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The effect of film composition on the diffusion of ethanol through soft gelatin films

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Abstract

Changes were made in the composition of plasticized gelatin gels, analogous to those used in the manufacture of soft shell capsules, and the effect of these changes on the diffusion of ethanol through the films was investigated. The substitution of glycerol by higher polyols such as xylitol, sorbitol and lycasin (hydrogenated corn syrup) caused a significant reduction in the diffusion process, as indicated by a reduction in the apparent diffusion co-efficient. When allowance was made for film moisture content, a 5–10-fold reduction in the apparent diffusion co-efficient was observed with the greatest reduction occurring in films having lower moisture contents. This reduction in apparent diffusion co-efficient is believed to be due to a 'phobic' interaction between ethanol and the higher polyols which increases the energy barrier to the diffusion process. A general case is postulated whereby any diffusion process will be modified by the inclusion of 'diffusantophilic' (increased rate of diffusion) or 'diffusantophobic' (reduced rate of diffusion) components in the barrier. The implications of the changes in the formulation of the films for the filling of soft shell capsules by the rotary-die method is discussed. Attempts to modify diffusion by inclusion of solid particles or liquid crystals in the gel structure were unsuccessful, as was the replacement of part of the gelatin by hydrolyzed gelatin. © 1998 Elsevier Science B.V.

Keywords: Soft gelatin film; Diffusion; Plasticizer; Polyols

1. Introduction

In a previous report (Moreton and Armstrong, 1995), methods were described for the preparation of glycerogelatin films, analogous to soft gelatin capsule shells and the investigation of the diffusion of ethanol through such films. In summary,

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the results given in that report identified the moisture content of the films as having a major effect on the diffusion process. Ethanol diffuses quite readily through conventional soft gelatin capsule shells, and the rate is such that most of the ethanol will have disappeared by the end of the drying phase in the manufacture of the capsules.

Ethanol is a useful co-solvent in its own right, but it was chosen for study because it is the smallest generally accepted pharmaceutical solvent molecule other than water. If methods could be identified which would reduce the diffusion of ethanol though soft gelatin capsule shells, such methods might allow the easier manufacture of soft gelatin capsule formulations containing ethanol. Furthermore any insights into the critical formulation parameters for ethanol might have applications for the use of other pharmaceutically acceptable solvents in soft shell capsules.

Water and gelatin are effectively fixed components of a soft gelatin capsule shell. In addition the shell contains a plasticizer and may contain other components such as titanium dioxide, colored lakes and trace amounts of preservatives. The plasticizer, most often glycerol, is normally present in relatively high concentrations (about 20% of the mass of the bulk gel). It is important to understand that glycerol interacts with the gelatin in the presence of water to give the unique properties of soft gelatin gels (Reich, 1994). Any modification to the soft gel formulation which would interfere with the complex synergistic interactions between the gelatin, glycerol and water could potentially both modify the diffusion process and affect the manufacture of the finished capsule.

The objective of the work reported here was to investigate the effect of changes in the soft gelatin shell formulation on the diffusion of ethanol through films prepared by methods analogous to those used in capsule manufacture, thereby identifying a means by which the diffusion of ethanol could be reduced. It is assumed that diffusion takes place via liquid-filled pores in the gel structure. Four categories of shell-formulation change were selected which might modify the diffusion process for ethanol.

