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# The release of drugs from monoglyceride-water liquid crystalline phases

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**Abstract**

The in vitro release of model drugs, with a wide range of aqueous solubilities, from monoolein-water liquid crystalline matrix systems has been investigated. Release of melatonin, pindolol, propranolol and pyrimethamine from individual systems with initial drug loading concentrations within the range 1–20% w/w and atenolol from systems at concentrations up to 10% w/w could be fitted to both diffusion-controlled or first-order kinetics. The release of atenolol at initial drug loading concentrations of 15 and 20% w/w could be fitted to a zero-order release model. Release rates have been related to the solubility of the drugs in the monoolein-water systems. Changes in the matrix monoolein/water weight ratio over the range 4:1–1:1 had no significant influence on drug release. Monoolein-water-drug systems prepared using drugs with either a high solubility (propranolol) or a low solubility (pyrimethamine) were stable when stored in the dark at 4°C for up to 6 months with no significant change in release characteristics. Systems incorporating propranolol were unstable when stored at 26°C for 15 days; storage of systems incorporating pyrimethamine under the same conditions were stable with no change in release characteristics.

*Keywords:* Liquid crystalline system; Drug release; Monoglyceride liquid crystal

## 1. Introduction

Monoolein is an amphiphilic monoglyceride which forms lyotropic liquid crystalline phases in the presence of water (Lutton, 1965). Lyotropic liquid crystalline phases have the ability to incorporate solutes (drugs) into their structures and the potential of these systems for the controlled release of drugs has been examined (Engström et al., 1988). The structure of the liquid crystalline phases of monoolein is dependent on several factors including; water content, temperature and the presence of any additional solutes. Thus, the addition of a drug to these liquid crystalline systems may modify the phase properties of the system, which in turn may influence the rate and extent of drug release. In this work we have investigated the in vitro release of model drug compounds, selected on the basis of their solubil-

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ity, from the liquid crystalline phases of monoolein. We have examined the influence on the drug release characteristics of the initial drug loading concentration, water content and the storage conditions.

## 2. Materials and methods

### 2.1. Materials

Monoolein (Sigma Chemical Co., purity > 99%) was used as received and liquid crystalline systems were prepared using singly distilled water. Melatonin, pindolol and pyrimethamine were supplied by Sigma Chemical Co. and atenolol and propranolol base were kindly donated by Cortecs Ltd.

### 2.2. Determination of drug solubility

The saturation solubility of each drug in the monoolein-water systems was determined by polarising microscopy. Monoolein-water-drug systems with a specified range of drug loadings were prepared on glass microscope slides and covered with glass cover slips. A narrow band of silicone rubber was applied around the edges of the cover slip, to ensure an effective seal between the cover slip and the glass slide. Systems were stored in the dark at a temperature of 37°C for 15 days and were examined (at 37°C) at selected intervals throughout this time period using polarising microscopy (Vickers Instruments or Olympus BH2).

The initial drug loading concentration was increased, in increments of approx. 0.25% w/w, from a concentration below the saturation solubility, until drug crystals were observed microscopically in the system. The highest drug concentration at which drug crystals were not observed after 15 days was considered to represent the saturation solubility of the drug in that particular system.

The saturation solubility of each drug in Sørensen's buffer, pH 7.4, was determined by the addition of excess amounts of drug in the buffer at 37°C for periods up to 14 days and subsequent analysis of the filtered solution by UV spectrophotometry.

### 2.3. In vitro drug release

The in vitro release investigations were conducted using a modified dissolution cell containing 250 ml of release medium (Sørensen's buffer pH 7.4) maintained at 37°C (Collett et al., 1972). The apparatus consisted of a perspex dissolution cell which was cylindrical in shape (internal diameter 9.7 cm, depth 8.0 cm). The release medium was agitated by means of a three-bladed propeller attached to an asynchronous motor (Crouzet Ltd) rotating at 90 rpm. An in vitro release module was constructed, which comprised a PTFE cylinder (depth 2.1 cm, external diameter 2.5 cm) with a centrally drilled cavity (depth 0.1 cm, diameter 0.8 cm) in the upper surface. A drug-loaded monoolein-water liquid crystalline system was compacted into this cavity such that the upper surface of the system was continuous with the upper surface of the release module, so restricting drug release to only one face. The module was positioned in a central cavity in the base of the dissolution cell such that its surface formed a continuous surface with the base of the dissolution cell. The release of drug from the monoolein-water systems was measured spectrophotometrically, (Cecil 202 with flow-through attachment, dead volume 3.6 ml) at the wavelength of maximum absorbance, $\lambda_{max}$. Values (nm) of $\lambda_{max}$ were: atenolol, 277; melatonin, 281; pindolol, 264; propranolol, 291; and pyrimethamine, 279.

