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Binding of drugs to monoglyceride-based drug delivery systems

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Abstract

Unsaturated monoglycerides such as glycerol monooleate or monolinoleate form a cubic phase at body temperature and with excess water. This mesophase has been used as sustained release carrier. During dissolution studies, an incomplete release of various highly water-soluble drugs was observed with the cubic phase. Amphiphilic drugs such as chlorpheniramine maleate, diltiazem HCl or propranolol HCl were bound to the monoglyceride and incompletely released. The absorption of various drugs to the monoglycerides was studied. The surface activity of the drugs—as measured by the surface tension of drug solutions—correlated well with the drug absorption to the cubic phase and the release profiles. A pH-dependent drug absorption was observed with the cationic drug, propranolol HCl. More drug was absorbed at a higher pH, probably because of the complexation with free fatty acids being present in the monoglyceride. The solubilization of the drug molecules in the different domains of the amphiphilic, hydrated monoglycerides affected the phase transformation. Above a certain concentration, hydrophilic drugs (e.g. chlorpheniramine maleate, propranolol HCl) transformed the cubic phase into a lamellar phase and lipophilic drugs (ibuprofen, propranolol) into an inverted hexagonal phase. © 1997 Elsevier Science B.V.

Keywords: Cubic phase; Lipids; Liquid crystalline phase; Monoglycerides; Sustained drug release

1. Introduction

Although polymers are predominantly used as sustained release carrier or coating materials, lipidic materials present several interesting features as drug carriers. They can be obtained with varying polarity, can be well characterized and their melts have, in contrast to polymer melts, a low melt viscosity. This allows processing without organic solvents.

Unsaturated monoglycerides such as glycerol monooleate or linoleate belong to the class of water-insoluble but amphiphilic lipids. Depending on the water content and temperature, they from various mesophases (Brokaw and Lyman, 1958;

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Lutton, 1965; Caffrey, 1987). At body temperature, a cubic phase is formed via reversed micellar and lamellar phases upon increasing the water content. The structure of the cubic phase can be described as isotropic with curved lipid bilayers extending in three dimensions separated by water channels (Hyde et al., 1984). The cubic phase is highly viscous and physically stable in excess water.

Because of its hydrophobic/hydrophilic domains and its physical properties, the cubic phase has been evaluated as a drug delivery system for both water-soluble and -insoluble drugs (Engström, 1990; Engström and Engström, 1992; Engström et al., 1995). Peptides were incorporated into the cubic phase to control their release and to obtain protection against enzymatic degradation (Ericsson et al., 1991). Because of its high viscosity, it is desirable to form the cubic phase in situ in the body (Engström et al., 1992; Chang and Bodmeier, 1995; Bodmeier and Chang, 1996). For example, for oral drug delivery, the drug-containing monoglyceride melt could be filled into hard gelatin capsules and be congealed. In contact with gastrointestinal fluids, the monoglyceride would transform into the cubic phase after dissolution of the gelatin capsule (Wyatt and Dorschel, 1992).

Various hydrophilic drugs were incorporated into glycerol monooleate (Wyatt and Dorschel, 1992). Their release in simulated gastric and intestinal fluids was sustained, but complete. Surprisingly, in this study, several water-soluble drugs were not completely released from the monoglyceride matrix. The objective of this study was to investigate the incomplete release, the drug binding to unsaturated monoglyceride matrix systems and the influence of the addition of drugs on the phase behavior.

2. Material and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: distilled monolinoleate and monooleate (Myverol® 18–92 and 18–99) (Eastman Chemical, Kingsport, TN), chlorpheniramine maleate, diltiazem HCl, griseofulvin, ibuprofen, phenylpropanolamine HCl, propranolol HCl (propranolol base was prepared through precipitation from a saturated aqueous solution of propranolol HCl with 0.1 N NaOH, washing with water and drying), pseudoephedrine HCl, theophylline anhydrous, 1-monolinoleoyl-*rac*-glycerol, 1-monooleoyl-*rac*-glycerol (Sigma, St. Louis, MO).

