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SOLUTE MIGRATION FROM OILY SOLUTIONS INTO GLYCEROL-GELATIN MIXTURES

N. Anthony Armstrong, Kenneth C. James, Debra Collett and Marion Thomas.

Welsh School of Pharmacy, University of Wales Institute of Science and Technology, PO Box 13, Cardiff, UK.

ABSTRACT

A new technique is reported for the study of migration of solutes from solution in oil to the glycerogelatin walls of soft capsules. The oily solution is applied to the top of a glycerogelatin column contained in a truncated disposable plastic syringe. The column is then extruded from the syringe, cut into slices, each slice analysed and diffusion coefficients calculated. The technique was validated by using bases of differing viscosity, and was used to study the effect of phenolic compounds and polysorbate on the permeability of glycerogelatin bases.

INTRODUCTION

The soft gelatin capsule is a widely used dosage form, particularly for oils and drugs which are to be dissolved in non-polar solvents. A number of advantages have been claimed for the soft gelatin capsule in terms of bioavailability.[1]. However it was shown by

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Armstrong et al [2] that considerable transfer from the oily solution to the capsule shell could take place. Further work showed that the degree of migration was dependent on the solute and the oily solvent, and that most migration took place during the drying stage of the manufacturing process [3].

It was considered of interest to study the uptake process in more detail, and this publication describes a simple method for determining the rate of transfer to the glycerogelatin mixture.

MATERIALS

4-Hydroxybenzoic acid, 4-methoxybenzoic acid, glycerol BP and gelatin BP were obtained from BDH Ltd., Poole, UK, isopropyl myristate from Fluka, Basel, Switzerland and soft gelatin capsule shell mixture (Base 3) from R.P.Scherer, Swindon, UK.

METHODS

Glycerol suppository base (Base 1) and a more viscous mixture (Base 2) were prepared as directed in the British Pharmacopoeia, 1980. Base 3, as used for the preparation of soft gelatin capsule shells, was obtained from R.P.Scherer Ltd.

The moulds for the columns were prepared from 5ml plastic disposable syringes (Plastipack, Becton Dickenson Ltd, London, UK). The minimum length of the tapered end of the barrel was cut off to leave a cylinder. This was then mounted vertically with the cut end uppermost, the plunger being in place, but fully withdrawn. The molten base was then poured carefully into the barrels up to approximately 2 cm from the cut end, giving a column about 4 cm long, and allowed to set. 1ml of an isopropyl myristate solution of the solute was then pipetted on to the top of the column, the whole covered with protective film and allowed to stand at room temperature. At convenient intervals of time, a column was selected for examination.

TABLE 1

Composition of glycerogelatin mixtures used

Base No	Glycerol	Gelatin	Glycerol/Gelatin ratio	Water
1	4.4	0.9	5	1.0
2	6.0	3.0	2	1.0
3	0.6	1.0	0.6	1.0

The solution was poured off the top of the column, and any remaining film of solution inside the barrel removed with tissue paper. The barrel was then mounted horizontally over a metal rule, and the column extruded from the barrel by pressure on the plunger. 1mm slices were sequentially removed from the column as extrusion proceded. The first slice was discarded, and the remainder were separately weighed, and dissolved in 0.1M hydrochloric acid for spectrophotometric assay.

Blank determinations, using glycerogelatin slices which had not been exposed to a solute, were used as a control. The reproducibility of these data also demonstrated the homogeneous nature of the columns.

RESULTS AND DISCUSSION

The technique was validated by using it to study the uptake of 4-hydroxybenzoic acid by glycerogelatin from isopropyl myristate solution. 4-hydroxybenzoic acid has been shown by Armstrong et al to be taken up by the shell to a very large extent when its solution in isopropyl myristate is encapsulated in a soft gelatin capsule [3]. Three glycerogelatin mixtures were used, their composition being given in Table 1. Base 1 is Glycerol Suppository Base, BP, and base 3 is the shell formulation for soft gelatin capsules.

Eversole and Doughty [4] studied the diffusion of molecules and ions in a motionless diffusion medium. They found that movement of the particles could be expressed by Equation 1.

$$\log c = \log c_o - \frac{x^2}{2.303 \times 4Dt} \quad \text{.....(1)}$$

where c is the concentration at a distance x from the junction with the original solution, whose concentration was c_o,
t is time and
D is an apparent diffusion coefficient.