Atenolol has a low specific absorptivity which precluded the use of large volumes of release medium. A dissolution cell of smaller internal diameter (6.2 cm) was substituted when examining the release of this drug, allowing a smaller volume of release medium to be used (110 ml). All other experimental conditions were kept constant. The low aqueous solubility of pyrimethamine necessitated that the volume of the release medium be increased to 500 ml (the maximum capacity of the release cell) at high initial drug loading concentrations, in order to maintain sink conditions, i.e. to ensure that the concentration

of drug in the release medium was less than 10% of the saturation concentration of the drug in the medium (Gould, 1983).

Drug-loaded monoolein systems were allowed to equilibrate in the release module under specified conditions (15 days at 4°C in the dark, unless otherwise stated). Surfaces of the samples in the cavity of the release module were sealed by means of a greased rubber 'O ring and cover glass, to prevent water loss. After equilibration, the cover was removed, the release module was located in the dissolution cell and, following addition of dissolution medium, drug release was measured. Experiments were conducted to examine the influence of the following formulation factors on drug release:

(i) The initial drug loading concentration within the range 1–20% w/w from liquid crystalline systems with monoolein/water weight ratios of 2:1. Each of the five drugs listed above was incorporated separately into monoolein-water systems (The monoolein and the drug were dry mixed before the appropriate quantity of water was added).

(ii) The water content of the monoolein-water systems of weight ratios 4:1, 2:1 and 1:1. The initial drug loading concentration was 10% w/w for all five drugs examined.

(iii) The period of storage of monoolein-water systems with a weight ratio 2:1. Propranolol or pyrimethamine, at an initial drug loading concentration of 10% w/w, was incorporated into the monoolein-water system. After preparation, the systems were stored in the dark at 4°C for a selected time interval within the range, 1 day to 6 months.

(iv) The storage temperature of monoolein-water systems with a weight ratio 2:1. Propranolol or pyrimethamine, at an initial drug loading concentration of 10% w/w, was incorporated into the system. The systems were subjected to one of the following storage conditions prior to the in vitro examination of drug release:

(1) In the dark at either 4 or 26°C for 8 or 15 days.

(2) In the dark at 4°C for 15 days and subsequent equilibration in the dark at 26°C for 2 h before analysis. Additional propranolol-loaded systems with selected initial drug loading concentrations within the range 1–20% w/w were also prepared and stored under these conditions.

## 3. Results and discussion

### 3.1. Saturation solubilities of drugs

The saturation solubilities of the drugs in the monoolein-water systems of monoolein/water weight ratio of 4:1, 2:1 and 1:1 are compared with those in the release medium (Sørensen's buffer) in Table 1. The precision of the solubility data for the drugs in the monoolein-water system was dependent on the size of the increment of drug concentration added, usually approx. 0.25% w/w. With the exception of melatonin, increases in the water content of the system led to an increase in the saturation solubility of the drug. Melatonin had the lowest saturation solubility in the monoolein-water system and hence the solubility data for this drug were subject to the largest error.

The solubility of each drug in a monoolein-water liquid crystalline system was greater than its solubility in Sørensen's buffer. Thus, it may be inferred that the drugs had been solubilised preferentially in the lipophilic region of the liquid crystalline phase, rather than in the hydrophilic region. For a given drug, there was generally an increased solubility with decreasing monoolein

Table 1
Saturation solubilities of drugs in monoolein-water systems and in Sørensen's buffer

| Drug | Saturation solubility in liquid crystalline system at 37°C (% w/w) (Monoolein/water weight ratio) | | | Solubility in Sørensen's buffer at 37°C (% w/w) |
|---|---|---|---|---|
| | 4:1 | 2:1 | 1:1 | |
| Atenolol | 6.1 | 6.3 | 8.8 | 2.55 |
| Melatonin | 1.0 | 1.4 | 1.0 | 0.21 |
| Pindolol | 3.1 | 4.1 | 6.0 | 0.19 |
| Propranolol | 13.2 | 13.2 | 14.6 | 0.31 |
| Pyrimethamine | 1.7 | 2.0 | 2.3 | 0.01 |

content of the system, which would appear to oppose the hypothesis of lipophilic solubilisation. However, in this study, the liquid crystalline phase which formed was identified as being the cubic phase (Larsson et al., 1980) and an increase in the water concentration of the system would cause an increased interfacial area of the cubic phase, and this may aid the solubilisation process (Engström, 1990).