1. The incorporation of a liquid crystal system into the film.
2. Physically blocking the pores by the incorporation of solid particles as a dispersed phase in the gel. Titanium dioxide, talc and fumed silica were used, all of which are pharmaceutically acceptable, and represent three chemically and physically different types of particles. The pore size of glycerogelatin gels has been estimated to be about 500 nm (Migun and Prokhorenko, 1987). The titanium dioxide and talc particles are larger than this, but Aerosil 200 particles are considerably smaller (Handbook of Pharmaceutical Excipients, 1994).
3. The inclusion of a hydrolyzed gelatin derivative into the film. Armstrong et al. (1990) observed that gelatin degradation products appeared to influence the diffusion of 4-hydroxybenzoic acid in soft gelatin gels. These workers suggested that the products of partial hydrolysis, being water soluble, would be found in the pores of the gel structure, increasing the viscosity of the aqueous fluid filling the pores, and hence retarding diffusion.
4. The replacement of glycerol (1,2,3-propane triol) by higher polyols e.g. xylitol (1,2,3,4,5-pentane pentol) and sorbitol (1,2,3,4,5,6-hexane hexol). Soft gelatin capsules can be prepared using sorbitol in place of glycerol (Stanley, 1986), though Reich (1996) has shown that the type of sorbitol used can have far-reaching effects on the properties of the capsule shell.

2. Materials, equipment and methods

2.1. Materials

The 150 Bloom limed bone gelatin, glycerol, methyl-4-hydroxybenzoate, absolute ethanol, lithium chloride, magnesium chloride hexahydrate, sodium dichromate and sodium chloride were as described previously (Moreton and Armstrong, 1995). In addition for these studies, polyoxyethylene sorbitan monopalmitate (Polysorbate 40, B.D.H., UK), isopropyl myristate (Crodamol IPM, Croda, UK), Talc B.P. (Evans Medical, UK), Aerosil 200 (Degussa, UK), titanium dioxide food grade (R.P. Scherer, UK), Byco C

(Croda Gelatins, UK), xylitol food grade (Xyrofin, UK), sorbitol (Neosorb 60, Roquette, UK) and Lycasin 80/85 (Roquette, UK) were also used as received. The water used throughout these studies was freshly distilled and cooled.

2.2. Equipment

The equipment used for the preparation of the gels, casting of the films, conditioning of the films, the diffusion cell and the detector (Lion AE-D3 Alcolmeter, Lion Laboratories, Barry, UK) have all been described in a previous report (Moreton and Armstrong, 1995).

2.3. Methods

The basic gel formulation around which all the modifications were based was gelatin (150 Bloom limed bone) 433.6 g, glycerol B.P. 200.1 g and water 366.3 g. The preservative (methyl-4-hydroxybenzoate, 0.1% w/w) included in the gels conditioned at about 75% relative humidity was added extra to the nominal batch total.

The preparation of the bulk gels incorporating Byco C was similar to the method described in the previous report (Moreton and Armstrong, 1995). For those gels incorporating dispersed solids, the solid was pre-dispersed in the glycerol–water mixture prior to incorporation into the gel mass at the hydration stage. The quantity of dispersed solid included in a given film was limited by the ability of the Micromelter equipment to process the molten gel. For those gels in which the glycerol was replaced by either xylitol or sorbitol, the polyol was prepared as a solution and used to hydrate the gelatin in a similar way to the conventional glycerol solution.

A different method was used to prepare films in which it was intended to incorporate a liquid crystal system. Firstly the liquid crystal region of mixtures of isopropyl myristate, polysorbate 40 and water was identified by constructing a ternary phase diagram and examining the different phases microscopically under crossed polarizers. Having identified the proportions required to achieve a liquid crystal system, and assuming what the moisture content would be after conditioning above a saturated electrolyte solution, the formulation of the bulk gel was calculated and the gel prepared. Unfortunately, the components of the liquid crystal system were incompatible with gelatin, with the result that the gel could not be prepared. This approach was therefore abandoned.

All the films used in the initial screening phase of this investigation were conditioned above saturated magnesium chloride solution (about 33% RH), and comparison was made with the results obtained from the conventional glycerogelatin film conditioned in the same way. Later studies with the successful formulation modifications were conducted over a wider range of moisture contents by using films conditioned over saturated sodium dichromate solution (55% RH) and saturated sodium chloride solution (75% RH).