Thus a graph of log c against x^2 gives a straight line of slope $1/9.212Dt$ and intercept c_o. This equation assumes that the original concentration does not change throughout the period of diffusion. In the present case, this will not necessarily be true, as the rate at which the solute is transferred from the oily phase to the top of the glycerogelatin column will depend on the distribution coefficient of the solute between isopropyl myristate and the column.

Figure 1 represents the migration of 4-hydroxybenzoic acid in glycerogelatin base 1 over periods up to 333 hours. Slopes of the lines, intercepts and correlation coefficients are given in Table 2. The experiments involving short time intervals give steeply sloping lines, and the gradient then decreases with increasing exposure time until it becomes relatively constant at about 0.3 log moles m^{-2}. It is suggested that the predominating factor in the earlier experiments is the transfer of solute to the column. Steady state transfer is then reached, and the solute can then diffuse through the column at a more or less constant rate. It is of interest to note that the intercepts do not differ greatly, and correspond to a mean calculated value of c_o of 0.033 molar. As the original concentration of 4-hydroxybenzoic acid in isopropyl myristate was 0.036 molar, this indicates that equilibrium between the isopropylmyristate solution and the glycerogelatin column is quickly established, and diffusion through

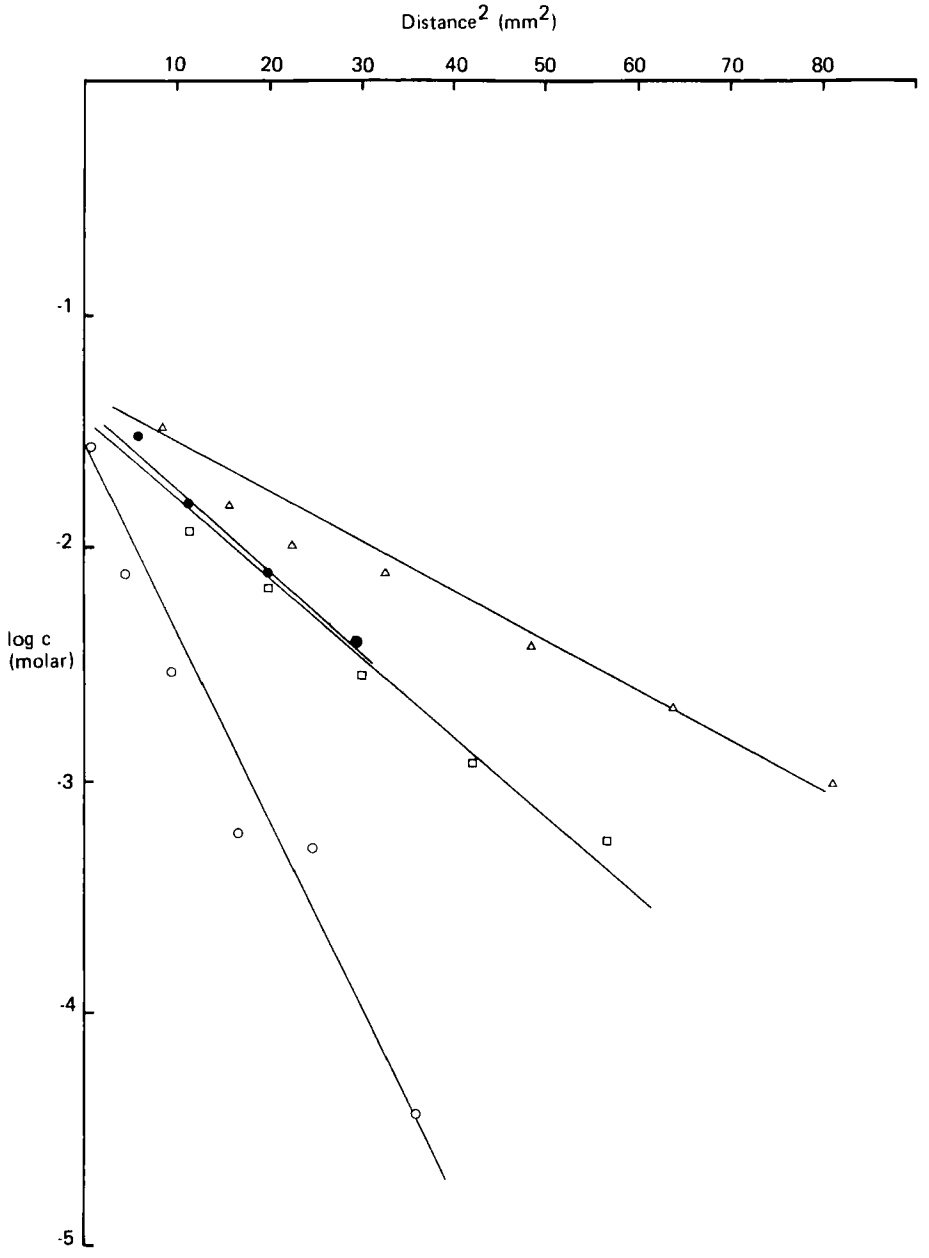

FIGURE 1

The migration of 4-hydroxybenzoic acid in low viscosity glycerogelatin columns (Base 1)

(○ , 54.5h; □ , 150.5h; ● , 238h; △ , 333h).

TABLE 2

The migration of 4-hydroxybenzoic acid in low viscosity glycerogelatin columns (Base 1): slopes, intercepts and correlation coefficients derived from Figure 1.

Time (h)	Slope ($-\log$ mol m^{-2}) ($\times 10^8$)	Intercept (log mol)	Correlation coefficient
54.5	7.26	-1.54	.971
150.5	3.43	-1.44	.987
238	3.47	-1.40	.993
333	1.97	-1.34	.992