2.2. Methods

Drug-containing monoglyceride matrices were prepared by the following procedure. The monoglycerides were molten at 50°C in a water bath. The drug crystals (10% w/w) were then added to the molten monoglyceride and homogeneously dispersed by using a magnetic stir bar. The entrapment of air bubbles was carefully prevented by adjusting the stirring speed. The molten drug-containing monoglyceride (3 g) was poured into petri-dishes (5 cm in diameter) and immediately congealed in a freezer (T = −15°C) to prevent the sedimentation of the drug crystals to the bottom of the petri-dishes. The monoglyceride matrices were then kept at room temperature prior to the dissolution studies.

A horizontal shaker method (37°C, 80 revs./min, 300 ml 0.1 M pH 7.4 phosphate buffer, $n = 3$, Lab-Line Orbit Environ-Shaker, Lab-Line Instruments, Melrose Park, IL) was used for dissolution studies. The filled petri-dishes were, placed into media-containing screw capped glass jars and samples were withdrawn at predetermined time intervals and assayed spectrophotometrically either directly or after appropriate dilution with the release medium (Hewlett Packard HP8452A Diode-array Spectrophotometer, Avondale, PA) (chlorpheniramine maleate, $\lambda_{max} = 262$ nm; diltiazem HCl, $\lambda_{max} = 235$ nm; phenylpropanolamine HCl, $\lambda_{max} = 270$ nm; pseudoephedrine HCl, $\lambda_{max} = 260$ nm; propranolol HCl, $\lambda_{max} = 290$ nm; theophylline anhydrous, $\lambda_{max} = 272$ nm).

The surface tension of the drug solutions was determined at room temperature by using a DuNouy tensiometer (Fisher Surface Tensiomat,

Model 21, Fisher Scientific, Houston, TX) with a platinum-iridium ring (6 cm mean circumference). The ring was heated in a flame before use. The drug solutions (10 ml, 0.1 M pH 7.4 phosphate buffer) were placed in petri dishes (6 cm diameter). The platinum-iridium ring was then wetted by the solution and pulled through the solution surface. The surface tension of double distilled water was used for calibration and the surface tension of the drug solutions in 0.1 M pH 7.4 phosphate buffer was recorded in dynes/cm after three consecutive measurements did not differ by not more than $\pm$ 5%.

Polarized light microscopy was used to characterize the liquid crystalline phases according to the textures described by Rosevear (1954). The cubic phase had an isotropic nature; it was easily identified by its high viscosity.

The absorption of propranolol HCl to pure monoglycerides (1-monolinoleoyl-*rac*-glycerol and 1-monooleoyl-*rac*-glycerol) was conducted directly in a quartz cuvette. The monoglyceride film (1 mg) was cast at the bottom of the cuvette from a methylene chloride solution. 3 ml propranolol HCl solution (50 μg/ml) (0.1 M pH 7.4 phosphate buffer, 23°C) was placed in the cuvette. The UV-absorption at a wavelength of 290 nm was measured with the spectrophotometer at fixed time intervals.

The drug absorption study was conducted by pouring 0.6 g of molten Myverol® 18–92 into 20-ml glass vials, followed by congealing at room temperature. Pre-warmed drug solutions (20 ml) (0.1 M pH 7.4 phosphate buffer) were then added. The concentration of the drugs (19.3–735.0 μg/ml) was selected in the range, which could be directly measured spectrophotometrically without dilution. The absorption study was conducted in a horizontal shaker as described with the release studies (37°C, 80 revs./min). The decrease of the drug solution concentration was determined spectrophotometrically (Hewlett Packard HP8452A Diode-array Spectrophotometer, Avondale, PA).

