AN IN VITRO MODEL FOR ASSESSING DRUG AVAILABILITY FROM LIPOPHILIC SOLUTIONS IN SOFT GELATIN CAPSULES

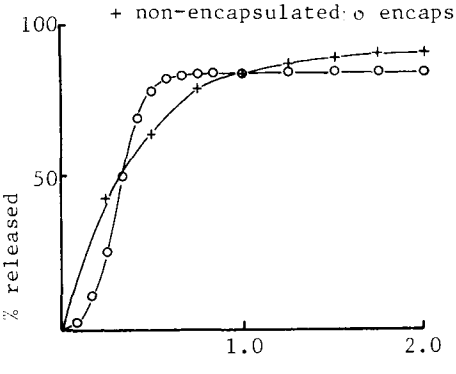
N.A.Armstrong, K.C.James and W.K.L.Pugh, Welsh School of Pharmacy, UWIST, Cardiff.

An apparatus for studying the release of solute from a water-immiscible solution has been described by Armstrong, James & Wong (1979). It consisted of two half cells separated by a simulated lipid membrane, one containing a buffer at pH 1.2 and the other containing buffer at pH 7.4. The non-aqueous solution was spread on to the surface of the acidic solution, and both aqueous phases monitored for the presence of solute. A large volume of non-aqueous solution (150ml) was used in the original study; it gave a general idea of solute release, but the process was slow and the volume was unrealistic compared with those used in soft gelatin capsules. The effect of volume size was therefore investigated by decreasing the quantity of non-aqueous solvent, and following the rates of transfer of solute into the aqueous phases. Reduction in volume resulted in a greater proportion of solute appearing in the aqueous phase. p-Hydroxybenzoic acid was used as solute, and octanol and isopropyl myristate as solvents. Both k_{AB}, the rate constant for transfer from lipid solution to acid buffer, and k_{BA} increased as the volume of lipid solution decreased, but k_{AB} increased more rapidly, so that the ratio k_{AB}/k_{BA} also increased with decreasing volume (Table). This is to be expected since the interfacial area remains constant, but as the volume of lipid solution is decreased, the layer becomes thinner and the solute has a shorter distance through which to migrate.

When capsules were examined, a background determination had to be carried out because gelatin absorbs in the same U.V. region. This was done with an identical capsule, differing only in the absence of solute. Solute release profiles on capsules containing p-hydroxybenzoic acid in isopropyl myristate showed a lag phase until the capsule shell ruptured. Solute concentration in the pH 1.2 phase reached a maximum from the encapsulated oil in about 40 min., the release rate being significantly quicker than from the unencapsulated oil (Figure). The difference is attributed to the fact that 90% of the solute had migrated into the capsule shell prior to the experiment. It is believed that transfer to the shell occurs during manufacture of the capsules, particularly during the drying stage. It therefore follows that release of solute from a soft gelatin capsule will depend not only on the oily liquid used to fill the capsule, but also on the composition of the capsule shell, the partition of solute between shell and contents, and also on the method of manufacture.

Solvent	Transfer rate (h^{-1})	Volume of solvent (ml)		
		150	100	50
n-octanol	k_{AB}	0.034	0.072	0.162
	k_{BA}	1.000	1.410	1.600
isopropyl myristate	k_{AB}	0.130	0.205	0.404
	k_{BA}	0.120	0.125	0.122

Release of p-hydroxybenzoic acid from isopropylmyristate
+ non-encapsulated o encapsulated



Armstrong, N.A. et al. J.Pharm.Pharmacol. (1979) 31:657-662

We thank P.Leiner & Sons for their support