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An apparatus for investigating drug migration into gelatin capsule shells

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Summary

An apparatus for the study of migration of a solute from its solution in a non-aqueous solvent into the walls of soft shell capsules is described. The solution is applied to the top of a glycerogelatin column contained in a truncated hypodermic syringe. After the required period of time, the column is extruded from the syringe, cut into slices, and each slice analysed . The reproducibility of the method was established by following the migration of 4-hydroxybenzoic acid from isopropyl myristate solution into glycerol suppository base, and the technique extended to soft and hard gelatin capsule bases. The influence of temperature indicated that Arrhenius type plots could be used for accelerated testing, and migration from 1-octanol, isopropyl myristate and blends of the two showed that the rate and extent of migration were dependent upon the partition coefficient.

Introduction

Drug migration into soft gelatin capsule shells from the oily contents is a factor which may influence bioavailability. Armstrong et al. (1984) have shown that considerable migration can take place, and that the process increases the availability of the drug in vitro. A novel method of following release from lipid solution into glycerogelatin bases has been described recently (Armstrong et al., 1985). The current communication describes the refinement of the procedure to improve its accuracy, and its application to soft and hard gelatin capsule shell formulations.

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Materials and Methods

Materials

4-Hydroxybenzoic acid, glycerol and gelatin were obtained from BDH, and 1-octanol and isopropyl myristate from Fluka. Glycerol Suppository Base was prepared by the method of the British Pharmacopoeia. The soft gelatin capsule base consisted of 38.5% gelatin, 38.5% water and 23% glycerol, and was prepared in the same way.

Experimental procedure

The apparatus is shown in Fig. 1. A portion of the needle end of the barrel of a 5 ml hypodermic syringe was cut off, and the remainder of the syringe used as a mould by standing it vertically with the plunger fully extended. The mould was housed in a suitable sized boiling tube, which was clamped in a constant temperature water bath.

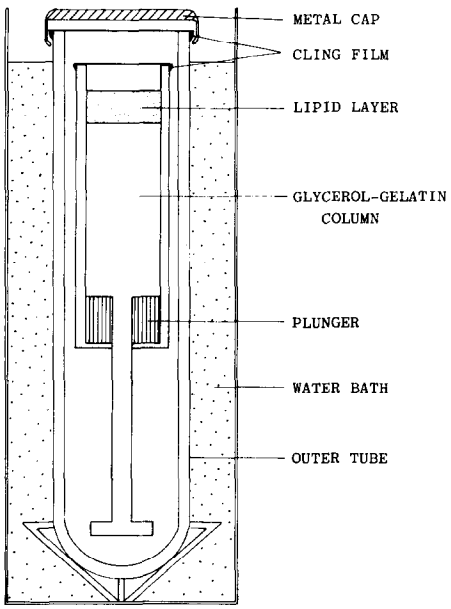

Fig. 1. Apparatus for studying migration in glycerogelatin columns.

When suppository or soft capsule bases were used, the molten base was poured into the syringe, which was maintained at an elevated temperature until all the bubbles had risen to the surface. The apparatus was then adjusted to the required temperature, and 1 ml of oily solution placed on the top of the base after it had solidified. Hard gelatin bases could not be poured in this way. Therefore the molten base was poured on to a glass plate, and allowed to form a film. The film was then cut into pieces, which were packed into the syringe, and allowed to melt at an elevated temperature. The tops of the syringe and boiling tube were sealed with cling film, and the boiling tube finally covered with a metal cap.

After a preselected period of time, the oily solution was poured off, and the film of solution adhering to the inside of the syringe removed with a tissue. The column was allowed to cool to room temperature, placed horizontally and slices were cut off as the column was extruded by means of the plunger. Slices were weighed immediately, dissolved in 0.1 M hydrochloric acid, and assayed spectrophotometrically. Control diffusions were carried out simultaneously.