The absorption of drugs to the monoglycerides was characterized by a weight ratio, $R = (W_t - W_a)/W_t$, wherein W_t represents the total amount of drug in the system, W_a represents the amount of drug in the aqueous phase and $(W_t - W_a)$ the amount of drug in the lipid phase. Three methods, a heating method, an absorption method and a desorption method were evaluated to determine the weight ratio of chlorpheniramine maleate. With all methods, 30 mg chiorpheniramine maleate were equilibrated with 0.3 g Myverol® 18–92 and 20 ml 0.1 M pH 7.4 buffer. The absorption method is the same as the one mentioned above. The desorption method was conducted by incorporating the drug in the monoglyceride matrices. The heating method was conducted by heating 20 ml of drug solution (1.5 mg/ml, 0.1 M pH 7.4 phosphate buffer) with 0.3 g of monoglycerides in a screw-capped glass vial to 100°C in a water bath. The mixture was then vigorously vortex-mixed for 1 min and shaken in a horizontal shaker until reaching room temperature. To separate the lipid phase from the aqueous phase, the vials were centrifuged at 2000 revs./min for 1 h (Model TJ-6 centrifuge, Beckman, Palo Alto, CA).

For the pH-dependent absorption study, 0.5 g Myverol® 18–92 were equilibrated with 20 ml drug solution [1.88 mg/ml (for Fig. 8) or varying concentration (for Fig. 9), 0.1 N HCl or 0.1 M pH 7.4 phosphate buffer] at 37°C for 4 days. The amount of the drug in the aqueous phase was determined spectrophotometrically (Hitachi U-1100 Spectrophotometer) at the specific wavelength for each drug. The amount of drug in the lipid phase was calculated by subtracting the amount of drug remaining in the aqueous phase from the total amount of drug in the solution.

3. Results and discussions

Unsaturated monoglycerides form various liquid crystalline phases depending on the temperature and water content. A highly viscous and physically stable mesophase, the cubic phase, forms at body temperature in contact with excess water. In this study, technical grade distilled unsaturated monoglycerides (Myverol® 18–92 and Myverol® 18–99) were evaluated as drug carriers. Myverol® 18–92 is mainly composed of 67.5% glyceryl monolinoleate and 18.7% glyceryl monooleate, while Myverol® 18–99 is mainly

composed of 60.9% glyceryl monooleate and 21.0% glyceryl monolinoleate. Both products are composed of more than 80% of unsaturated monoglycerides and more than 95% of monoglycerides.

The cubic phase has been reported to provide sustained release for hydrophilic drugs (Wyatt and Dorschel, 1992). Surprisingly, chlorpheniramine maleate, a water-soluble drug, was not completely released from the monoglyceride matrix (Myverol 18–92), which transformed into a cubic phase in contact with the dissolution medium (Fig. 1). The release of the drug was highly sustained and levelled of at about 60% drug released. No further drug release was observed in the 48 to 168 h time-interval. Since the dissolution study was conducted under sink conditions, the incomplete release was not due to a limited solubility of the drug in the dissolution medium. This suggested that a fraction of the drug was bound to the swollen liquid crystalline phase. After replacing the dissolution medium repeatedly with fresh medium, further portions of the drug were released and a new equilibrium state was obtained without further drug release (Fig. 1).

It was therefore interesting to investigate the release behaviour and binding of various drugs to the monoglyceride carrier. The model drugs selected were: chlorpheniramine maleate, diltiazem HCl, phenylpropanolamine HCl, propranolol HCl, pseudoephedrine HCl and theophylline anhydrous. The release profiles of the drugs from Myverol 18–99 matrices in pH 7.4 phopsphate buffer are shown in Fig. 2. A nearly complete release was observed with pseudoephedrine HCl, phenylpropanolamine HCl and theophylline anhydrous, while chlorpheniramine maleate, propranolol HCl and diltiazem HCl were not completely released. With many drug delivery systems, the solubility of the drug is a decisive factor affecting the rate of drug release. The solubility of the drugs was not a determining factor for the incomplete drug release with the monoglyceride matrices. For example, theophylline was completely released, however, it had the lowest solubility of all drugs investigated. Chlorpheniramine maleate had a higher solubility than phenylpropanolamine HCl, however, phenylpropanolamine HCl was completely released within 24 h. This indicated that interactions between the three drugs which were not completely released and the monoglyceride matrices occurred. Since monoglycerides are amphiphilic polar lipids, the solubilization of the drug in the amphiphilic monoglycerides or in the mesophases may play an important role. Various drugs have been reported to interact with amphiphilic lipids (Müller-Goymann and Hamann, 1993; Papantoniou and Müller-Goymann, 1995; Bodmeier and Chang, 1996).