the column rather than across the interface is the rate-determining step. Comparison of the extrapolated value of 0.033 molar to the intial concentration in isopropyl myristate of 0.036 molar indicates that about 11/12, or approximately 90% of the solute has migrated to the glycerogelatin column. It is of interest to note that Armstrong et al [3] found an identical degree of migration of 4-hydroxybenzoic acid to soft gelatin capsule shells from an encapsulated isopropyl myristate solution.

It would be expected that if diffusion were allowed to continue for a much longer time, the slope of the line would decrease further. The column is not of infinite length, and so there would come a time when solute would reach the distal end of the column. Non-sink conditions would then prevail, and diffusion would then continue at an ever-decreasing rate until a uniform concentration of solute was attained throughout the whole length of the column. However none of the slices used in this study were taken from within 20 mm of the bottom of the column, and so this factor can be disregarded.

The effect of viscosity on the diffusional process can be seen in Table 3, which shows the relationship between the apparent diffusion coefficient and exposure time for Bases 1 and 2. Because the solute

TABLE 3

Diffusion of 4-hydroxybenzoic acid and 4-methoxybenzoic acid through glycerogelatin columns.

Apparent diffusion coefficient (m^2s^{-1})					
Exposure time (h)	4-Hydroxybenzoic acid Base 1	Base 2	Exposure time (h)	4-Methoxybenzoic acid Base 1	Base 2
54.5	7.62		69	1.88	
77		2.46	92	3.60	
95		3.41	162.5	2.90	
150.5	5.84		213		0.51
164		1.98	259	3.58	
238	3.65		331		1.59
263		3.42	405		1.30
333	4.59				

has greater difficulty in diffusing through the column as the viscosity of the latter increases, the slope of the concentration gradient is steeper, and at any given time, the amount diffused is less in moving from Base 1 to Base 2. The difference between apparent diffusion coefficients for Base 1 and Base 2 is significant for $P^1=0.95$ as calculated by the Student's t test.

The technique has been used to investigate if the presence of phenolic compounds has any effect on the gel structure. Marriott and Kellaway [5] suggested that phenolic compounds disrupted gelatin gel structures. If this is so, then the viscosity of the glycerogelatin columns would decrease, and hence migration would accelerate.