Results and Discussion

A major problem with the technique was that slices of a uniform and precise thickness could not be obtained. Each assay gave the mean concentration of 4-hydroxybenzoic acid in its slice, but did not represent a constant concentration throughout. At one end of the slice, the true concentration would be greater than the mean, but less than the mean at the other end, with a narrow band somewhere between the two where the concentration corresponded exactly with the assay result. Armstrong et al. (1985) have shown that the process followed Eqn. 1, originally proposed by Eversole and Doughty (1935) in which C_0 is the concentration at the proximal end of the column, and C the concentration X mm away. D is the diffusion coefficient, and t time.

$$\ln C = \text{Ln } C_0 - \frac{X^2}{4Dt} \qquad (1)$$

To conform with Eqn. 1, the band corresponding to the mean concentration should be the root mean squared distance (X), i.e. Eqn. 2 applies

$$X = \left(\frac{X_1^2 + X_2^2}{2} \right)^{1/2} \qquad (2)$$

X_1 and X_2 are the distances of the extremities of the slice from the interface, and were determined from the weights of the slices, the radius of the syringe and the density of the gel. As shown in Fig. 2, plots of X^2 against the logarithm of the concentration were rectilinear, from which diffusion coefficients could be calculated. A typical set of results is given in Table 1. Each mean diffusion coefficient is the average of 8 replicates and Table 1 shows that after a period of about 96 h, a constant value (0.0220 ± 0.0014 $mm^2 \cdot h^{-1}$) ($\pm$S.E.) is obtained.

It was considered of interest to ascertain whether the diffusion process could be followed at elevated temperatures, with a view to obtaining a relationship between the rate of diffusion and temperature analogous to the Arrhenius equation. If such a relationship could be obtained, it would have a number of advantages. Diffusion data could be obtained more quickly and hence a wider range