The surface activity of drug molecules can be determined by measuring the surface tension of drug solutions (Fig. 3). A decrease in surface tension was observed for diltiazem HCl, chlorpheniramine maleate and propranolol HCl solu-

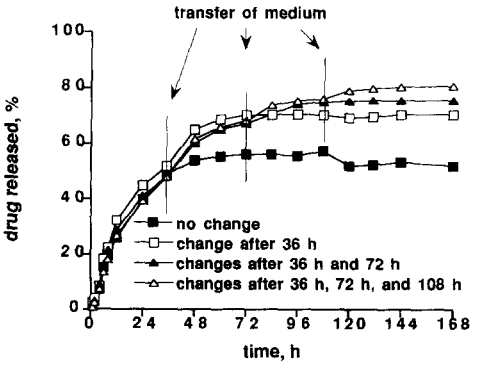

Fig. 1. Effect of changing the dissolution medium (0.1 M pH 7.4 phosphate buffer) on the chlorpheniramine maleate release from Myverol® 18–92 matrices.

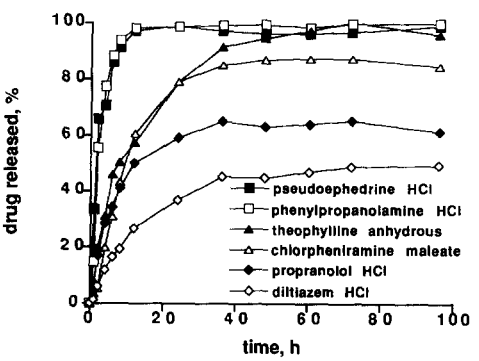

Fig. 2. Release from various drugs from Myverol® 18–99 matrices in 0.1 M pH 7.4 phosphate buffer.

tions in 0.1 M pH 7.4 phosphate buffer. The other drugs, phenylpropanolamine HCl and pseudoephedrine HCl, did not significantly affect the surface tension and were non-amphiphilic molecules. A good qualitative match was obtained by comparing the maximum amount of drug released and the surface tension. The amphiphilic drug molecules could associate at the monoglyceride-water interface. The high interfacial area of the monoglyceride mesophase is able to solubilize significant amounts of amphiphilic drug molecules. Diltiazem HCl showed the lowest percentage of drug release; however, the surface tension of diltiazem HCl solutions was higher than that of propranolol HCl solutions. The pK_a value of diltiazem HCl is 7.7; therefore, approximately 50% of the drug was unionized at pH 7.4. This explained the slower release when compared with propranolol HCl, which was completely ionized at pH 7.4.

The addition of a drug to the monoglycerides may affect the formation and structure of the mesophases. The unsaturated monoglycerides form liquid crystals that consist of three domains: a hydrophilic domain, a hydrophobic domain and an interface between the hydrophilic and hydrophobic domains. The drug can be present in the hydrophilic domain (hydrophilic drugs), hydrophobic domain (lipophilic drugs), or at the interface (amphiphilic drugs). The presence of the drug in the different domains can affect the phase behavior. This can be described by

$$R = \frac{V_h}{a_0 l_c}$$

Ninham's ratio (Mitchell and Ninham, 1981) where V_h is the volume of the hydrocarbon chain, a_0 is the cross-sectional area of the polar group, and l_c is the length of the amphiphile. Since l_c is considered constant, the transformation of the mesophases is affected by V_h and a_0. The location of the solubilized drug component influences these two parameters. If V_h is equal to a_0, a lamellar phase may form. If $V_h > a_0$, an inverted cubic, hexagonal or micellar phase may form and if $V_h < a_0$, a normal hexagonal phase or a micellar phase may form. Theoretically, the unsaturated monoglyceride cubic phase has a larger V_h than a_0. If the added drug stays preferentially in the hydrophilic portion, a_0 will increase; this may transform the cubic phase into a lamellar phase. Further increasing the amount of drug may transform this phase into a hexagonal and even into a micellar phase. For lipophilic substances, increasing the amount of the drug will increase V_h and, therefore, transform the cubic phase into an inverted hexagonal phase or an inverted micellar phase. If the drug is surface active and favorably remains at the interface, both V_h and a_0 may increase, but to a different extent.