The calculation of the virtual temperature for the diffusion experiments and the apparent diffusion co-efficients were as described previously (Moreton and Armstrong, 1995). In view of the small range of temperatures, it was concluded that there were no significant effects caused by changes of temperature in this series of experiments.

3. Results and discussion

3.1. The inclusion of dispersed solid materials

These results are presented in Table 1 and the effect of inclusion of the dispersed solid materials on the apparent diffusion co-efficient is shown in Fig. 1. For ease of comparison, data from a conventional glycerogelatin film conditioned above saturated magnesium chloride solution are also included in Table 1 and Fig. 1.

The incorporation of the three dispersed solids (4% for titanium dioxide and talc, 2% for fumed silica) had a negligible effect on the apparent diffusion co-efficient. Higuchi and Higuchi (1960) considered the effect of dispersed solids on diffusion through heterogeneous films, and suggested that a concentration of about 30% would be needed for a significant reduction of diffusion to be observed. However, such a high concentration was not possible in the present work. Allowing for

Table 1
The apparent diffusion co-efficient for ethanol through glycerogelatin films containing dispersed solid particles in the continuous phase, conditioned above saturated magnesium chloride solution (about 33% RH)

Virtual temperature (°C)	Moisture content (% w/w)	Air flow rate (ml·min^{-1})	Lag time (min)	Apparent diffusion co-efficient (mm^2·min^{-1})
20% w/w Glycerol				
21.5	8.72	26.4	472	4.60×10^{-5}
22.0	7.74	26.4	472	4.94×10^{-5}
22.5	9.32	26.4	437	5.17×10^{-5}
22.9	7.43	26.2	394	5.24×10^{-5}
2% w/w Aerosil and 20% w/w glycerol				
21.0	8.88	26.0	458	5.12×10^{-5}
23.0	8.17	25.9	387	5.58×10^{-5}
22.4	8.11	25.9	424	5.06×10^{-5}
4% w/w Titanium dioxide and 20% w/w glycerol				
23.4	7.36	39.6	556	4.99×10^{-5}
23.6	6.86	39.5	545	5.17×10^{-5}
23.4	7.19	39.7	477	4.97×10^{-5}
4% w/w Talc and 20% w/w glycerol				
22.9	7.85	39.9	500	5.01×10^{-5}
22.8	7.95	40.1	488	4.65×10^{-5}
22.5	7.01	40.0	419	4.46×10^{-5}

the loss of water in the film, the bulk gel would need to contain about 20% dispersed phase. This was not feasible with the Micromelter, which could barely cope with the gels produced in this study.

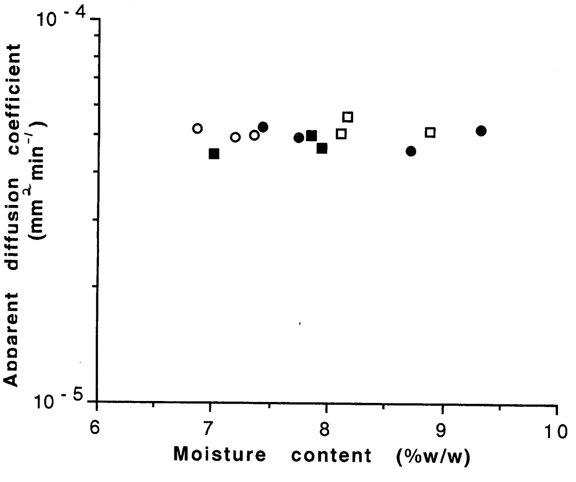

Fig. 1. The effect of solid fillers on the apparent diffusion co-efficient of ethanol through glycerogelatin films conditioned at 33% relative humidity: (●) no solid; (○) titanium dioxide 4% w/w; (□) aerosil 200 2% w/w; (■) talc 4% w/w.