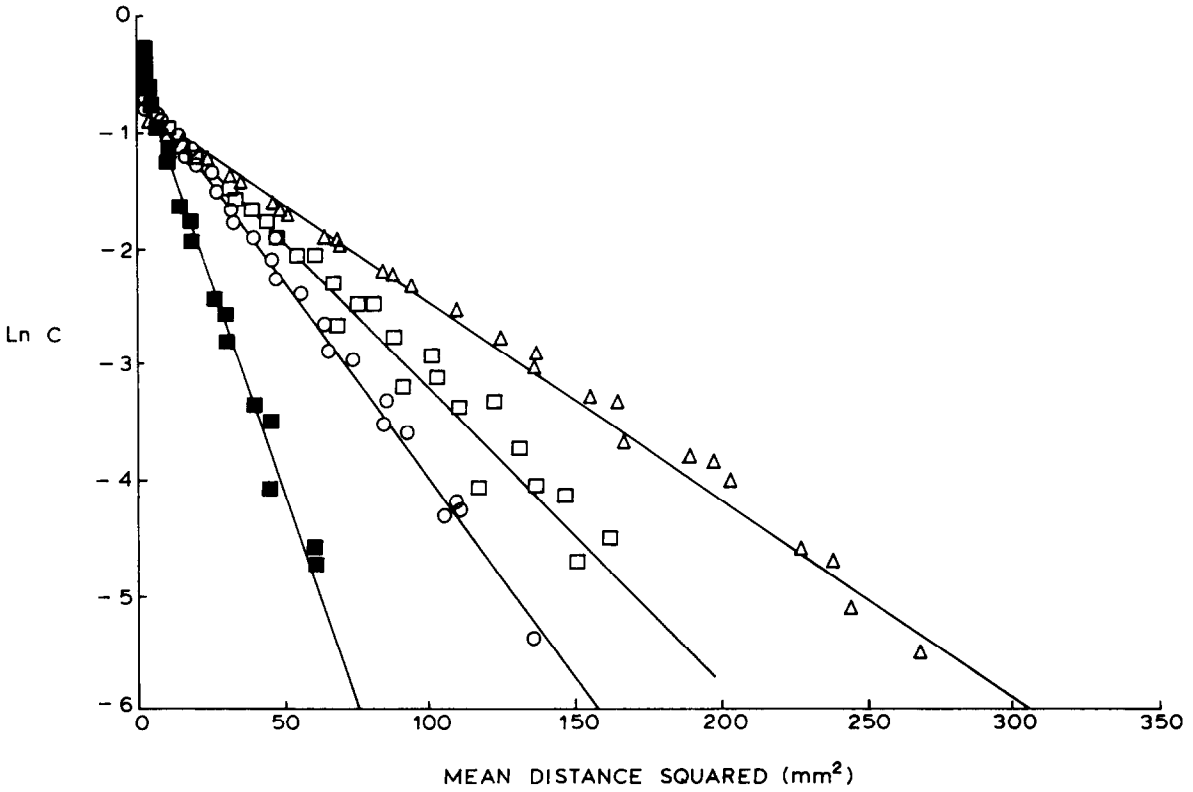

Fig. 2. Migration of 4-hydroxybenzoic acid from isopropyl myristate into a glycerogelatin column. (■, 72 h; ○, 144 h; □, 216 h; △, 288 h).

of glycerogelatin bases could be used. This latter is of especial interest in view of the growing use of hard gelatin capsules filled with semi-solid, non-polar materials (Walker et al., 1980).

Hard capsule shells contain not more than 15% water and no glycerol. They were too hard to examine by the current technique, so determinations at elevated temperatures were considered, with a view to extrapolating to ambient temperature. Preliminary experiments with both Glycerol Suppository Base and soft elastic gelatin capsule shells were carried out, and indicated that this approach was feasible. The maximum to which the temperature could be elevated was limited by the fusion of the mix, since at temperatures in excess of 35 °C it became semi-solid, and could not be extruded intact. Nevertheless, an adequate result was obtained with 5 points between 25 and 35 °C, and the soft capsule base results are shown in Fig. 3. The plot of ln D against the reciprocal of temperature was rectilinear, suggesting that a similar exercise (with harder bases) could yield a plot which could be extrapolated to ambient temperature. However, application of the technique at elevated temperatures to a base containing 85% gelatin and 15% water was unsuccessful, as the

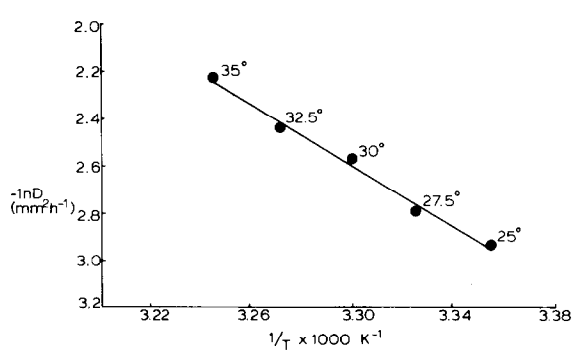

Fig. 3. The relationship between the diffusion coefficient and temperature.

TABLE 1

MEAN DIFFUSION COEFFICIENTS IN GLYCEROL SUPPOSITORY BASE, B.P. FROM ISOPROPYL MYRISTATE SOLUTION AT 22.5 ± 0.1°C

Time (h)	Mean diffusion coefficient ($mm^2 \cdot h^{-1}$) ($n = 8$)	Standard error ($P = 0.01$)
48	0.017	0.001
72	0.017	0.002
96	0.020	0.002
120	0.021	0.003
144	0.021	0.002
168	0.021	0.008
192	0.022	0.001
216	0.022	0.0003
240	0.022	0.001
264	0.022	0.001
288	0.026	0.001
312	0.021	0.001
336	0.024	0.002
360	0.025	0.001
384	0.022	0.003
408	0.020	0.004

base would not set to a homogeneous mixture in the syringe, and was difficult to cut after extrusion.