Acicular crystals were observed in monoolein-water systems containing pindolol and propranolol which melted at temperatures close to the melting point of the respective drugs. The crystals, which were of different habit to the bulk drug used initially, were considered to arise from recrystallisation of the drugs.

The saturation solubilities quoted in Table 1 are for the drugs in their original crystal form not the acicular form. The solubilities quoted for pindolol and propranolol may be overestimates of the true values since the presence of the acicular crystals often obscured the entire field of view, preventing the observation of drug in its original crystal form.

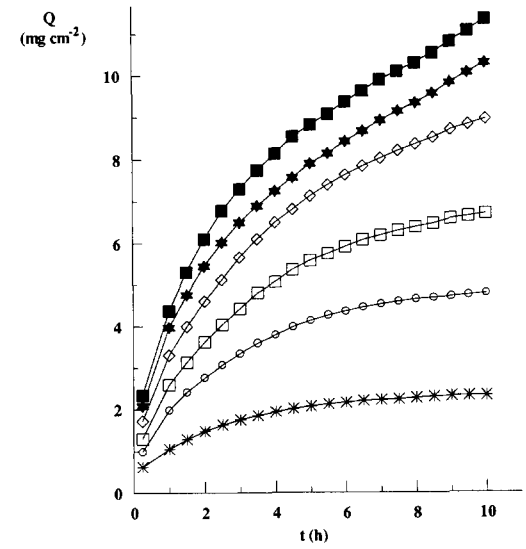


Fig. 1. Cumulative amount of atenolol released per unit surface area of a monoolein-water system, as a function of time, for initial drug loading concentrations of: (∗) 2.5%; (○) 5.0%; (□) 7.5%; (◇) 10.0%; (★) 15.0%; (■) 20.0%.

### *3.2. Influence of initial drug loading on release characteristics*

Fig. 1 and 2 show the cumulative amount of drug released per unit surface area of the monoolein-water system, as a function of time, for atenolol and pyrimethamine. Similar release curves (not shown) were obtained for the other drugs of this study. For each drug several selected initial drug loading concentrations are presented. For clarity, only a representative sample of the data points is given on the graphs. It can be seen from Fig. 1 that an increase in the initial drug loading concentration led to an increase in the rate and the amount of drug released. A similar trend was observed for the release of melatonin, pindolol and propranolol. This effect was less marked with the monoolein-water-pyrimethamine systems (Fig. 2) where an increase in the initial drug loading concentration above 10% w/w had little significant effect on the release characteristics. Examination of the release profiles for the different drugs revealed that the higher the aqueous solubility of the drug, the greater the amount of drug released over a specified time interval, for a given initial drug loading concentration.

At the end of the in vitro release experiments on monoolein-water systems containing initial propranolol concentrations of either 30 or 40% w/w, the dissolution media were found to contain dispersed globules of monoolein, i.e., these liquid crystalline systems were unstable. In contrast, systems prepared containing similarly high concentrations of pyrimethamine were stable. It is thought that an interaction between the highly soluble propranolol (saturation solubility 13.2% w/w) and the liquid crystalline system resulted in the precipitation of drug crystals into the system and subsequent instability. Systems containing high initial drug loading concentrations of pyrimethamine were stable because the pyrimethamine was less soluble than propranolol in the monoolein-water system (saturation solubility approx. 2.0% w/w) and did not recrystallise in the system.

### 3.3. Assignment of a release model

Several mathematical models have been used to describe the release of drugs from matrix systems (Higuchi, 1960; Paul and McSpadden, 1976; Peppas and Korsmeyer, 1987). The release data obtained in this study were analysed in order to test the hypothesis that the drug release was described by models which assumed: (i) that drug release was controlled by the diffusion of the drug through the matrix (Higuchi, 1960, 1961) or (ii) that release could be described by first-order kinetics (Schwartz et al., 1968; Sciarra and Gidwani, 1972).

In diffusion-controlled release the cumulative amount, $Q$, of drug released per unit surface area of the system is proportional to the square root of time, $t$:

$$Q = kt^{\frac{1}{2}} \quad (1)$$

where $k$ is a release rate constant.