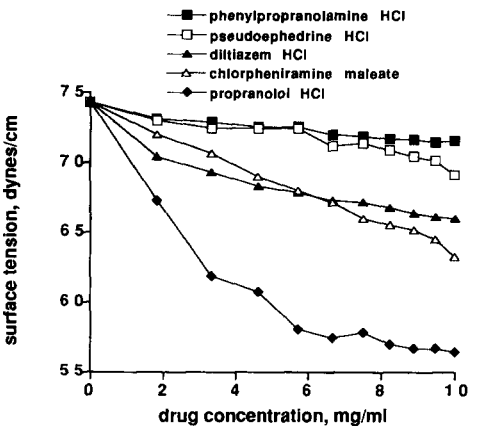

Fig. 3. Surface tension measurements of various drug solutions (22°C, 0.1 M pH 7.4 phosphate buffer).

Drug substances with different solubilities were selected for the phase transformation studies. Various amounts of drugs were incorporated into the cubic phase (30% water); the mesophases were identified by polarized light microscopy. Adding more than 2% of chlorpheniramine maleate, a water soluble drug, to the cubic phase transformed it into a lamellar phase. The viscosity of the lamellar phase decreased with increasing drug loading. The same results were obtained with the other hydrophilic drugs, diltiazem HCl, propranolol HCl and pseudoephedrine HCl. The incorporation of ibuprofen, a lipophilic drug, transformed the cubic phase into an inverted hexagonal phase. The inverted hexagonal phase was more viscous than the lamellar phase, however, less viscous than the cubic phase. An inverted micellar phase was formed at a drug loading of 20%; the system became flowable. The

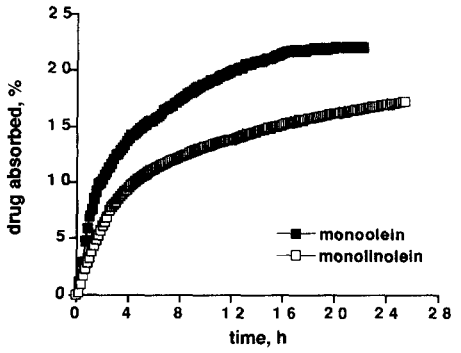

Fig. 4. Absorption of propranolol HCl to pure glyceryl monoleate and glyceryl monolinoleate from 0.1 M pH 7.4 phosphate buffer.

anisotropic phase was dispersed into the isotropic phase. Propranolol also transformed the cubic phase into an inverted hexagonal phase. At 15% propranolol, the inverted hexagonal phase transformed into an emulsion. Griseofulvin, a drug which is neither soluble in water nor the monoglyceride, showed almost no effect on the phase transformation. Dispersed drug crystals were observed under a polarized microscope. Unless the drug can be solubilized in the mesophase, no effect on the mesophase transformation is expected.

In a previous study, the formation of insoluble ion pairs between fatty acids being present in the monoglycerides and cationic drugs was partly responsible for the sustained and incomplete drug release (Chang, 1995). In order to be certain that the incomplete drug release was not due to the ionic interaction between cationic drug molecules and the ionized free fatty acids, the absorption of propranolol HCl to pure monoglycerides (glyceryl monooleate and glyceryl monolinoleate with a purity of approximately 99%) was investigated (Fig. 4). Propranolol HCl was absorbed by the monoglycerides, the absorption being faster with glyceryl monooleate than with glyceryl monolinoleate. The affinity of the drug molecules to the monoglyceride mesophase therefore limited the amount of drug released.