An alternative approach was to measure diffusion coefficients of more pliable masses containing more than 15% of water, and extrapolate a plot of diffusion coefficient against gelatin concentration to the required water level. Four gelatin concentrations, namely 50, 60, 70 and 80% were examined at 35°C, but the plot was curved, and could not be extrapolated accurately. The diffusion coefficient is given by Eqn. 3, in which R is the gas constant, T temperature, η the viscosity of the mixture, r the radius of the migrating molecules and N Avogadro's number.

$$D = \frac{RT}{6\,\eta r N} \tag{3}$$

All the terms except viscosity and diffusion coefficient are constant, so that $D = k/\eta$, where k is the overall constant. The viscosity of a moderately concentrated colloidal dispersion is given by Eqn. 4 (Martin et al., 1964).

$$\eta = \eta_0(1 + k_1 C + k_2 C^2) \tag{4}$$

η is the viscosity of a solution of gelatin of concentration C and η_0 the viscosity of the medium when C = zero. k_1 and k_2 are constants. Comparison of Eqn. 3 with Eqn. 4 places k/D equal to the right hand side of Eqn. 4. Multiple regression analysis of the experimental values of 1/D against two predictors, C and C^2 yielded Eqn. 5, which gave good correlation with the experimental results, as shown in Fig. 4.

$$\frac{1}{D} = 102 - 4.32C + 0.048C^2 \tag{5}$$

Substitution into Eqn. 5 of the gelatin content of bases which are too hard to measure directly thus provides a method for predicting the diffusion coefficient.

Although this apparatus affords a means of measuring solute diffusion through a glycerogelatin mass, it must be remembered that diffusion through the mass is preceded by transfer from the oily solution. Armstrong et al. (1984) examined four solutes, dissolved in isopropyl myristate and contained in soft gelatin capsules, and found that the degree of migration into the shells increased with increasing aqueous solubility of the substrate. The degree of migration was also dependent on the partition coefficient between the solvent and water, but independent of the solubility in the non-aqueous solvent. The results of the experiments, using the current technique, are shown in Table 2. The proportions of 4-hydroxybenzoic acid

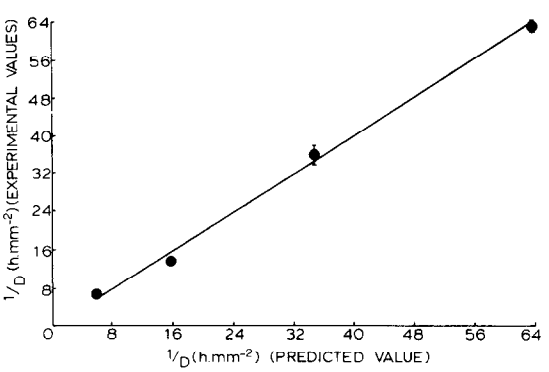

Fig. 4. The relationship between the predicted and experimentally obtained diffusion coefficients.

TABLE 2

PARTITION COEFFICIENT (OIL : pH 1.2 BUFFER), DIFFUSION COEFFICIENTS AND FRACTION OF 4-HYDROXYBENZOIC ACID MIGRATED

Solvent	1-Octanol	Octanol : ipm (50 : 50)	Octanol : imp (25 : 75)	ipm
Partition coefficient	25.44	19.57	9.84	0.564
Fraction migrated after 144 h	0.125	0.179	0.288	0.860
Diffusion coefficient ($mm^2 \cdot h^{-1}$)	0.035	0.039	0.0455	0.0496

which migrated from the oily solution to the gelatin base increase as the partition coefficients decrease, but the two sets of results are not in simple, inverse proportion. This is because only the volume of base in the immediate vicinity of the oil–gelatin interface is in equilibrium with the non-aqueous phase, and the remainder of the substrate in the gelatin mix is represented by a time-dependent concentration gradient along the column. Diffusion coefficients varied in a similar way, increasing with decreasing partition coefficient, but the change was smaller.

Conclusion

From the foregoing, it would appear that the proposed method affords a simple, reproducible technique for predicting solute migration from an oily solution into and through glycero-gelatin mixtures of the type used for soft and hard shell gelatin capsules, both during storage at ambient temperatures and at more elevated temperatures such as those achieved during the manufacture of soft shell capsules. By using the information so obtained, it should be possible, if required, to minimise or at least control migration from the capsule contents to the shell.

Acknowledgement

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