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Low viscosity monoglyceride-based drug delivery systems transforming into a highly viscous cubic phase

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Abstract

A highly viscous, but not injectable, cubic phase with sustained drug release properties forms from unsaturated monoglycerides (glycerol monooleate or monolinoleate) in contact with aqueous media. In order to obtain a flowable, injectable system, low viscosity monoglyceride-based formulations (lamellar phase, isotropic solution phase or hexagonal phase), which transform into the cubic phase after contact with dissolution fluids, were developed. The addition of either drugs (drug-induced) or organic solvents (solvent-induced) to the monoglyceride–water system resulted in low viscosity systems. Chlorpheniramine maleate (CPM) and propranolol (PPL) HCl were selected as model drugs for the drug-induced systems, and injectable solvents (e.g. ethanol, polyethylene glycol, propylene glycol, *N*-methyl-2-pyrrolidone) for the solvent-induced systems. Triangular phase diagrams were used to characterize the three-component mixtures, and the different mesophases were identified by polarized light microscopy. Various monoglyceride compositions with low viscosities were investigated in drug release studies, during which they transformed into the cubic phase. For the drug-induced low viscosity formulations, the drug release decreased with increasing monoglyceride content and decreasing drug content. In comparison, the release of PPL HCl from the ethanol-induced formulation was faster, but still sustained, when compared to the release from drug-induced formulation.

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

1. Introduction

Sustained/controlled release injectable preparations have been developed to circumvent gastrointestinal degradation or a first-pass effect of the drug and to deliver drugs for periods of time

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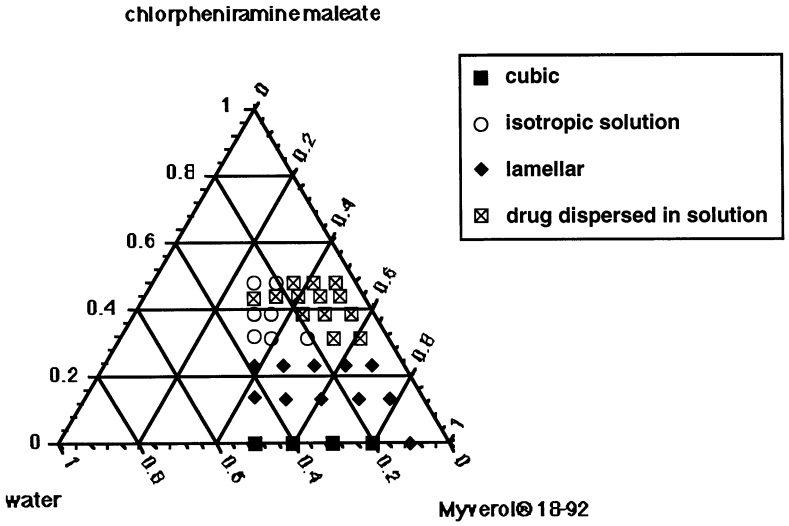

Fig. 1. Triangular phase diagram of the chlorpheniramine maleate–Myverol® 18-92–water system.

exceeding release periods achievable with oral drug delivery systems. These systems include injectable oils, emulsions, suspensions, liposomes, and polymeric delivery systems in the form of implants or microparticles. Intramuscular and subcutaneous injections are the most common routes of administration for injectable sustained release dosage forms.

Besides the dominant use of polymers, lipids have received attention as retarding carrier materials (Bodmeier and Herrmann, 1997). Amphiphilic polar lipids such as monoglycerides have shown promise in sustaining the drug release. Unsaturated monoglycerides such as monoolein or monolinolein form various types of liquid crystalline phases upon swelling in aqueous media. At body temperature, a cubic phase is formed via reversed micellar and lamellar phases upon increasing the water content (Lutton, 1965). The cubic phase can be described as a very viscous, transparent gel. It is isotropic with curved liquid bilayers extending in three dimensions and separated by water channels (Hyde et al., 1984). When compared to other liquid crystalline systems, the cubic phase is physically stable upon contact with excess water; it does not transform into other phases upon dilution with aqueous media such as body fluids.

