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Drug migration into soft gelatin capsule shells and its effect on in-vitro availability

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Analysis of the shells and contents of soft gelatin capsules containing acetomenaphthone, ephedrine, 4-hydroxybenzoic acid or phenobarbitone, dissolved in isopropyl myristate, revealed that the percentage of solute taken up by the shells increased with increasing aqueous solubility of the substrate. Thus no acetomenaphthone, which has a negligible aqueous solubility, was found in the shells, in comparison with 92% of the 4-hydroxybenzoic acid, which has a significant solubility in water. Uptake was not influenced by the solubility in isopropyl myristate. The effect of the oily solvent was studied using blends of 1-octanol and isopropyl myristate in which either 4-hydroxybenzoic acid or phenobarbitone were dissolved. Solute release shows that both release and migration can be predicted from a knowledge of the aqueous solubility of the solute and its partition coefficient between water and the non-polar solvent. Samples of capsules containing 4-hydroxybenzoic acid in isopropyl myristate were withdrawn at various stages of the manufacturing process, and the distributions between shell and contents noted. Most of the transfer took place while the capsules were being dried in rotating basket driers, and at this point 67% of the acid had migrated. This increased to 92% during tray drying, and remained so for at least 6 months after manufacture.

Although no general pattern appears to exist that explains drug availability from dosage forms containing lipophilic liquids, Kakemi et al (1966) have suggested that the major mechanism for drug absorption involves the liberation of the drug from the oily vehicle into the aqueous luminal fluid, followed by absorption through the wall of the gastrointestinal tract. The first stage of this process has been studied in soft gelatin capsules by Armstrong et al (1982), using an apparatus designed to simulate drug release from non-polar media (Armstrong et al 1979).

In the course of this investigation, it was found that with some solutes, considerable migration of solute from the oily vehicle to the capsule shell took place and that this affected the rate of release from the oil (Armstrong et al 1982), and it was suggested that availability and migration could be optimized by judicious choice of solvent.

The present communication describes drug release from, and migration in, capsules containing solutes exhibiting a range of polarities, and also the effect of the nature of the solvent on the degree of migration.

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MATERIALS AND METHODS

Materials

Isopropyl myristate, acetomenaphthone, ephedrine and phenobarbitone were of BP and Pharmaceutical Codex quality. 4-Hydroxybenzoic acid and 1-octanol were obtained from BDH Ltd., who claimed a purity in excess of 99%. All were used without further purification.

Partition-permeation apparatus. This apparatus, for studying the release of solute from water-immiscible solutions has been described by Armstrong et al (1979), and later adapted for use with soft gelatin capsules (Armstrong et al 1984). It consisted of two half cells, separated by a simulated lipid membrane. One cell contained buffer at pH 1·2 and the other buffer at pH 7·4. The non-aqueous phase was spread on the surface of the acidic solution, and both aqueous phases were monitored for the concentration of solute.

Capsule manufacture. Capsules were prepared by the rotary die process at R. P. Scherer Ltd., Treforest, Mid Glamorgan, under standard manufacturing conditions. Capsule shells consisted of 45·5% gelatin, 38·3% glycerol and 16·2% water; to avoid spectrophotometric problems, no preservative was included. Capsules were packed into polythene bags and stored in a sealed glass container at a relative humidity of 23%, produced by a saturated

solution of potassium acetate (Rockland 1960). Capsules were removed from the container and exposed directly to 23% humidity for 2 to 3 days before experimentation.

Determination of solute concentration. Aqueous samples were diluted with pH 1·2 buffer, while non-aqueous solutions were diluted with spectroscopic cyclohexane. Both were assayed by uv spectrophotometry. Preliminary experiments established the wavelengths of maximum absorption, and adherence to Beer's law.

Distribution of solute in the capsule. Each capsule was opened with a scalpel, and the contents totally extruded. The shell was rinsed in n-hexane, and allowed to dry after all the cleansing solvent had drained off. The shell was then reweighed. The difference gave the weight of capsule contents, which could then be converted into volume by dividing by density. Capsule shells and contents were analysed spectrophotometrically.

The procedure was repeated with capsules, which were identical except for the absence of solute, and the drug content was determined by difference.

Determination of solubilities and partition coefficients. Saturated solutions were prepared by percolation, using the bent tube technique described by Roberts (1969), and assayed by uv spectrophotometry. Results are the mean of three determinations. For partition coefficients, 10 ml of the pH 1·2 buffer, pre-equilibrated with the non-aqueous solvent was delivered into a 50 ml jacketed tap funnel, which was maintained at constant temperature by circulated water at 37 °C. 10 ml of a solution of the solute in the non-aqueous solvent was added, and the funnel shaken at about 150 strokes min^{-1} for 12 h. After shaking, the mixtures were allowed to stand for 36 h at 37 °C before the aqueous layer was analysed spectrophotometrically. For each system, several initial concentrations were examined to establish that the partition coefficient was not concentration-dependent.