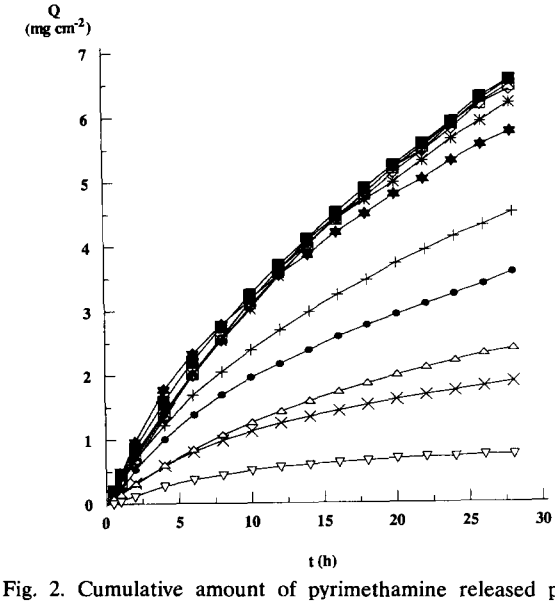


Fig. 2. Cumulative amount of pyrimethamine released per unit surface area of a monoolein-water system, as a function of time, for initial drug loading concentrations of: (▽) 1.0%; (×) 2.5%; (△) 5.0%; (●) 7.5%; (+) 10.0%;. (★) 15.0%; (*) 17.5%; (□) 20.0%; (◇) 22.5%; (○) 25.0%; (■) 30.0%. Volume of release medium for samples with initial drug loading concentrations 1–10% = 250 ml. Volume of release medium for samples with initial drug loading concentrations 15–30% = 500 ml.

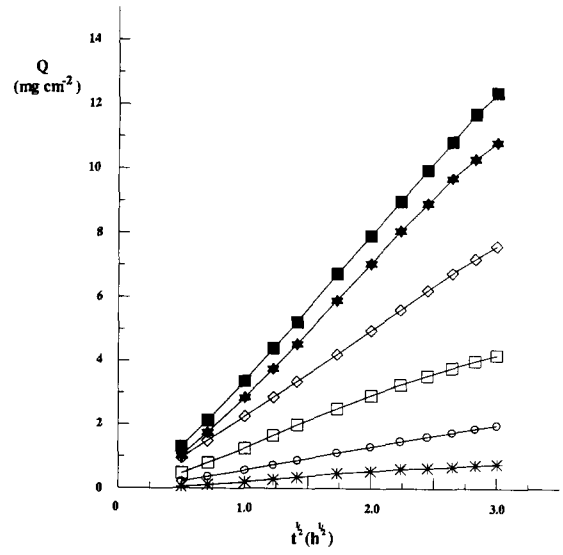


Fig. 3. Cumulative amount of propranolol released per unit surface area of a monoolein-water system, as a function of the square root of time, for initial drug loading concentrations of: (*) 1.0%; (○) 2.5%; (□) 5.0%; (◇) 10.0%; (★) 15.0%; (■) 20.0%.

Fig. 3 shows the data for the release of propranolol plotted in accordance with Eq. 1. Similar plots were obtained for all the drugs (except atenolol at high drug loading) showing linearity until at least 60% of drug had been released. These findings are in agreement with reports that the release of drugs from a matrix delivery system continues to be proportional to the square root of time up to the release of at least 50% of the drug content, and possibly up to 75% (Zarrintan and Groves, 1991). The data obtained for release of atenolol from systems with initial drug loading concentrations of 15% and 20% w/w showed evidence of curvature, indicating that release did not conform to the diffusion model.

The gradients of plots of amount released against the square root of time increase with increases in the initial drug loading concentration (see Fig. 4). It is interesting to note that the plot for pyrimethamine, for which release was measured over a wider concentration range than the other drugs, reached a limiting value when the initial pyrimethamine loading concentration exceeded 17.5% w/w. In order to maintain sink

conditions at initial drug loading concentrations of pyrimethamine greater than 10% w/w, the volume of the release medium was increased to 500 ml. It is possible that this increase in the volume of the release medium may have had a significant effect on the release of pyrimethamine because of an alteration in the hydrodynamics of the in vitro release system. The thickness of the hydrodynamic diffusion layer on the surface of the monoolein-water system, which offers resistance to the release of drug, should ideally be kept to a minimum by the appropriate adjustment of the agitation intensity to achieve infinite agitation (Falson-Reig et al., 1990). The increase in the volume of the release medium may have caused a decrease in the agitation intensity of the medium and a resulting increase in the thickness of the hydrodynamic diffusion layer, causing sufficient resistance to drug release to affect the amount of pyrimethamine released from the system. For example, the gradients of plots of amount released as a function of the square root of time for pyrimethamine, only increased by a factor of 1.2 as the initial drug loading concentration was doubled from 15 to 30% w/w, compared