Recently, several studies have described its use as a sustained release carrier for both conventional and peptide/protein drugs (Doelker and Doelker, 1982, Engström, 1988, 1990, Ericsson et al., 1988, Lee, 1988, Collet et al., 1990, Damani, 1991, Engström et al., 1992, Norling et al., 1992, Leslie et al., 1996, Chang and Bodmeier, 1997a,b,c, Geraghty et al., 1997). For oral delivery, the drug-containing monoglycerides can be melt-filled into capsules and then transformed in situ into the cubic phase upon contact with gastrointestinal body fluids (Wyatt and Dorschel, 1992).

Unfortunately, for parenteral delivery, the monoglyceride or the cubic phase are too viscous to be injected directly either intramuscularly or subcutaneously. Various polymeric systems have been developed whereby highly viscous polymer solutions are formed after injection of a low viscosity drug-containing polymer system into the body or body cavities. The viscosity increase/precipitation of the polymer has been achieved through a temperature change (e.g. Pluronics), ions (e.g. gellan gum) or through solvent/water exchange.

The objective of this study was to develop low viscosity monoglyceride-based systems that transform into the highly viscous cubic phase after injection into the body. Although the lamellar phase has a lower viscosity and can be injected,

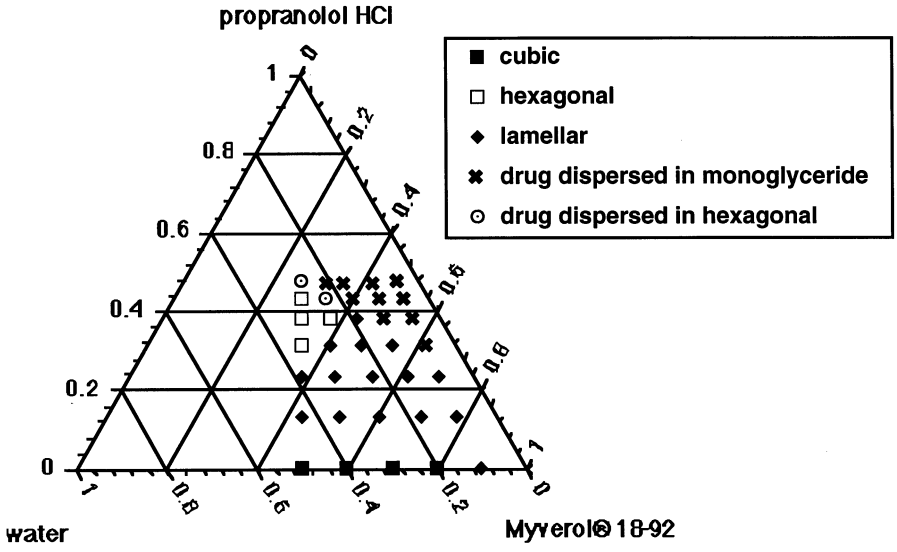

Fig. 2. Triangular phase diagram of the propranolol HCl–Myverol® 18-92–water system.

the water content of this phase is lower than that of the cubic phase. Upon dilution with an aqueous phase, the lamellar phase transforms into the cubic phase. Water will be taken up from the surrounding tissues, which may cause irritation. Therefore, a fully swollen, but injectable, monoglyceride-based vehicle is desired. Ideally, the monoglyceride-based formulation should contain enough water in order not to absorb additional water from the surrounding tissues after injection. In addition, the formulation should have a relatively low viscosity to be injectable through needles. In this study, low viscosity monoglyceride delivery systems were obtained through the addition of a third component besides the monoglyceride and water. The low viscosity was achieved either by the drug itself (drug-induced low viscosity systems) or by the addition of injectable organic solvents (solvent-induced).

