.e., both liquids or both gases. In the experiments reported here, the donor compartment contains a liquid phase and the receiver compartment a gaseous phase. Thus, a phase change occurs across the film.

The curves from these experiment were seen to contain three distinct regions as shown in Fig. 2. There is an initial lag phase which is followed by the steady-state portion of the curve. However, after the steady-state period the flux curve is seen to deviate from the steady state and there is a gradual reduction in the flux. This is particularly evident in experiments with higher moisture contents. Since it was not certain that the underlying process responsible for these deviations was not occurring during the preceding phases of diffusion, the steady-state portion of the curve must be referred to as quasi-steady state.

Because of the phase change across the film, and also the departure from steady state, the diffusion coefficients determined by these experiments must be regarded as apparent diffusion coefficients (D'). Thus, Eq. 1 should more properly be written in the form:

$$L = \frac{l^2}{6D'} \tag{2}$$

where D' is the apparent diffusion coefficient.

The lag time is determined from a plot of the cumulative amount of diffusant appearing in the receiver compartment against time obtained by integrating the concentration vs time curve with respect to both time and flow rate. The concen-

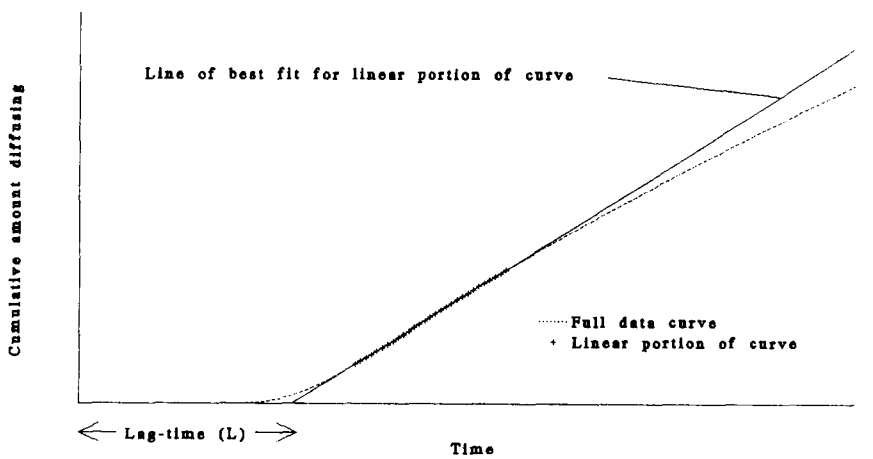

Fig. 3. Example of a diffusion curve obtained using plasticized gelatin films.

tration vs time curve is complex and integration is not straightforward. However, assuming a constant air flow rate through the receiver compartment, and having repetitive sampling at 10-min intervals, it is possible to use a mathematical approximation for the calculation of the area under the curve, the trapezium rule. The steady-state portion of the curve was identified by reference to a plot of a moving average of five of the concentration data points. Fig. 3 gives an example of such a treatment for the data shown in Fig. 2.

The diffusion process in glycerogelatin gels has been shown to be temperature dependent (Gebre-Mariam, 1988). The concept of virtual temperature is well established in the stability testing of pharmaceutical products. The problem of identifying an ambient temperature for the stability tests, which will give an equivalent rate of degradation to that which would occur during storage at the ambient temperatures prevailing in different parts of the world has been addressed by Haynes (1971), who defined the virtual temperature of a system. In simple terms, the virtual temperature is a form of 'average' temperature where the averaging is based on kinetic considerations rather than a simple arithmetic mean.

The problem of the temperature variation in these experiments is far less complex. The time span of the experiments is much shorter, and the temperature variations are much less than for the storage conditions discussed by Haynes (1971). Over such a short range of temperature fluctuations (approx. 0.4° C) the effect of temperature on the diffusion process is assumed to be linear. Accordingly, a virtual temperature was calculated for these experiments as the arithmetic mean of the temperature recorded at 10-min intervals throughout the experiment.