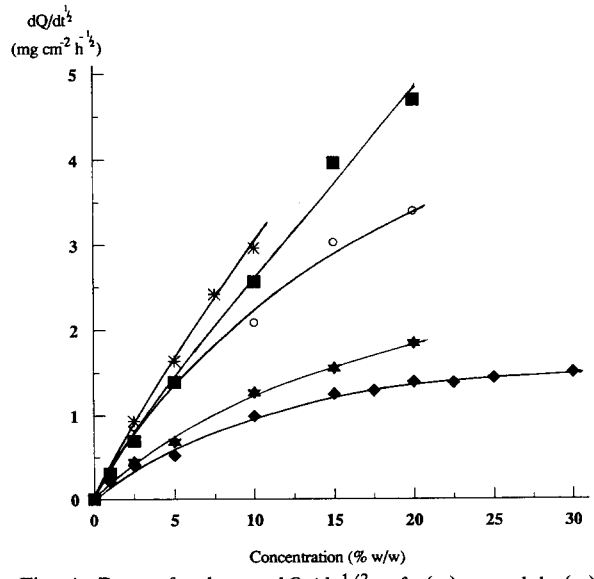


Fig. 4. Rate of release, $dQ/dt^{1/2}$, of: (*) atenolol; (○) melatonin; (★) pindolol; (■) propranolol; and (◆) pyrimethamine, from a monoolein-water system, as a function of the initial drug loading concentration.

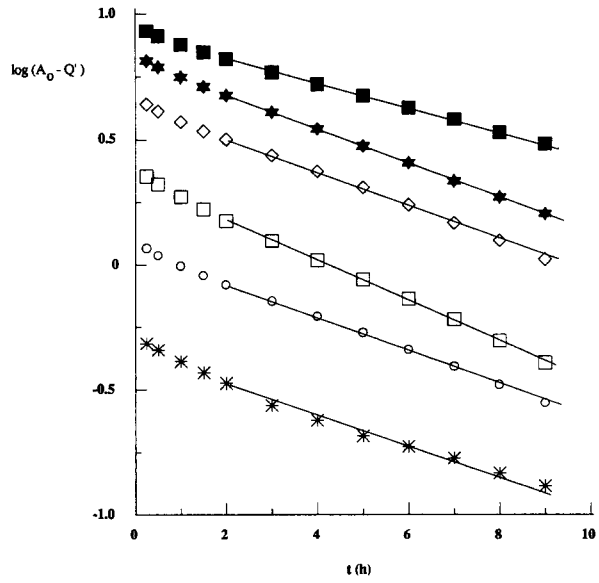


Fig. 5. Log amount of propranolol remaining in a monoolein-water system (mg), as a function of time, for initial drug loading concentrations of: (*) 1.0%; (○) 2.5%; (□) 5.0%; (◇) 10.0%; (★) 15.0%; (■) 20.0%.

to an almost 2-fold increase in the gradient when the initial drug loading concentration was increased from 5 to 10% w/w.

First-order release is described by:

$$\log(A_0 - Q') = \log A_0 - (k_1 t/2.303) \qquad (2)$$

where $A_0$ is the initial amount of drug present, $Q'$ represents the cumulative amount of drug released, $k_1$ is the first-order rate constant and $t$ denotes the time elapsed from the start of the release. Thus, plots of log amount of drug remaining in the system $(A_0 - Q')$ as a function of time are linear for systems in which drug release conforms to first-order kinetics.

Representative plots for propranolol (Fig. 5) show that the release data for this drug can be fitted to Eq. 2. Any initial deviation away from linearity can be accounted for by the presence of surface drug and may be ignored (Donbrow and Friedman, 1975). Similar plots were obtained for the other drugs examined, with the exception of atenolol systems of high initial drug loading concentration (15 and 20% w/w) which showed evidence of curvature. It was also noted that release

data obtained from pindolol systems showed an increased deviation from linearity when fitted to the first-order equation, rather than the diffusion model

The rate constant, $k_1$, was calculated from the release data for each initial drug loading concentration. Table 2 shows the mean rate constant ± standard deviation, as a function of the initial drug loading concentration, for the five drugs examined. As the initial drug loading concentration increased, there was generally a decrease in the rate constant except those for pindolol and pyrimethamine which reached limiting values. Rate constants for first-order release should be independent of initial drug loading concentration (Schwartz et al., 1968; Donbrow and Friedman, 1975). The concentration dependence of $k_1$ may be a consequence of the properties of these monoolein-drug systems, some of which contain drug concentrations exceeding the saturation solubility.

In an attempt to distinguish between diffusion-controlled and first-order models, both of which gave satisfactory fits of release data, an approach proposed by Schwartz et al. (1968) was used. This analytical treatment of data has previously been shown to be successful in assigning a model for drug release from several matrix systems (Hecquet et al., 1984; Ritschel and Udeshi, 1987; Abdallah et al., 1988).