Table 1
Compositions of selected chlorpheniramine maleate-induced low viscosity formulations for drug release study

Formulation	Myverol® (%)	Water (%)	Drug (%)
A	43.48	43.48	13.04
B	60.87	26.09	13.04
C	78.26	8.70	13.04
D	34.48	34.48	31.03
E	48.28	20.69	31.03
F	26.32	26.32	47.37

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: distilled monolinoleate (GML; T_m 41°C; Myverol® 18-92) and distilled monooleate (GMO; T_m 35°C; Myverol® 18-99) from Eastman (Kingsport, TN); chlorpheniramine maleate (CPM), propranolol (PPN; prepared through precipitation of the base from the hydrochloride salt) and propranolol HCl (PPN HCl) from Sigma (St. Louis, MO); ethanol, polyethylene glycol 300 and propylene glycol from Fisher Scientific (Fair Lawn, NJ); *N*-methyl-2-pyrrolidone and 2-pyrrolidone from ISP Technologies (Wayne, NJ).

2.2. Methods

Triangular phase diagrams were generated in order to investigate the different phases of the three component systems, monoglyceride–water–

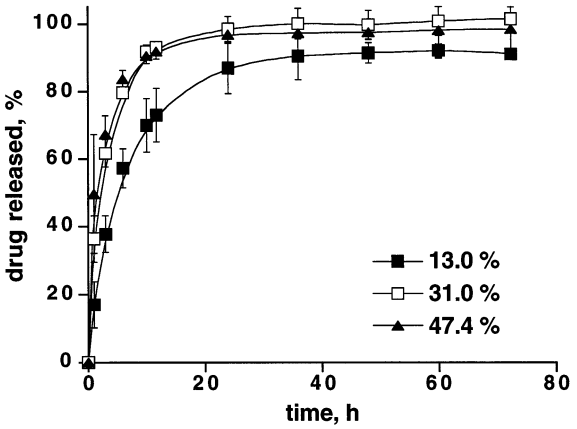

Fig. 3. Effect of chlorpheniramine maleate loading on the drug release from drug-induced low viscosity formulations in 0.1 M pH 7.4 buffer (Myverol® 18-99–water, 1:1).

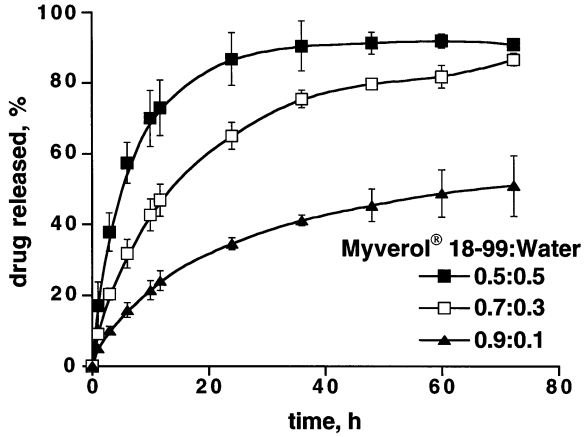

Fig. 4. Effect of Myverol® 18-99:water ratio on the chlorpheniramine maleate release from drug-induced low viscosity formulations in 0.1 M pH 7.4 buffer (13% drug loading).

drug or solvent and to identify compositions with low viscosities.

For drug-induced systems, samples with various ratios of drug:monoglyceride:water were prepared. CPM and PPL HCl were chosen as model drugs. The monoglyceride and water were mixed in ratios of 9:1 to 5:5 (w/w) in screw-capped vials; 0.3–1.8 g of drug were then added into the monoglyceride–water mixtures (2 g). The samples were heated to 100°C for 5 min, vortex-mixed, then cooled to room temperature and centrifuged for 30 min at 2000 rpm. The samples were observed by a polarized light microscope after 48 h for the identification of the different mesophases (Rosevear, 1954).