At the highest relative humidity it was necessary to incorporate 0.1% w/w methyl 4-hydroxy-

Table 1
Data for films prepared from gels containing 20% w/w glycerol

Virtual temperature (° C)	Moisture content (% w/w)	Film thickness (mm)	Lag time (L) (min)	Apparent diffusion coefficient (D') ($mm^2\ min^{-1}$)
Conditioned above saturated lithium chloride solution (approx. 11% RH)				
22.00	4.56	0.304	427	3.61×10^{-5}
23.00	6.44	0.305	407	3.81×10^{-5}
22.00	5.89	0.284	390	3.45×10^{-5}
Conditioned above saturated magnesium chloride solution (approx. 33% RH)				
21.50	8.72	0.361	472	4.60×10^{-5}
22.00	7.74	0.374	472	4.94×10^{-5}
22.50	9.32	0.368	437	5.17×10^{-5}
22.85	7.43	0.352	394	5.24×10^{-5}
Conditioned above saturated sodium dichromate solution (approx. 54% RH)				
22.50	19.80	0.392	234	1.09×10^{-4}
22.00	16.20	0.382	283	8.61×10^{-5}
22.60	17.30	0.404	58.9	4.62×10^{-4}
22.50	14.50	0.382	116	2.10×10^{-4}
22.40	13.20	0.368	128	1.77×10^{-4}
Conditioned above saturated sodium chloride solution [a] (approx. 75% RH)				
23.70	34.10	0.521	67.5	6.71×10^{-4}
23.60	34.00	0.559	76.5	6.81×10^{-4}
23:40	30.70	0.445	63.8	5.17×10^{-4}
Conditioned above saturated sodium chloride solution; contact side to donor phase [a] (approx. 75% RH)				
22.70	40.69	0.515	55.3	8.00×10^{-4}
22.70	41.83	0.555	44.1	1.16×10^{-3}
22.70	36.90	0.559	48.4	1.08×10^{-3}

[a] Films contained 0.1% w/w methyl 4-hydroxybenzoate as preservative.

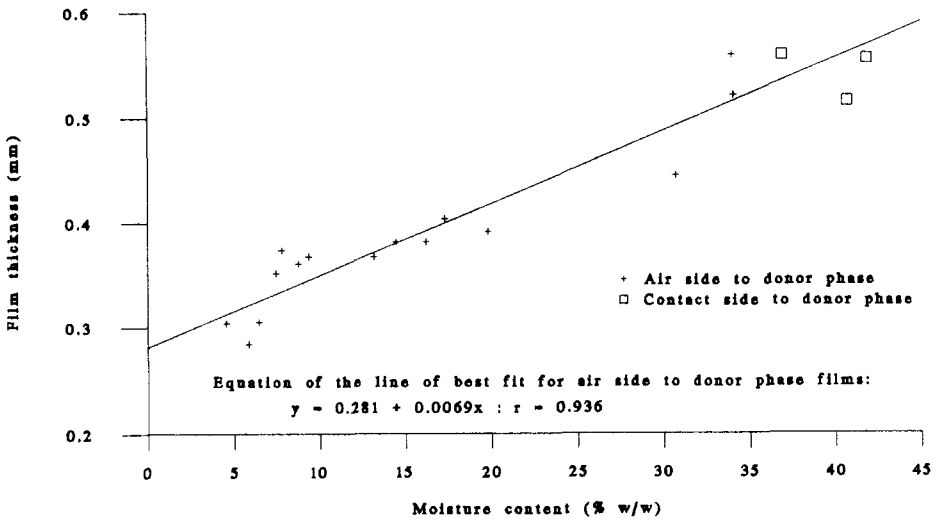

Fig. 4. Effect of moisture content on film thickness for glycerogelatin films.

benzoate into the bulk gel to prevent mould growth. The preservative was assumed to have a negligible effect on ethanol diffusion.

3. Results and discussion

3.1. Effect of film moisture content on diffusion

The results presented in Table 1 include films having moisture contents in the range 4.5–42% w/w.

The virtual temperatures for these experiments ranged from 21.5 to 23.7° C. This variation reflects the general variation in laboratory ambient temperature during the course of this work and confirmed there were no substantial differences in temperature during the series of experiments.