Furthermore, at such a high solids loading, the structure of the gel might have been so altered as to prevent processing into capsules. Samura et al. (1993) have investigated soft gels with high solids loadings (glass and titanium dioxide) and demonstrated that mechanical properties of films such as Young's modulus were directly dependent on the concentration of dispersed solid.

3.2. Incorporation of hydrolyzed gelatin

The results of this part of the investigation are presented in Table 2. Two levels of incorporation of the hydrolyzed gelatin were used. In both cases, the amount of normal gelatin was correspondingly reduced to maintain the total gelatin material in the bulk gel at about 40% w/w. The two levels of incorporation (4 and 9% w/w) were chosen to provide a comparison with the level of incorporation of the talc and titanium dioxide (4% w/w) and also with the results obtained for 4-hydroxybenzoic acid by Armstrong et al. (1990).

Table 2
The apparent diffusion co-efficient of ethanol through gelatin films containing Byco C, xylitol or sorbitol conditioned above saturated magnesium chloride solution (about 33% RH)

Virtual temperature (°C)	Moisture content (% w/w)	Air flow rate ($ml \cdot min^{-1}$)	Lag time (min)	Apparent diffusion co-efficient ($mm^2 \cdot min^{-1}$)
20% w/w Glycerol in bulk gel				
21.5	8.72	26.4	472	4.60×10^{-5}
22.0	7.74	26.4	472	4.94×10^{-5}
22.5	9.32	26.4	437	5.17×10^{-5}
22.8	7.43	26.2	394	5.24×10^{-5}
4% w/w Byco C, 36% w/w gelatin and 20% w/w glycerol in the bulk gel				
22.2	8.28	32.2	439	4.92×10^{-5}
22.9	8.30	32.1	389	5.01×10^{-5}
22.8	7.20	31.4	410	5.12×10^{-5}
9% w/w Byco C, 31% w/w gelatin and 20% w/w glycerol in the bulk gel				
22.9	9.33	31.5	449	5.22×10^{-5}
23.1	8.18	31.5	428	5.36×10^{-5}
22.8	8.10	31.6	442	5.02×10^{-5}
20% w/w Xylitol in bulk gel				
22.6	8.14	31.9	No diffusion detected	
23.1	8.00	31.3	No diffusion detected	
20% w/w Sorbitol in bulk gel				
23.3	8.82	32.0	No diffusion detected	
23.6	8.58	31.9	No diffusion detected	

Fig. 2 shows that incorporating hydrolyzed gelatin had no effect on the apparent diffusion co-efficient for ethanol. Armstrong et al. (1990) demonstrated a significant reduction in the diffusion of 4-hydroxybenzoic acid in glycerogelatin gels having moisture contents much closer to the freshly prepared gel when using a level of incorporation of about 9% w/w of the bulk gel. It would appear therefore that the factors which influence the diffusion of ethanol are not the same as those which influence the migration of 4-hydroxybenzoic acid. It is suggested that both the molecular volume and the chemical nature of the two molecules could be important in this respect.

3.3. The effect of substitution of glycerol with higher polyols

The data for this part of the investigation are also presented in Table 2. In contrast to the other formulation changes investigated, the change from glycerol to the higher polyols xylitol and sorbitol produced a marked reduction in the diffusion of ethanol. Using films conditioned above saturated magnesium chloride solution, no trace of ethanol could be detected in the receiver compartment effluent airstream. Since it has been shown that increased moisture content in glycerogelatin films made them more permeable to ethanol, it was considered of interest to ascertain if this also applied to films containing higher polyols. Xylitol was chosen for this purpose, using films conditioned at higher relative humidities (saturated sodium dichromate and sodium chloride solutions), and therefore having higher moisture contents.

The effect on the apparent diffusion co-efficient for ethanol of the substitution of glycerol by xylitol is shown in Fig. 3. For completeness, the data of comparable glycerogelatin films are also included. These data were reported previously by Moreton and Armstrong, 1995.