The absorption of drugs to the monoglycerides was investigated by equilibrating 20 ml drug solution with 0.5 g Myverol® 18–92 in a 20 ml vial at 37°C. Fig. 5 shows the fraction of the drug remaining in the aqueous phase vs. time during the absorption studies. Large amounts of propranolol HCl, diltiazem HCl and chlorpheniramine maleate were absorbed. The order of the amount of drug absorbed followed the same order as the order obtained with surface tension measurement. The amphiphilic properties of the drug molecules determined the absorption of the drug to the cubic phase and therefore affected the drug release. Pseudoephedrine HCl, theophylline anhydrous and phenylpropanolamine HCl, drugs, which were not absorbed by the monoglycerides, were completely released.

The absorption of chlorpheniramine maleate into the monoglycerides was investigated with three different methods: the heating, the absorption and the desorption methods. In the heating method, the monoglyceride was incubated with the aqueous drug solution at 100°C until the L_2-phase formed. After vortex-mixing, the system was centrifuged, cooled to 37°C and the supernatant was analyzed for unbound drug. When compared to the absorption and desorption method, the heating method was faster. The absorption and desorption methods took longer to reach equilibrium. All these methods were promising and gave the same weight ratio (defined as the ratio between the amount of drug in the lipid phase to the total amount of drug in the system) for the drug absorption (Fig. 6).

The absorption of various drugs into the monoglycerides at different drug concentrations was

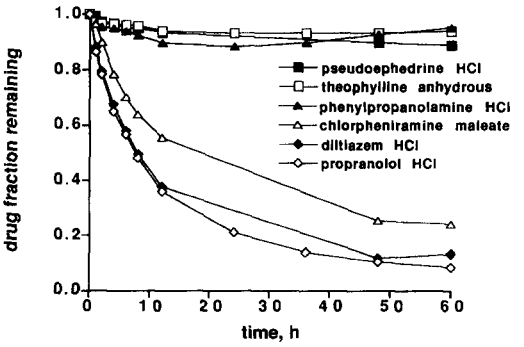

Fig. 5. Absorption of drugs to Myverol® 18–92 matrices from 0.1 M pH 7.4 phosphate buffer.

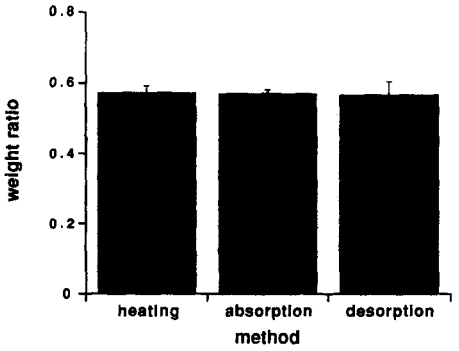

Fig. 6. Weight ratios of chlorpheniramine maleate–Myverol® 18–92 matrices determined by different methods (0.1 M pH 7.4 phosphate buffer, 37°C).

studied by the absorption method (Fig. 7). Except for pseudoephedrine HCl, proportionally more drug was taken up at low drug concentrations. For example, the weight ratio of propranolol HCl was above 0.85 at a concentration of 0.1 mg/ml, then it dropped to less than 0.47 at a drug concentration of 10 mg/ml. It was speculated that at lower drug concentrations, the interfacial area of the cubic phase is still available for drug molecules. With increasing drug concentration, the interface became saturated with drug molecules. The weight ratio then levelled off upon further increasing the drug concentration. No effect was shown for pseudoephedrine HCl due to the almost non-existent absorption of pseudoephedrine HCl to the monoglyceride mesophases.

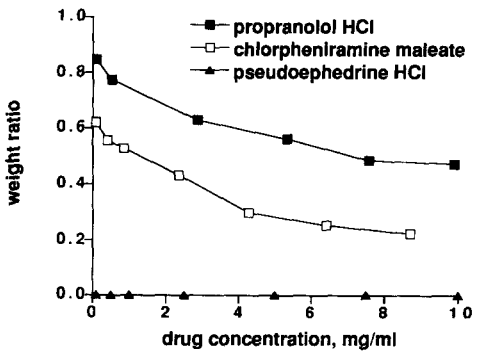

Fig. 7. Effect of drug concentration on the weight ratio (Myverol® 18–92, 0.1 M pH 7.4 phosphate buffer, 37°C).