Triangular phase diagrams of monoglyceride–water–organic solvent systems were prepared by first mixing an organic solvent with the molten monoglyceride in ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (w/w) (20 g). A specific amount of each mixture was transferred into a 3-ml glass vial and mixed with water in ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (w/w) to a total weight of 2 g. The preparations were then homogeneously vortex-mixed and centrifuged at 2000 rpm for 30 min. The mixtures were stored for 48 h for mesophase identification. The composition of water–GML–ethanol 16:64:20 was selected for drug release studies. PPL HCl (2–10%) and PPL (10%) were loaded in the vehicles for dissolution studies.

The release of CPM and PPL HCl from the drug-induced low viscosity preparations, as well as the release of PPL and PPL HCl from ethanol-induced low viscosity preparations, were investigated. First, the preparations (1 g) were filled into dialysis membrane tubing (MWCO 6000–8000, Spectra/Por®; Spectrum Medical Industries, Houston, TX), the dialysis bags were closed and then placed in 0.1 M pH 7.4 phosphate buffer (300 ml, 37°C) in glass bottles, which were placed in a horizontal shaker (37°C, 80 rpm; Lab-Line Orbit Environ-Shaker, Lab-Line Instruments,

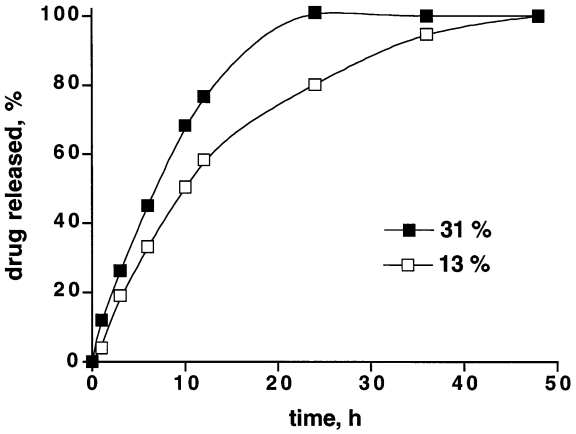

Fig. 5. Effect of propranolol hydrochloride loading on the drug release from drug-induced low viscosity formulations in 0.1 M pH 7.4 buffer (Myverol® 18-92–water, 0.7:0.3).

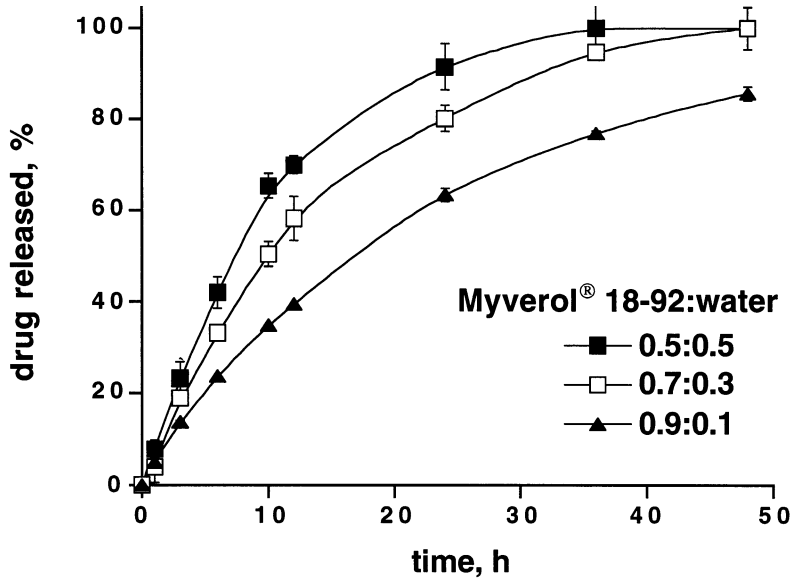

Fig. 6. Effect of Myverol® 18-92:water ratio on the propranolol hydrochloride release from drug-induced low viscosity formulations in 0.1 M pH 7.4 buffer (13% drug loading).