Differentiation of Eq. 1 gives the change of cumulative amount of drug release, $Q'$, with time ($Q' = QS$, where $S$ is the surface area of the system):

$$dQ'/dt = k^2S^2/2Q' \quad (3)$$

Eq. 3 can now be compared with the first-order equation written in the form:

$$dQ'/dt = k_1A_0 - k_1Q' \quad (4)$$

Thus, $dQ'/dt$ is directly proportional to $Q'$ for first-order kinetics, but inversely proportional to $Q'$ for the diffusion model. Plots of the rate of drug release as a function of $Q'$ and $1/Q'$ can thus, in principle, be used to determine the release model. The rate of drug release was calculated on a point to point basis from the data of cumulative amount of drug released as a function of time (Benita and Donbrow, 1982), using the same time intervals as those shown in Fig. 1 and 2. The plots of $dQ'/dt$ as a function of $Q'$, and $dQ'/dt$ as a function of $1/Q'$, for a monoolein-water system loaded with 2.5% w/w propranolol, are shown in Fig. 6. On the assumption that the first few data points may be ignored because of surface effects, linear plots are obtained for both models, i.e., this method of data treatment cannot be used to distinguish between the applicability of the two release models. A similar conclusion was drawn from analysis of the release data of each of the drugs studied, with the exception of atenolol, as discussed above.

Application of residuals analysis to the release data was also unsuccessful in allocating a release

Table 2
First-order rate constants for drug release from monoolein-water liquid crystalline systems (S.D., standard deviation)

| Concentration (% w/w) | Rate constant ($h^{-1}$) (mean ± S.D.) | | | | |
|---|---|---|---|---|---|
| | Atenolol | Melatonin | Pindolol | Propranolol | Pyrimethamine |
| 1.0 | | 0.18 ± 0.02 | 0.15 ± 0.03 | 0.19 ± 0.06 | 0.08 ± 0.014 |
| 2.5 | 0.37 ± 0.07 | 0.24 ± 0.06 | 0.08 ± 0.01 | 0.17 ± 0.05 | 0.04 ± 0.001 |
| 5.0 | 0.27 ± 0.15 | 0.16 ± 0.04 | 0.05 ± 0.00 | 0.20 ± 0.28 | 0.02 ± 0.003 |
| 7.5 | 0.26 ± 0.02 | | | | |
| 10.0 | 0.22 ± 0.01 | 0.12 ± 0.02 | 0.04 ± 0.07 | 0.18 ± 0.06 | 0.02 ± 0.003 |
| 15.0 | | 0.09 ± 0.02 | 0.04 ± 0.01 | 0.14 ± 0.02 | 0.02 ± 0.004 |
| 17.5 | | | | | 0.01 ± 0.001 |
| 20.0 | | 0.06 ± 0.00 | 0.03 ± 0.00 | 0.11 ± 0.01 | 0.01 ± 0.002 |
| 22.5 | | | | | 0.01 ± 0.001 |
| 25.0 | | | | | 0.01 ± 0.001 |
| 30.0 | | | | | 0.01 ± 0.001 |

model. No significant trends in the residual values were noted which allowed the unequivocal assignment of release model.

### 3.4. Zero-order release of atenolol

Examination of the release profile for atenolol systems with initial drug loading concentrations of 15 and 20% w/w (Fig. 1) shows that the release after 4 h appeared to conform to a zero-order (time-independent) release model (Peppas, 1985). In addition, release data for these high initial drug loading concentrations could not be fitted to either diffusion-controlled or first-order equations. The release of drug from a monoolein-water system where the initial drug loading concentration is greater than the saturation solubility of the drug can be assumed to follow a three-stage process involving the dissolution of suspended drug in the monoolein-water system as dissolved drug is released; the diffusion of dissolved drug through the monoolein-water system and the transfer of drug across the monoolein-water system/release medium interface. A similar process was described for steroid release from elastomers (Haleblian et al., 1971). If the dissolution of the suspended drug is the rate-limiting step for drug release, then the release of drug becomes time independent, i.e., the release data can be fitted to a zero-order release model (Chandrasekaran and Paul, 1982; Chang and Himmelstein, 1990).