Film thickness varied from approx. 0.28 mm for one of the drier films to approx. 0.56 mm for one of the more moist films. There was a general increase in film thickness with increasing moisture content. This is shown in Fig. 4. The correlation coefficient of the line of best fit was 0.936 ($p < 0.001$).

The apparent diffusion coefficients obtained were in the range 3.45×10^{-5}–1.16×10^{-3} mm^2 min^{-1}. The relationship between apparent diffusion coefficient and film moisture content was found to be curvilinear and is presented in Fig. 5 as a semi-logarithmic plot.

The correlation coefficient for the line of best fit was 0.914 ($p < 0.001$), which permits the conclusion that diffusion is controlled to a large extent by the water content of the film. The correlation coefficient also provides information on the fraction of the variance that is not accounted for by the regression line (Snedecor and Cochran, 1980):

$$\frac{s_{y.x}^2}{s_y^2} = \frac{(n-1)(1-r^2)}{(n-2)} \tag{3}$$

where n is the number of data points and r denotes the correlation coefficient.

It therefore follows that the fraction of the variation accounted for by the regression is given by:

$$1 - \left(\frac{s_{x.y}^2}{s_y^2} \right) \tag{4}$$

For the data presented in Fig. 6 with $n = 15$ and $r = 0.914$, the fraction of the variance not associated with the regression is 0.177, thus the fraction of the variance associated with the re-

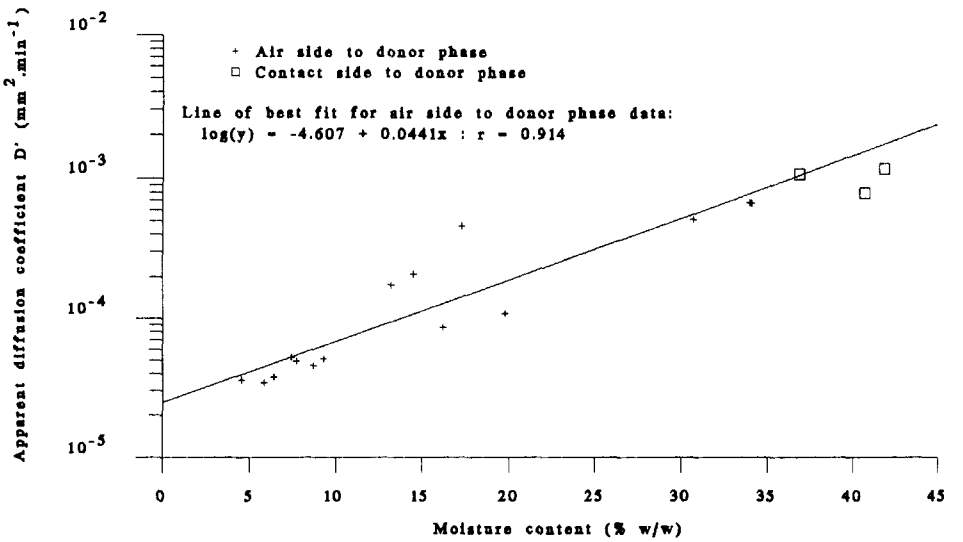

Fig. 5. Variation of apparent diffusion coefficient (D') with moisture content for glycerogelatin films.

gression is 0.823, i.e., 82.3% of the variance is accounted for by the regression.

3.2. Effect of film orientation on the diffusion process

During the preparation of films, the molten gel is cast onto a cold plate-glass platen, and allowed to set and cool before being placed on a glass shelf for conditioning in a humidity cabinet. Thus, during setting and cooling, the heat is extracted principally from the lower surface in contact with the platen. During conditioning, moisture exchange (loss) occurred from the upper surface of the film. Anderson et al. (1973) have reported a 3–4-fold difference for the diffusion of urea