Comparison of diffusion coefficients derived from the slopes obtained with 4-hydroxybenzoic acid and 4-methoxybenzoic acid show that at any given time, the coefficients obtained with 4-methoxybenzoic acid are significantly less than those of 4-

hydroxybenzoic acid. (P^1=0.95). Due to the lower solubility of 4-methoxybenzoic acid than 4-hydroxybenzoic acid in water, the partition coefficient is less favorable for transfer to the polar phase. Armstrong et al [6] quote partition coefficients between isopropyl myristate and water of 0.545 for 4-hydroxybenzoic acid and 8.720 for 4-methoxybenzoic acid. However, once either solute has been transferred to the aqueous phase, migration should proceed in an identical manner, affected only by the molecular size if the gel structure remains intact in both cases. A slight decrease in diffusivity with 4-methoxybenzoic acid would be expected due to its greater molecular size. Florence and Attwood [7] quote a reduction in diffusion coefficient of about 6% for an increase of 17 in the molecular weights of aromatic acids, and so a similar reduction might be expected in this case. It must therefore be concluded that the phenolic group does have an effect on the viscosity of the glycerogelatin.

Surface active agents are sometimes incorporated into the oily contents of soft gelatin capsules [8]. It is suggested that they facilitate break-up of the oil into small droplets after ingestion and shell disruption, though Armstrong et al [9] could find little evidence of this in vivo. A disadvantage associated with the use of surface active agents in soft gelatin capsules is the increased incidence of leakage There are two possible causes for this. The surfactant may affect the shell in some way as to increase its permeability. Alternatively it may act as a wetting agent, increasing oil penetration through pores already present in the shell but which are too small to permit passage of the oil

The technique described in this communication has also been used to investigate this point. It is highly unlikely that the glycerogelatin columns have pores running through their whole length, and so if any increased migration is detected, it is almost certainly due to an interaction with the surfactant increasing the permeability of the glycerogelatin column.

Table 4 shows the effect of three concentrations of polysorbate 80 at three time intervals on the calculated diffusion coefficients of

TABLE 4

The effect of polysorbate 80 on diffusion of 4-hydroxybenzoic acid through glycerogelatin columns

Time (h)	Apparent diffusion coefficients (m^2s^{-1}) Concentration of polysorbate 80 (%w/w)			
	0	1	2	5
50	18.5	10.0	10.7	12.5
73	21.0	15.0	15.8	14.1
170	15.6	13.6	16.1	15.6

4-hydroxybenzoic acid, using a glycerogelatin mixture corresponding to that of a soft gelatin capsule shell (Base 3). In all cases, the speed of migration is reduced rather than increased in the presence of polysorbate.

Thus it must be concluded that increased leakage from soft capsules in the presence of surfactants is not brought about by increased permeability of the shell, and must thus be attributed to the wetting effect of the surfactant exacerbating leakage through pores which are already present.

Wan and Lee [10] quote the critical micelle concentration of polysorbate 80 as 0.0014%w/v in water. Thus even a concentration of 1% is considerably in excess of its critical micelle concentration, assuming that such a hydrophilic molecule will quickly migrate into the glycerogelatin column. The reduction in ease of diffusion may well be due to the presence of polysorbate as micelles, which will in turn solubilise the 4-hydroxybenzoic acid. Passage of the large molecular aggregates will be slow, and hence the apparent reduction in diffusion of the solute was observed.

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REFERENCES

1. F. S. Hom and J. J. Miskel, J. Pharm. Sci., 59, 827 (1970).
2. N. A. Armstrong, K. C. James and W. K. L. Pugh, J. Pharm. Pharmacol., 34, 5P (1982).
3. N. A. Armstrong, K. C. James and W. K. L. Pugh, J. Pharm. Pharmacol., 36, 361 (1984).
4. W. G. Eversole and E. W. Doughty, J. Phys. Chem., 39, 289 (1935).
5. C. Mariott and I. W. Kellaway, Drug Devel. Ind. Pharm. 4, 195 (1978).
6. N. A. Armstrong, K. C. James and C. K. Wong, J. Pharm. Pharmacol., 31, 627 (1979).
7. A. T. Florence and D. Attwood, "Physicochemical Aspects of Pharmacy", Macmillan, London, 1981.
8. C. W. Pouton, J. Pharm. Pharmacol., 36, 51P (1984).
9. N. A. Armstrong, K. C. James, H. Girardin, S. Bataille, A. Burch, R. L. Davies and G. M. Mitchell, Int. J. Pharm. Tech. Prod. Manuf., 4(4), 10 (1983).
10. L. S. Wan and P. F. S. Lee, J. Pharm. Sci., 63, 136 (1974).