RESULTS AND DISCUSSION

Initial attempts to determine the drug contents of the capsules gave scattered results. It was noted that the variation in the weights of the shells (6%) was 4 times greater than the variation in the fill weight. Since the shell constituents contribute to the absorbance obtained with solutions of the complete capsules, this variation was considered to be the probable cause of the scatter, and a method was therefore developed to reduce the error arising from shell weight. The total weights and shell weights of 30 capsules were graded into weight ranges of 5 mg, and the number of capsules falling into each group are plotted against capsule and shell weights in Fig. 1. The two graphs are almost superimposable, and between the total weight limits, shell weights varied by only 1·4% (0·360 to 0·365 g). Similar results were obtained with 30 control capsules containing solvent only, which indicated that for a shell weight between 0·360 and 0·365 g, a total capsule weight between 2·165 and 2·170 g was required.

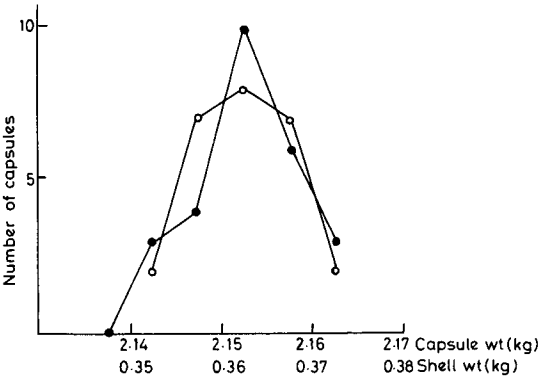

FIG. 1. Frequency distribution of total and shell weights of 40 minim round capsules. ○, total weight; ●, shell weight.

This procedure provided a means of selecting control capsules identical to experimental capsules, except for the absence of the solute. By this means, the overall analytical error was reduced to 3%.

The fractions of solute that migrated from isopropyl myristate solution into the capsule shells is shown in Table 1. Each result is the mean of 10 replicates. Mole fraction solubilities in water and in encapsulating solvent are also given, and indicate that the percentages which have passed into the shells follow the same rank order as the aqueous solubilities, but show no obvious relationship to the

Table 1. Solubilities and the fraction of solute transferred from encapsulated isopropyl myristate solutions.

Solute	Mole fraction solubility: Buffer pH 7·4 × 10^5	Mole fraction solubility: Isopropyl myristate × 10^2	Fraction of solute present in shell after 3 h
Acetomenaphthone	0·500	1·73	0·00
Phenobarbitone	23·7	0·51	0·12
Ephedrine	113	1·95	0·36
4-Hydroxybenzoic acid	231	2·11	0·92

solubilities in isopropyl myristate. The plot of percentage migrated against aqueous solubility was not rectilinear, but followed a uniform curve (Armstrong et al 1982). It therefore appears that if a solute has a low aqueous solubility, uptake by the capsule shell will be negligible, and since the soft gelatin capsule is a dosage form normally used for water-insoluble materials, it is not anticipated that extensive migration into the capsule shell will be a common occurrence.

The results obtained with the partition-permeation apparatus agreed with these observations. The quantities of acetomenaphthone, ephedrine, 4-hydroxybenzoic acid and phenobarbitone which were transported into compartment 2 are plotted against time in Fig. 2. Acetomenaphthone has a definite lag phase, extending to about 15 min, suggesting that absorption into the shell was negligible, and that the solute was not released until after

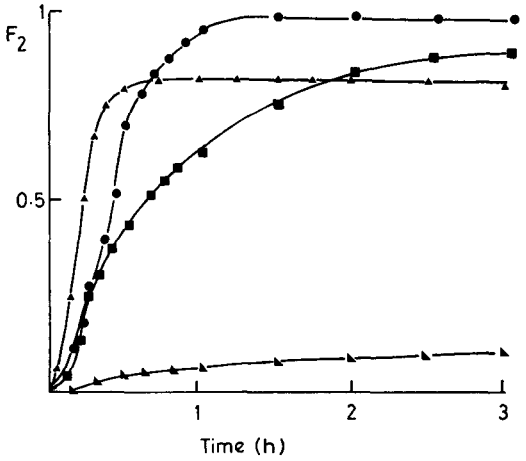

FIG. 2. The fraction of solute released into the pH 1·2 phase from an 80 minim round soft capsule containing a solution in isopropyl myristate. ▲, 4-hydroxybenzoic acid, initial concentration 0·02%; ■, phenobarbitone, initial concentration 0·15%; ●, ephedrine, initial concentration 0·5%; ◣, acetomenaphthone, initial concentration 0·03%.