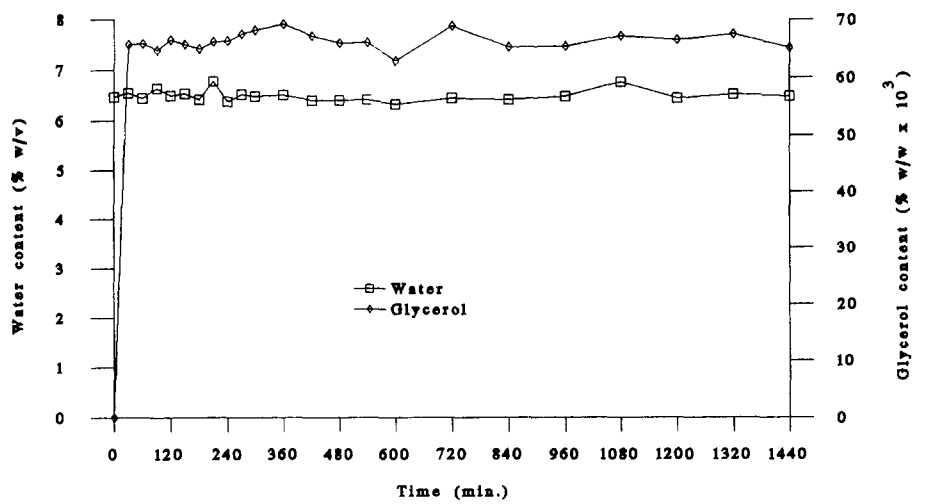

Fig. 6. Variation in donor phase water and glycerol contents for an experiment using a film conditioned above saturated $MgCl_2$ solution.

through polymethacrylate-polymethylmethacrylate co-polymer films depending on film orientation, and so it was important to establish if film orientation played a role in the diffusion process in glycerogelatin films.

The data for this investigation are also included in Table 1 and Fig. 5. All differences in the apparent diffusion coefficients can be explained in terms of differences in the moisture contents of the films and thus film orientation appears to have no effect. Nevertheless, it was considered prudent to maintain a constant orientation and in all subsequent experiments the film surface which had been exposed to the conditioning atmosphere was placed in contact with the donor phase when mounted in the cell.

3.3. Form of the curves obtained from the diffusion experiments

The departure of the diffusion process from steady state implies some change in the film or diffusant which takes place during the experiment. There are several explanations which might account for the deviation from steady-state diffusion:

(a) Development of non-sink conditions in the receiver compartment.
(b) Spontaneous changes in the film structure which are a consequence of the nature of gelatin, such as the formation of further, or the extension of existing, helical regions.
(c) Changes in the water content of the film.
(d) Changes in the ethanol concentration in the donor phase.
(e) Some interaction between the film and the ethanol diffusing through it.
(f) Combinations of the mechanisms listed above.

The development of non-sink conditions in the receiver compartment is most unlikely, since the air was not recycled after passing through the detector.

The composition of the donor phase was monitored during a diffusion experiment using a film conditioned above saturated magnesium chloride solution. The variation in moisture contents and glycerol contents of the donor phase over the course of an experiment (24 h) are presented in Fig. 6. During the course of the experiment (24 h), there were no observable trends in the moisture content of the donor phase samples. Within the limits of experimental error, the concentration of water in the donor phase remained constant at approx. 6.5% w/v.

On the basis of this experiment it was felt that diffusion of water into the donor phase was not a problem for films conditioned above saturated magnesium chloride solution. However, the effect would be expected to be greater with films having higher moisture contents. The phenomenon was monitored by measuring the moisture contents of the material recovered from the donor compartment at the end of the diffusion experiments. The samples from the donor phases from diffusion experiments using films conditioned above saturated sodium chloride solution were found to have higher moisture contents (approx. 12% w/w) than those for similar films conditioned above saturated magnesium chloride solution (approx. 8% w/w). This relatively modest increase in moisture content of the donor phase was believed to be acceptable.

The fact that the experiment also showed deviation from steady-state diffusion whilst showing no change in the water concentration in the donor phase suggests the deviations from steady state are not due to changes in the ethanol concentration gradient across the film.