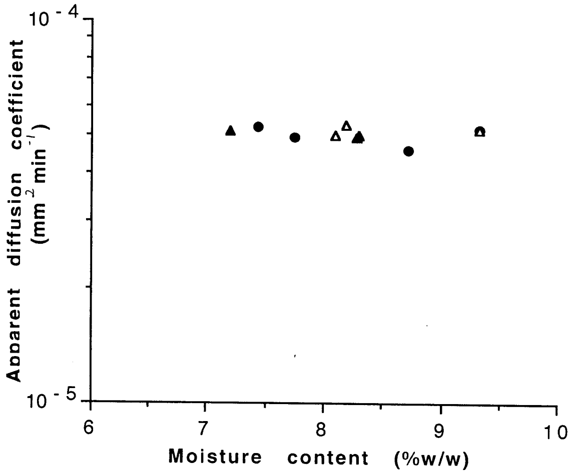

Fig. 2. The effect of the replacement of part of the gelatin in a glycerogelatin gel by Byco C on the apparent diffusion co-efficient of ethanol through films of that gel: (●) glycerogelatin gel; (▲) Byco C 4% w/w; (△) Byco C 9% w/w.

On visual examination, there would appear to be differences between the regression line for films containing glycerol and that for those containing xylitol. It is possible to compare two regression lines using analysis of co-variance (Snedecor and Cochran, 1980). This analysis compares two sets of data using three criteria:

1. Homogeneity of the residual variances by means of an F-test on the residual mean squares.
2. Comparison of the slopes of the regression lines (how close the lines are to being parallel).
3. Comparison of the elevations of the regression lines (how far apart the lines are).

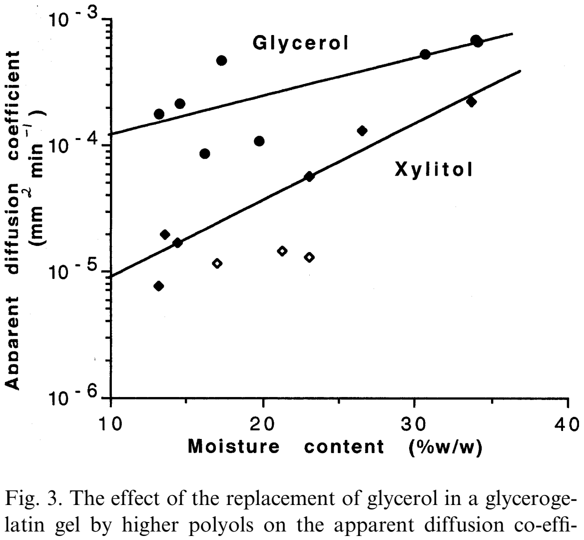

Fig. 3. The effect of the replacement of glycerol in a glycerogelatin gel by higher polyols on the apparent diffusion co-efficient of ethanol through films of that gel: (●) glycerogelatin gel; (◆) xylitol; (◇) Lycasin.

The testing is sequential, i.e. the homogeneity of the residual variances must not be significant in order to proceed to the comparison of the slopes, and the comparison of the slopes must not be significant in order to proceed to the comparison of the elevations. For the two regression lines presented in Fig. 3, the analysis of variance gave the following results: residual mean squares, $F = 57.75$ ($v_1 = 6$, $v_2 = 4$); comparison of slopes, $F = 1.907$ ($v_1 = 1$, $v_2 = 10$); comparison of elevations $F = 5.283$ ($v_1 = 1$, $v_2 = 11$).

The F-ratio for the comparison of residual mean squares was found to be highly significant ($P < 0.01$). Thus the variances are not homogeneous and the assumptions for the comparison of slopes and comparison of elevations are not met, and normally the analysis of co-variance would be halted at this stage.