Melrose Park, IL). At predetermined time intervals, 2 ml of release medium was withdrawn and assayed spectrophotometrically (HP8452A Diode-array Spectrophotometer; Hewlett Packard, Avondale, PA) either directly or after appropriate dilution with the release medium (CPM, λ_{max} 262 nm; PPL and PPL HCl, λ_{max} 290 nm).

3. Results and discussions

3.1. Drug-induced low viscosity sytems

The solubilization of drug substances in the mesophase transformed the monoglyceride mesophases differently, depending upon the type of drug substances. In this section, the application of this phenomena to the formulation of low viscosity injectable formulations is discussed.

CPM and PPL HCl were used as model drugs to induce phase transformation. Triangular phase diagrams of drug–GML (Myverol® 18-92)–water systems were prepared to optimize the formulations (Fig. 1). Upon increasing the drug content, the cubic phase was transformed into the lamellar phase and then into an isotropic solution phase. The solubility of the drug in the formulations increased with increasing water content; drug crystals were visible at higher drug and lower water contents. A slightly different phase transformation was noticed with the PPL HCl induced systems (Fig. 2). With increasing PPL HCl content, the lamellar phase was induced from the cubic phase; however, no isotropic solution phase was formed with increasing drug content. A hexagonal phase appeared at higher PPL HCl content. Again, drug crystals appeared at low water contents.

Since the lamellar, hexagonal and isotropic solution phases have a low viscosity and can be injected through syringe needles, the injectable formulations from these regions were selected for drug release studies. The compositions of the CPM-induced solution and lamellar phases selected for the drug release study are shown in Table 1. Formulations A, B and C had the same drug loading of 13%; formulations D and E had a drug loading of 31% but with different ratios of monoglyceride–water. The ratio of GMO and water was fixed at 1:1 for preparations A, D and F, and at 0.7:0.3 for B and E. The release of CPM from formulations with a 1:1 ratio of GMO–

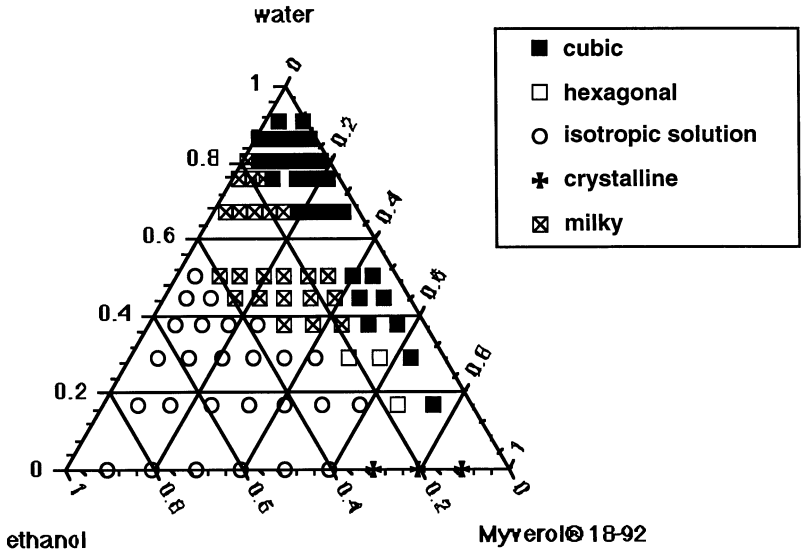

Fig. 7. Triangular phase diagram of the ethanol–Myverol® 18-92–water system.

water, but various drug loadings, is shown in Fig. 3. The drug release increased with increasing drug loading, because the increase in drug content transformed the lamellar phase into an isotropic solution phase prior to the addition to the release medium, from which the drug was then released more rapidly. The solution phases with different drug loadings (31.0 and 47.4%) had the same release pattern. Upon contact with the dissolution medium, both the solution and lamellar phases converted into the cubic phase. During dissolution studies, the system might be non-homogeneous, with a cubic phase forming on the surface and further solvent penetration occurring at a slower rate.