the shell had ruptured. There is a marked lag phase with phenobarbitone, but it is not as great as with acetomenaphthone, and the plot can be extrapolated to the origin, indicating that there was some phenobarbitone in the shell. Ephedrine and 4-hydroxybenzoic acid, appreciable quantities of which were found in their capsule shells, exhibited no lag phases. The ephedrine plot levelled out when almost 100% had transferred to compartment 2, while with 4-hydroxybenzoic acid, the graph levelled at around 80%. This does not mean that more ephedrine transferred to compartment 2 than 4-hydroxybenzoic acid. The difference highlights a weakness in the operation of the partition-permeation apparatus, in that it functions with acids, which are readily scavenged by the pH 7·4 buffer, leaving the pH 1·2 phase depleted of 4-hydroxybenzoic acid. However, the apparatus is not normally suitable for bases, such as ephedrine, which are only slightly soluble in pH 7·4 buffer, and therefore accumulate in compartment 2. In this particular instance, the quantity of ephedrine was sufficiently small for the apparatus to cope.

The influence of capsule size on the uptake by the shell was investigated by determining the shell concentrations of ephedrine and phenobarbitone transferred from isopropyl myristate solutions in 40 and 80 minim round capsules. Results are shown in Table 2. Since the capsules are spherical, and the volumes of their contents are known, the radius of the contents can be calculated, and from this, the interfacial area between contents and shell determined. These are given in Table 2. The volume of the shell is equal to the interfacial area multiplied by the shell thickness, so that if the thicknesses of the 40 and 80 minim capsule shells are considered equal, the relative quantities of solute taken up by the shells will be equal to the ratio of the interfacial areas per unit volume i.e. 3·908/3·079. If the percentage of phenobarbitone found in the shell of the 80 minim round capsules is multiplied by this factor, an estimated uptake of 15% for the 40 minim round capsule is obtained, in good agreement with the experimental result.

Table 2. Comparison of the transfer of solutes to the shell in two different sized capsules.

		40 minim round	80 minim round
Volume (ml)		1·894	3·874
Interfacial area (cm^2)		7·39	11·93
Area of contact per unit volume ($cm^2\ ml^{-1}$)		3·908	3·079
% found in shell	Ephedrine	50	36
	Phenobarbitone	15	12

The effect of the oil on the degree of migration to the capsule shell was investigated by using either 4-hydroxybenzoic acid or phenobarbitone dissolved in blends of 1-octanol and isopropyl myristate, the results being shown in Figs 3 and 4 respectively. Both graphs show that an increase in the proportion of isopropyl myristate in the blend results in an increase in the amount of solute released by the oil. A consequence of this is that the greater the release, the greater the quantity of drug which will pass across the model biomembrane.

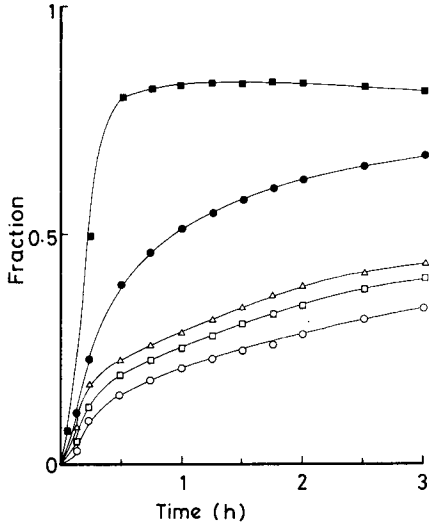

FIG. 3. Weight fraction of 4-hydroxybenzoic acid appearing in the aqueous pH 1·2 compartment from 80 minim round soft gelatin capsules containing 0·02% w/v solutions in blends of 1-octanol and isopropyl myristate. Blend constitution (% v/v) octanol-isopropyl myristate: ○, 100:0; □, 75:25; △, 50:50; ●, 25:75; ■, 0:100.

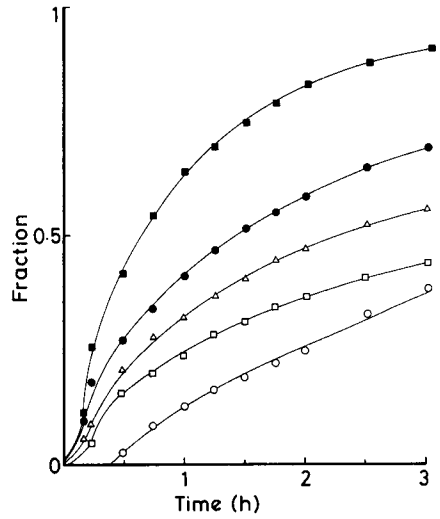

FIG. 4. Weight fraction of phenobarbitone appearing in the aqueous pH 1·2 compartment from 80 minim round soft gelatin capsules containing 0·15% w/v solutions in blends of 1-octanol and isopropyl myristate. Symbols are as in Fig. 3.