However, the data pairs for the glycerogelatin films presented in Fig. 3 only include those films conditioned above the same saturated salt solutions as the xylitol-containing films. If the analysis of variance is undertaken using the complete set of data pairs for the glycerogelatin films (i.e. including films conditioned at lower relative humidities), then the F-ratio for the residual mean squares is not significant. It is believed that the high mean squares value for the glycerogelatin films in the truncated set of data pairs is caused by the comparatively wide spread of data points towards the lower end of this set of data. The influence of these three data points would be diminished in the full set of data since they would lie towards the middle of the full data set.

If the significant result for the residual mean squares is ignored (using the foregoing argument), and the analysis is continued to include comparison of slopes and comparison of elevations, then the F-ratio for the comparison of slopes is not significant, whereas the F-ratio for the comparison of elevations was found to be significant ($P < 0.05$). This would allow the conclusion that the diffusion of ethanol through films containing xylitol is significantly slower than that for glycerogelatin films.

Since xylitol and sorbitol had been so effective in modifying the diffusion of ethanol, it was believed that polyols of even higher molecular weight might be even more effective. Polyols are hydrogenated sugars. Lycasin is a hydrogenated corn syrup containing hydrogenated mono-, di- and trisaccharides, i.e. the equivalent of higher polyols. The diffusion of ethanol through films prepared using a Lycasin-containing gel was therefore investigated. The results are presented in Table 4 and Fig. 3, which for ease of comparison also includes the data for both the glycerol- and xylitol-containing films. Due to the effectiveness of the Lycasin-containing films only one set of data points could be produced, using films conditioned above saturated sodium chloride solution. This is insufficient data to allow meaningful statistical comparison. However, the results seem to show that the use of higher polyols has indeed further retarded the diffusion of ethanol.

To explain more fully these results it is necessary to understand the nature of the interactions of ethanol with glycerol, xylitol, sorbitol and other higher polyols. Glycerol is completely miscible with ethanol, whereas xylitol is only soluble in 80 parts of ethanol (Handbook of Pharmaceutical Excipients, 1994). sorbitol and Lycasin are also only sparingly soluble in ethanol, indicating a major difference between glycerol and the other polyols investigated. It is suggested that ethanol diffusion is retarded in the presence of xylitol, sorbitol and the higher polyols because of some form of 'phobic' interaction: more energy is required to overcome the diffusion barrier. The fact that ethanol is completely miscible with glycerol and thus presents a much lower energy barrier to diffusion explains why the other formulation variations had little or no effect on the diffusion process. The glycerol is providing a low energy bypass to the barrier, which is sufficient to maintain diffusion even if the pores are partly blocked by solids or the viscosity of the fluid filling the pores is increased.

Applying these observations to the general case for any diffusant, it follows that a more effective barrier will be obtained if material forming the diffusant pathway is 'diffusantophobic'. Even if some form of physical barrier component is introduced, if there is a 'diffusantophilic' component present in sufficient concentration, it will serve to create a low energy bypass to the diffusion barrier. In the studies reported here, xylitol, sorbitol and Lycasin are considered to be 'diffusantophobes' and glycerol a 'diffusantophile'.

In the specific case of the ethanol results presented here, the barrier effect appears to increase with increasing molecular weight, given that the use of Lycasin produced an even greater reduction in the diffusion co-efficient than xylitol for a given film moisture content.

Though substitution of glycerol by higher polyols causes a significant reduction in diffusion, the effects of this change in gel formulation on production of capsules must be considered. The physical properties of the shell depend on many factors, two of which are moisture content of the glycerogelatin film and its formulation (Hom and Jimerson, 1990).

During this present study, it was observed (Tables 3 and 4) that films containing the different polyol plasticizers appeared to have slightly different moisture contents when conditioned at the same relative humidity. and that these were different to the moisture contents of the glycerogelatin films investigated previously (Moreton and Armstrong, 1995). There appears to be reductions in the equilibrium moisture contents of the films with increasing polyol chain length. This could have implications for the relative hardness of the shell and the sealing of capsules produced from gel masses containing either xylitol or Lycasin. However, capsules can be prepared using sorbitol as plasticizer, and on the basis of the very limited work reported here, it would be expected that sorbitol would be as effective as xylitol. It would therefore seem appropriate to investigate the manufacture of capsules containing sorbitol as plasticizer should there be sealing problems with Lycasin or xylitol, bearing in mind the effect that the type of sorbitol can have on shell properties (Reich, 1996).