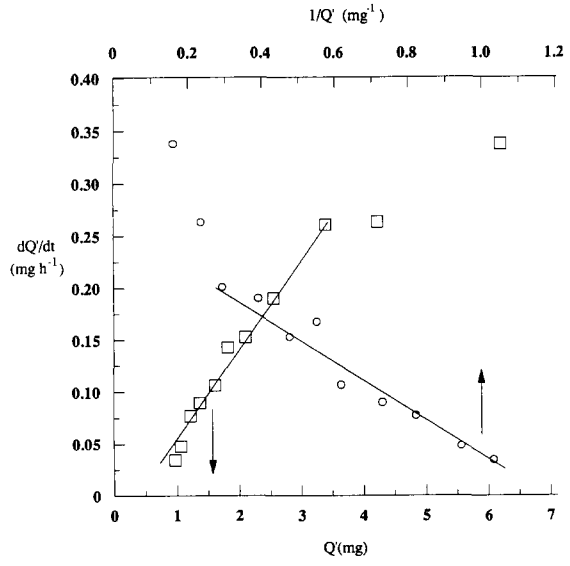


Fig. 6. Rate of release (mg $h^{-1}$) as a function of reciprocal amount of drug released ($1/Q'$) or as a function of amount of drug released ($Q'$). Data generated from a monoolein-water system containing an initial drug loading concentration of 2.5% w/w propranolol.

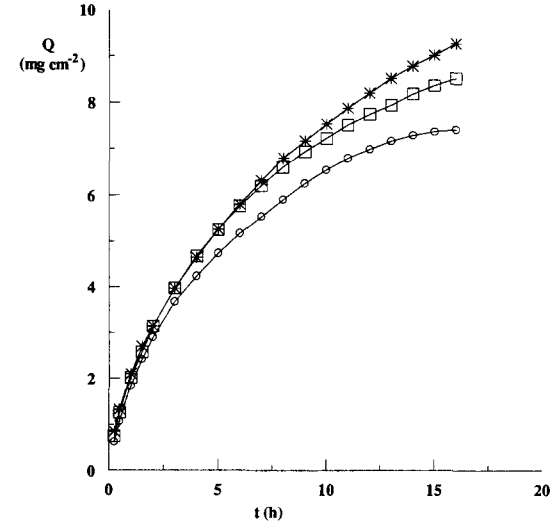


Fig. 7. Cumulative amount of melatonin released as a function of time, for monoolein-water systems of weight ratios: (*) 4:1; (○) 2:1; (□) 1:1, (monoolein/water). Initial drug loading concentration = 10% w/w.

It is possible that the high aqueous solubility of atenolol (2.5% w/w), may have promoted a significant increase in the diffusion of the drug from the monoolein-water system, such that the dissolution of the suspended drug became the rate-limiting step for drug release in systems of high atenolol loading.

### 3.5. Influence of water content on release characteristics

The cumulative amount of drug released from monoolein-water systems of several different weight ratios was measured as a function of time. Fig. 7 shows the release profiles obtained for melatonin, similar plots were obtained for all five drugs examined, at all monoolein/water weight ratios. The gradient of the linear portion ob-

tained when the data were plotted according to the diffusion model was used for comparing the effect of changes in the monoolein/water weight ratio on the release of drugs from the system (see Table 3). Statistical analysis, using one-way analysis of variance, on the release data shown in Table 3, revealed that there was no significant difference ($p = 0.05$) in the release characteristics of the drug over the monoolein-water weight ratio investigated.

In the presence of excess water, monoolein will absorb sufficient water to form the cubic phase (Engström et al., 1988). A drug incorporated into the monoolein-water liquid crystalline system should therefore always be released from the cubic phase (Engström et al., 1989). However, if incorporated drug modifies the phase behaviour of the system, then a cubic phase may not necessarily form in excess water. Any modification of the type of liquid crystalline phase formed may cause changes in the amount of drug taken into the liquid crystalline system and its site of incorporation. To investigate possible changes in phase behaviour, phase studies were carried out on monoolein-water systems of weight ratios; 4:1, 2:1 or 1:1, with a drug loading concentration of 10% w/w. All systems had viscous isotropic properties, demonstrating the existence of a cubic phase (Lindblom et al., 1979; Larsson et al., 1980). Thus, it may be anticipated that each of the systems reported in this study, irrespective of the initial water content, would swell to its maximum water capacity upon the addition of the release medium. Hence, the drug would be released from the fully swollen cubic phase which formed in situ when the release medium was added, rather than from the partially swollen cubic phase which was present when the system was prepared initially.

A monoolein/water weight ratio of 1:1 may be considered to produce a fully swollen system, (the maximum water capacity of a monoolein-water cubic phase is approx. 41% w/w, (Patton and Carey, 1979)). It was therefore probable that these 1:1 systems had excess water present and indeed small quantities of excess water were sometimes discernible during their preparation, although it did not appear to influence the formation of these systems.