Although increase in the amount of isopropyl myristate in the solvent blend causes an increase in solute release with both solutes, the initial stages of the curves differ, particularly with high concentrations of isopropyl myristate. This is attributed to the proportion of solute present in the capsule shell, since the greater this quantity, the more dependent will release be on shell dissolution.

Table 3. The percentage of solute appearing in the capsule shell for different blends of solvents encapsulated.

Blend constitution (% v/v)		% in the capsule shell	
Isopropyl myristate	1-Octanol	4-Hydroxy benzoic acid	Pheno-barbitone
100	0	92	12
75	25	30	6
50	50	14	3
25	75	9	0
0	100	6	0

Table 3 shows that the greater the proportion of 1-octanol in the blend, the less drug is transferred to the capsule shell. Consequently the less dependent is release on shell dissolution. This applies to both 4-hydroxybenzoic acid and phenobarbitone, although considerably more of the 4-hydroxybenzoic acid is transferred to the shell with any particular blend.

Since the proportion of solute transferred to the shell depends on both the nature of the solute and on the solvent, it would appear that migration is controlled by the partition coefficient between the oil and shell. In an attempt to verify this, aqueous solubilities and partition coefficients were determined for 4-hydroxybenzoic acid and phenobarbitone.

Comparison of the partition coefficients of 4-hydroxybenzoic acid and phenobarbitone in the various solvent blends, together with the amount appearing in the capsule shell is given in Table 4. These data demonstrate that both solubility and partition coefficient control the amount transferred to the shell. The partition coefficients for the two solutes are similar, but because of its higher aqueous solubility, much more 4-hydroxybenzoic acid is found in the shell than is phenobarbitone. If the solubility in the shell is assumed to be roughly equal to that in the pH 7·4 buffer, it can be shown that even

Table 4. Relationship between solvent: pH 1·2 buffer partition coefficient and the proportion of solute appearing in the capsule shell.

Solvent system (% v/v)		4-Hydroxy benzoic acid		Phenobarbitone	
Isopropyl myristate	Octanol	Part. coeff.	% in shell	Part. coeff.	% in shell
0	100	25·4	6	24·3	0
25	75	23·9	9	21·6	0
50	50	19·5	12	17·7	3
75	25	9·84	30	12·1	6
100	0	0·56	92	2·31	12

after transfer is completed, the water in the shell is still not saturated with solute.

The foregoing data show that drug release from an oily solution, and also solute migration from oil to a capsule shell, can be controlled by selection of an appropriate solvent or mixture of solvents.

Having established that some of the solute transfers to the shell, we considered it of interest to ascertain at what stage in the manufacturing process this transfer took place. This was achieved by taking samples of the capsules at various stages of production. The stages, time elapsed after manufacture and distribution between shell and capsule contents are given in Table 5. The capsules used in this study contained 4-hydroxybenzoic acid in isopropyl myristate. After manufacture, they were stored in sealed containers at room temperature.

Table 5. Transfer of 4-hydroxybenzoic acid from an encapsulated isopropyl myristate solution to the capsule shell.

Time after manufacture	Fraction in capsule contents	Fraction in capsule shell
Encapsulation		
↓ ← 1 min	0·80	0·19
Naphtha wash		
↓ ← 3 min	0·78	0·19
Basket drier 76 °F, 36% RH for 45 min		
↓ ← 45 min	0·25	0·62
Tray drier 72 °F, 21% RH for 3 days		
↓ ← 3 days	0·09	0·80
IMS rinse Packaging and storage		
↓ 5 days	0·07	0·80
Further storage		
| ← 6 months	0·07	0·80

Whilst some transfer of solute from oil to shell took place during or immediately after manufacture, most transfer took place when the capsules were being dried in rotating basket driers, with the heat presumably acting as the driving force. After this stage, 67% of the solute was present in the shell, and this increased further during tray drying, when 80% had migrated. Subsequent to this, storage for up to six months at room temperature caused no further migration, indicating that equilibrium had been reached, or that solute diffusion into the shell, which was now much more viscous due to water loss, is impossible.

After drying is complete, only 89% of the original amount of solute is present in shell and oil combined. Some of the solute is believed to migrate to the outer surface of the capsule, from which it can be eroded by friction, or else removed by washing.

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