Further work by Reich (1995) has demonstrated the importance of drying rate and temper-

Table 3
The effect of change in moisture content on the apparent diffusion co-efficient of ethanol through films prepared from bulk gels containing 20% w/w xylitol

Virtual temperature (°C)	Moisture content (% w/w)	Air flow rate (ml·min^{-1})	Lag time (min)	Apparent diffusion co-efficient (mm^2·min^{-1})
Saturated magnesium chloride solution (about 33% RH)				
22.6	8.14	31.9	No diffusion detected	
23.1	8.00	31.1	No diffusion detected	
Saturated sodium dichromate solution (about 54% RH)				
23.2	13.10	1.68	2930	7.59×10^{-6}
23.0	13.64	10.3	1120	1.19×10^{-5}
23.2	14.39	10.2	1150	1.68×10^{-5}
Saturated sodium chloride solution (about 75% RH)				
23.0	26.50	27.2	273	1.30×10^{-4}
23.1	33.67	32.8	601	5.67×10^{-5}
23.3	33.67	32.2	183	2.21×10^{-4}

ature on the properties of capsule shells. Therefore, the reduced moisture contents of the xylitol- and Lycasin-containing films could also indicate that such films would dry more rapidly during filling and subsequent processing. This might be an advantage since the benefits of inclusion of the higher polyols appear to be increased at reduced moisture contents and quicker drying could therefore be beneficial to the integrity of the fill formulation.

Table 4
The effect of change of polyol plasticizers conditioned above saturated sodium chloride solution (about 75% RH) on the apparent diffusion co-efficient of ethanol

Virtual temperature (°C)	Moisture content (% w/w)	Air flow rate (ml·min^{-1})	Lag time (min)	Apparent diffusion co-efficient (mm^2·min^{-1})
20% w/w Glycerol in the bulk gel[a]				
23.7	34.1	200	67.5	6.71×10^{-4}
23.6	34.0	199	76.5	6.81×10^{-4}
23.4	30.7	198	63.8	5.17×10^{-4}
20% w/w Xylitol in the bulk gel				
23.0	26.5	27.2	273	1.30×10^{-4}
23.1	23.1	32.8	601	5.67×10^{-5}
23.3	33.67	32.2	183	2.21×10^{-4}
20% w/w Lycasin in the bulk gel				
23.5	17.00	28.8	2670	1.16×10^{-5}
23.7[a]	21.30	8.20	1870	1.47×10^{-5}
23.2[a]	23.10	8.26	2370	1.32×10^{-5}

[a] 0.1% w/w Methyl-4-hydroxybenzoate included in the bulk gel as a preservative.

4. Conclusions

The inclusion of solid particles in glycerogelatin films did not cause any reduction in the diffusion of ethanol through such films. This can be explained by the fact that the concentration of dispersed phase in these films was too low to achieve the desired effect (Higuchi and Higuchi, 1960) and also because these films contained glycerol which acted as a bypass to the diffusion process. The diffusion of ethanol through films containing partially hydrolyzed gelatin was also not reduced.

The rate of diffusion of ethanol through films in which the glycerol was replaced by higher polyols (xylitol, sorbitol and Lycasin) was reduced significantly. It would seem that besides the physical barriers discussed by Higuchi and Higuchi (1960), it is possible to create what might be termed a thermodynamic barrier to diffusion by means of a 'phobic' interaction. Alternatively it would seem that the 'particles' of the heterogeneous films had been reduced in size to molecular dimensions by use of a film component incompatible with the diffusant.

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