Increasing the monoglyceride:water ratio decreased the drug release (Fig. 4). In the same lamellar phase region, lamellar phases with different water content have different water layer thicknesses. The increase in water content increased the water layer thickness and, therefore, increased the diffusivity and the release of the water-soluble drug. In the solution phase, no such differences exist and therefore no differences in the release were seen at different water contents in this phase region (data not shown). Similar results were also obtained with GML instead of GMO. In general, at the same quantitative composition, the release was faster from GML than from GMO preparations, which could be a result of the higher swelling capacity of the GML compared to the GMO (Chang and Bodmeier, 1997c).

Next, the release of PPL HCl from drug-induced GML–water systems with varying drug (Fig. 5) and water content (Fig. 6) was investigated. Results were similar to those of the CPM systems. However, with the high drug content formulation (31%), no fast drug release was observed. When compared with the CPM phase diagram, none of the PPL HCL formulations formed isotropic solutions; a hexagonal phase was formed with the high water and PPL HCL content systems (Fig. 2).

3.2. Solvent-induced low viscosity systems

In the second approach to form low viscosity, injectable monoglyceride systems, organic solvents were added to the monoglyceride–water system. Only very few organic solvents have been reported to be safe for injection purposes. In this study, ethyl alcohol, polyethylene glycol 300, propylene glycol, 2-pyrrolidone and *N*-methyl-2-pyrrolidone (the last solvent being the solvent of choice with

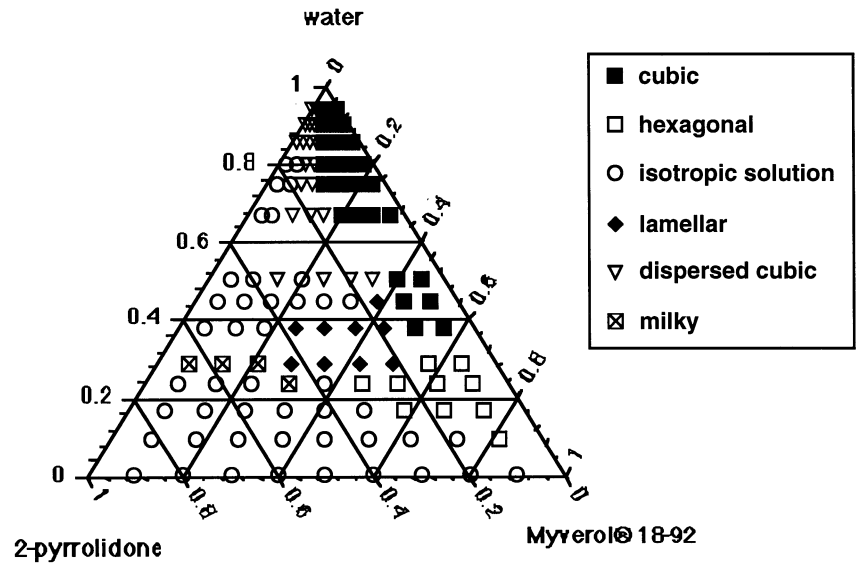

Fig. 8. Triangular phase diagram of the 2-pyrrolidone–Myverol® 18-92–water system.

the Atrix-polymer technology) were utilized for formulating solvent-induced mesophases.

The triangular phase diagram of the GML–water–ethanol system is shown in Fig. 7. The cubic phase formed at an ethanol content of less than 20%. With increasing ethanol content in GML–water mixtures, the amount of water required to form the cubic phase increased. A hexagonal region was obtained in the low water and ethanol content regions. A large area of a clear solution phase, which had a low viscosity, was obtained at higher ethanol contents. The cubic phase formed in situ upon injection of formulations from this solution phase area into water. The ethanol diffused into the aqueous phase, water was taken up, and the highly viscous cubic phase formed. Thus,