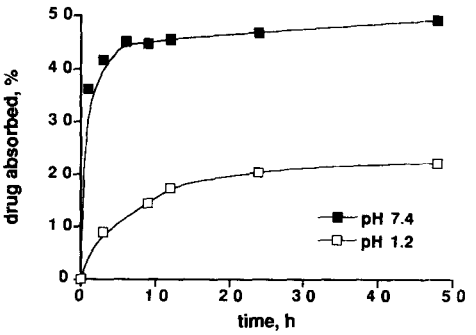

Fig. 8. Effect of pH on the propranolol HCl absorption to Myverol® 18–99.

Since the pH of the medium affects the ionization of free fatty acids in the monoglycerides and the mesophase formation, the drug absorption will also be influenced by the pH of the medium. As mentioned previously, the swelling capacity of monoglycerides in 0.1 N HCl was lower than in pH 7.4 buffer, however the release of the cationic drug, propranolol HCl, was slower in pH 7.4 buffer because of the complexation of the drug with oppositely charged fatty acids. Fig. 8 shows the absorption of propranolol HCl in 0.1 N HCl and pH 7.4 buffer. A significantly higher amount of propranolol HCl was absorbed in pH 7.4 buffer, the difference being more than 2-fold. This was probably caused by the interaction between free fatty acids and propranolol HCl in pH 7.4 buffer. Fig. 9 shows the effect of drug concentration on the weight fraction of propranolol HCl absorbed. Again, a higher drug absorption in the pH 7.4 buffer medium was observed.

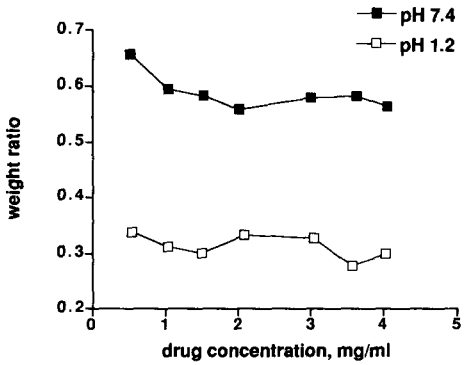

Fig. 9. Effect of the propranolol HCl concentration and pH on the weight ratio (Myverol® 18–92).

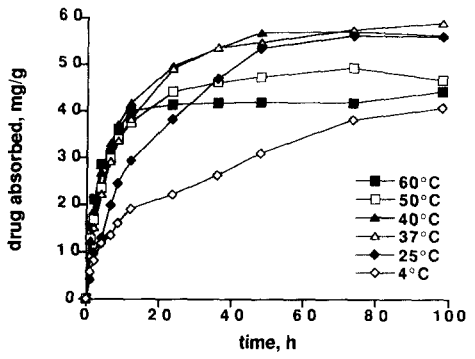

Fig. 10. Effect of temperature on the absorption of propranolol HCl to Myverol® 18–92 matrices (0.1 M pH 7.4 phosphate buffer).

Lyotropic liquid crystalline phases are sensitive to temperature changes, for example during storage; phase transformations and changes in water content might occur as a function of temperature. As described previously, the swelling of monoglycerides was sensitive to temperature (Chang, 1995). The swelling capacity of the monoglyceride decreased as the temperature increased. However, the drug diffusivity increased as the temperature increased. In this study, the influence of temperature on drug absorption was investigated (Fig. 10). The drug absorption was studied at 4°C, 25°C, 37°C, 40°C, 50°C and 60°C. Both the maximum amount of drug absorbed and the absorption rate were found to be sensitive to temperature. Myverol® 18–92 formed a gel phase a 4°C and a cubic phase at temperatures above room temperature. Except with 4°C, the maximum drug uptake decreased with increasing temperature and leveled off at temperatures above 50°C.

In conclusion, the addition of drugs to monoglyceride matrices affected their phase and release behaviour in water. The incomplete release of several hydrophilic drugs from the monoglyceride systems was due to the binding of the drug molecules to the monoglyceride mesophases.

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