THE RELEASE OF DRUGS WITH LOW AQUEOUS SOLUBILITY FROM LIQUID CRYSTALLINE PHASES

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The amphiphilic monoglyceride, monoolein, forms lyotropic liquid crystals in the presence of water (Lutton 1965). These liquid crystalline structures possess the ability to incorporate solutes into their structures (Larsson and Lindblom 1982), and as monoglycerides are biocompatible, they therefore have the potential to act as drug delivery systems.

In this work we have investigated, using a modified dissolution cell, the *in vitro* release of two model compounds, propranolol base and pyrimethamine, which have widely differing solubilities. The drugs were released into Sorensen's buffer (pH 7.4).

Polarising microscopic evidence showed that propranolol was soluble in the liquid crystalline system; whereas only 2.5% w/w of pyrimethamine was required to saturate the system, above this concentration pyrimethamine crystals became visible in the sample.

A typical plot of amount of drug released, into the buffer, as a function of time is shown in Figure 1. The data were fitted to the Higuchi diffusion model and release rates were determined from the gradients of plots of amount released as a function of root time. Figure 2 shows a linear relationship between the rate of release and the initial drug loading concentration of propranolol in the system. In contrast, the rate of release of pyrimethamine does not increase linearly with initial drug loading concentration.

The difference in release characteristics between the two drugs is thought to be a consequence of their differing solubilities. The solubility of propranolol (3.14mg/ml), is such that release is diffusion rate limited. However, because of the low solubility of pyrimethamine (0.0562mg/ml) the controlling factor for pyrimethamine release is the dissolution of the drug. With increasing pyrimethamine concentrations, from 1% to 20% w/w, the increased surface area of the drug exposed produces a corresponding increase in the rate and amount of drug dissolving. Eventually, a point is reached when the rate of dissolution equals the rate of diffusion through the liquid crystalline phase. At this point the suspended drug acts as a depot for release and zero order release kinetics are observed. This phenomenon has been demonstrated in this work for a 20% w/w pyrimethamine concentration.

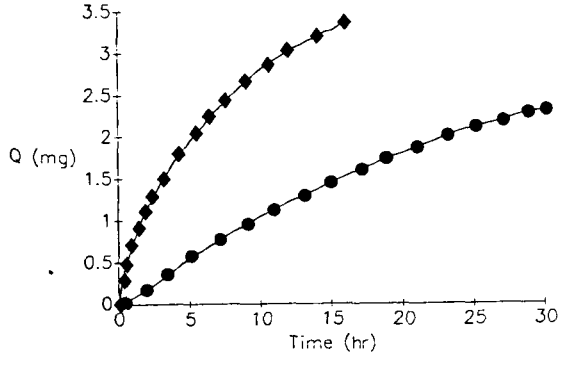

Figure 1. Amount of drug released (Q) as a function of time for the drugs propranolol (◆) and pyrimethamine (●). Drug loading is equivalent to 10% w/w for both compounds.

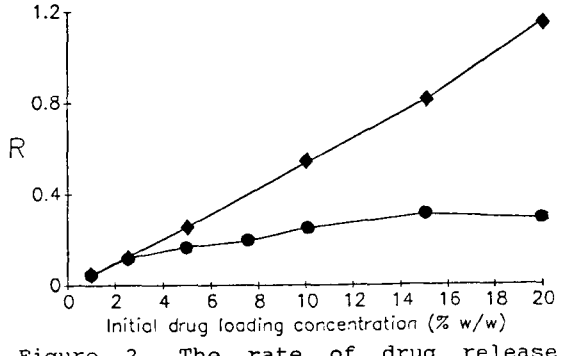

Figure 2. The rate of drug release ($R, mgh^{-\frac{1}{2}}cm^{-2}$), from the monoolein/water system as a function of the initial drug loading concentration (% w/w). Propranolol(◆), pyrimethamine (●).

Lutton,L. (1965) J.Am.Oil Chem.Soc 42:1068-1670
Larsson,K., Lindblom,G. (1982) J.Disp.Sci.Tech 3:61-66