The glycerol content of the donor phase increased by the time of the first sample (30 min) from 0 to approx. 0.065% w/v but remained constant thereafter. This was attributed to glycerol being 'stripped' from the surface of the film.

Gelatin is denatured by ethanol although the interactions between gelatin and the lower alcohols are not straightforward with methanol behaving somewhat differently to the other low molecular weight monohydric alcohols. Saunders (1937) and Naryshkina et al. (1983) have shown that ethanol denaturation of gelatin is reversible.

Whilst Herskovits et al. (1970) have shown that ethanol can bring about the denaturation of globular proteins, its effects on gelatin appear to be rather different. Dolinnyi and Izmailova (1978) have reported that ethanol can stabilize collagen

and promote the formation of collagen-like helices in aqueous solutions of gelatin. Some form of interaction between ethanol and gelatin could be occurring which gives rise to a gradual change in the structure of the gelatin film, e.g., enlarged regions of helical cross-linking which could increase the tortuosity of the films thereby retarding diffusion.

Spontaneous changes in the structure of the films, not induced by either interaction with ethanol or moisture loss, might also be occurring. However, the films were conditioned for at least 5 days in a humidity cabinet, followed by at least 2 days in a desiccator, stored above the relevant saturated salt solution, before in situ conditioning for 24 h prior to the start of the experiment. It is believed that any spontaneous changes in the film which might be expected to occur would have already largely taken place by the time the experiments commenced. Evidence is available which suggests that the changes in the mechanical properties of films, which are known to occur in freshly cast films, do continue for some time after casting. However, the process follows a form of exponential decay and after 3–4 days is virtually complete for glycerogelatin films (Messrs R.P. Scherer Ltd, private communication). Since a minimum of 8 days total conditioning occurred prior to the start of each diffusion experiment, it is believed the form of the deviation observed would be substantially different, particularly for films having higher moisture contents, if the deviations were due to the spontaneous changes not induced by either ethanol interaction or moisture loss.

The nature of the deviation of the flux curves from the quasi steady-state region appears to suggest the reduction in diffusion is not constant, and that there is a further steady-state region. This is best illustrated by reference to Fig. 2 in which it can be seen that the concentration of ethanol in the receiver compartment effluent airstream appears to be approaching a constant in the latter stages of the experiment. The rate at which this second quasi steady state is achieved appears to be related to the moisture content of the film in as much as the process is more rapid with films having a higher moisture content, and shorter lag times, and shorter apparent steady-state regions as a consequence.

Having regard to the time scales involved, the reduction in flux is believed to be the result of changes in the structure of the of the film as a result of the interaction between ethanol and gelatin, possibly linked with minor changes in the film moisture content. However, further work would be necessary to confirm this.

A mechanism whereby the triple-helical, cross-linking regions might be extended in the presence of ethanol could be via some form of 'phobic' interaction, such that ethanol induces a change in the interstitial continuum. In the vicinity of the gelatin fibrils, i.e., the solvation layer surrounding the fibrils, it is suggested this interaction causes the fibrils to re-orientate to a structure which is less energetic, i.e., triple helix formation, and which will reduce the contact between the ethanol and the gelatin. The constraints imposed by the fact that it is a cross-linked gel structure, and therefore the fibril chains are not completely free to rotate, would serve to limit the process in two ways. The rate of re-orientation would be slower than in dilute solution, and as the triple-helical region got larger, it would be progressively more difficult for the process to continue, which would be consistent with a further apparent steady-state period. An equilibrium of forces is thus created; the energy lowering achieved by the re-orientation is no longer sufficient to overcome the resistance imposed by the restrictions on chain movement.

4. Conclusions

The use of the diffusion cell has allowed the investigation of the diffusion of ethanol in glycerogelatin films having moisture contents in the range 4.5–42% w/w. This has permitted the investigation of diffusion in films analogous to the finished, dried capsule shells.

There was a curvilinear correlation between apparent diffusion coefficient and film moisture content; the higher the film moisture content, the higher the apparent diffusion coefficient.

As anticipated film moisture content was also correlated with film thickness.

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