Table 3
Drug release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) from monoolein-water systems with the monoolein/water weight ratios indicated (the initial drug loading concentration was 10% w/w in all cases; S.D., standard deviation)

| Drug | Release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) (mean ± S.D.) | | |
|---|---|---|---|
| | Monoolein/water weight ratio | | |
| | 4:1 | 2:1 | 1:1 |
| Atenolol | 2.73 ± 0.14 | 2.96 ± 0.19 | 2.67 ± 0.14 |
| Melatonin | 2.52 ± 0.11 | 2.08 ± 0.14 | 2.61 ± 0.32 |
| Pindolol | 1.36 ± 0.09 | 1.27 ± 0.11 | 1.17 ± 0.11 |
| Propranolol | 2.14 ± 0.19 | 2.56 ± 0.40 | 3.01 ± 0.22 |
| Pyrimethamine | 0.96 ± 0.01 | 0.99 ± 0.13 | 0.97 ± 0.03 |

Table 4
Influence of storage conditions on drug release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) from a monoolein-water system (2:1 monoolein/water) containing 10% w/w propranolol or pyrimethamine (S.D., standard deviation)

| Storage condition | Release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) (mean ± S.D.) | |
|---|---|---|
| | Propranolol | Pyrimethamine |
| 1 day at 4°C | 2.75 ± 0.34 | 0.96 ± 0.13 |
| 8 days at 4°C | 2.61 ± 0.08 | 0.94 ± 0.04 |
| 15 days at 4°C | 2.56 ± 0.40 | 0.99 ± 0.13 |
| 1 month at 4°C | 2.64 ± 0.26 | 0.85 ± 0.07 |
| 2 months at 4°C | 2.46 ± 0.09 | 0.84 ± 0.03 |
| 6 months at 4°C | 2.12 ± 0.20 | 0.92 ± 0.15 |
| 8 days at 26°C | [a] | 0.90 ± 0.12 |
| 15 days at 26°C | [a] | 0.91 ± 0.08 |
| 15 days at 4°C, removed and equilibrated to 26°C for 2 h | 2.21 ± 0.30 | 0.94 ± 0.12 |

[a] Systems were unstable.

### 3.6. Influence of storage conditions on release characteristics

The release data obtained from these experiments were fitted to the diffusion model to allow comparison of the data. Table 4 shows the release characteristics of propranolol and pyrimethamine from monoolein-water systems stored under the conditions specified for selected time intervals.

There was no significant difference ($p = 0.05$) in the release of either propranolol or pyrimethamine from the monoolein-water systems when stored in the dark at 4°C for a period of up to 6 months. Some systems which were stored for 6 months, however, deteriorated in appearance showing what appeared to be microbial growth and these data were excluded.

There was no significant difference ($p = 0.05$) in the release of pyrimethamine when the storage temperature was either 4°C or 26°C, or if the system was allowed to equilibrate at 26°C for 2 h prior to examination of in vitro drug release, after storage at 4°C for 15 days. In contrast, there was a significant difference in the release of propranolol from monoolein-water systems stored at different storage temperatures. Propranolol systems stored at 26°C for 8 or 15 days were less viscous than the systems stored at 4°C and examination of the dissolution medium at the end of release experiments involving these systems revealed the presence of dispersed liquid crystalline globules, indicating instability. It is probable that the instability of these systems arose from the recrystallisation of propranolol into the system and the higher temperature of storage, which may have caused an interaction between propranolol and the monoolein-water system which did not occur at 4°C.

Table 5 shows that the release of propranolol from systems which had been stored at 4°C and then allowed to equilibrate to 26°C for 2 h prior to the in vitro drug release studies, was, at all initial drug loading concentrations, not different statistically ($p = 0.05$) from systems stored at 4°C and then analysed almost immediately. These systems were stable, in contrast to those which were stored for longer periods at 26°C.

Table 5
Influence of storage conditions on drug release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) from monoolein-water systems (2:1 monoolein/water) containing propranolol (S.D., standard deviation)

| Concentration (% w/w) | Release (mg $h^{-\frac{1}{2}}$ $cm^{-2}$) (mean ± S.D.) | |
|---|---|---|
| | 15 days at 4°C | 15 days at 4°C + 2 h at 26°C |
| 1.0 | 0.31 ± 0.02 | 0.27 ± 0.03 |
| 2.5 | 0.69 ± 0.05 | 0.69 ± 0.03 |
| 5.0 | 1.39 ± 0.13 | 1.20 ± 0.05 |
| 10.0 | 2.56 ± 0.40 | 2.21 ± 0.30 |
| 15.0 | 3.96 ± 0.15 | 3.69 ± 0.06 |
| 20.0 | 4.70 ± 0.40 | 4.73 ± 0.37 |

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