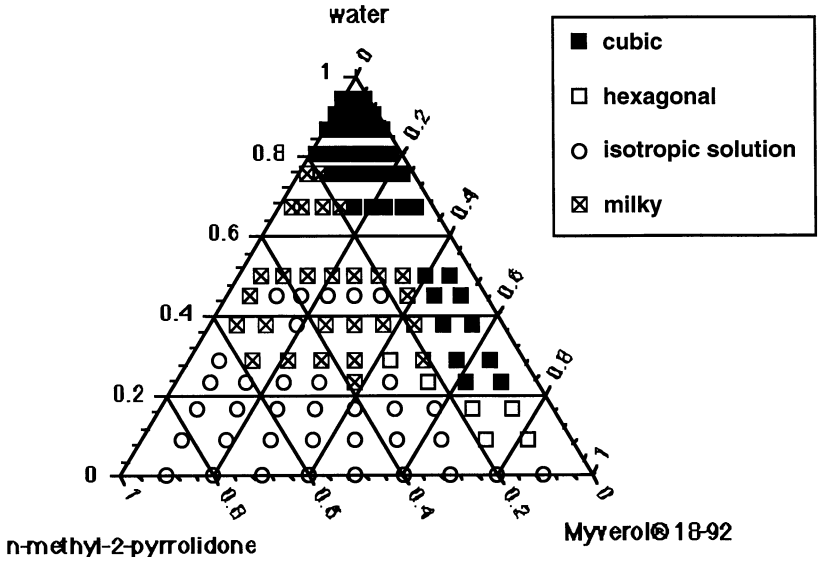

Fig. 9. Triangular phase diagram of the *N*-methyl-2-pyrrolidone–Myverol® 18-92–water system.

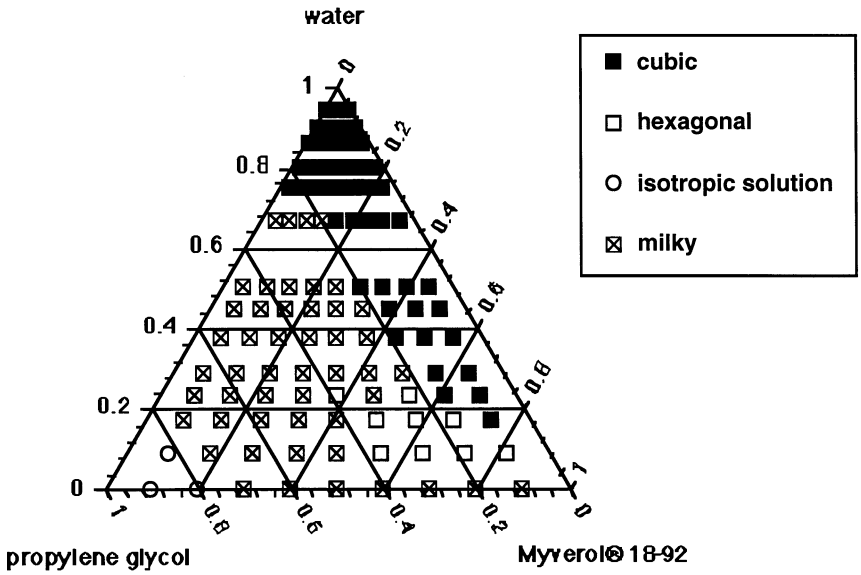

Fig. 10. Triangular phase diagram of propylene glycol–Myverol® 18-92–water system.

formulations from this region might be capable of being utilized as injectable formulations.

For the 2-pyrrolidone system, five single phases were observed in the triangular phase diagram (Fig. 8). The hexagonal phase region was located at 2-pyrrolidone:GML ratios of less than 6:4 and the lamellar phase was located at the center of the phase diagram. An isotropic solution phase was located inthe higher 2-pyrrolidone:GML ratio region with a water content above 30%. A large area of the cubic phase formed in the low solvent content region and the area expanded with increasing water content. For the *N*-methyl-2-pyrrolidone–GML–water system, no lamellar

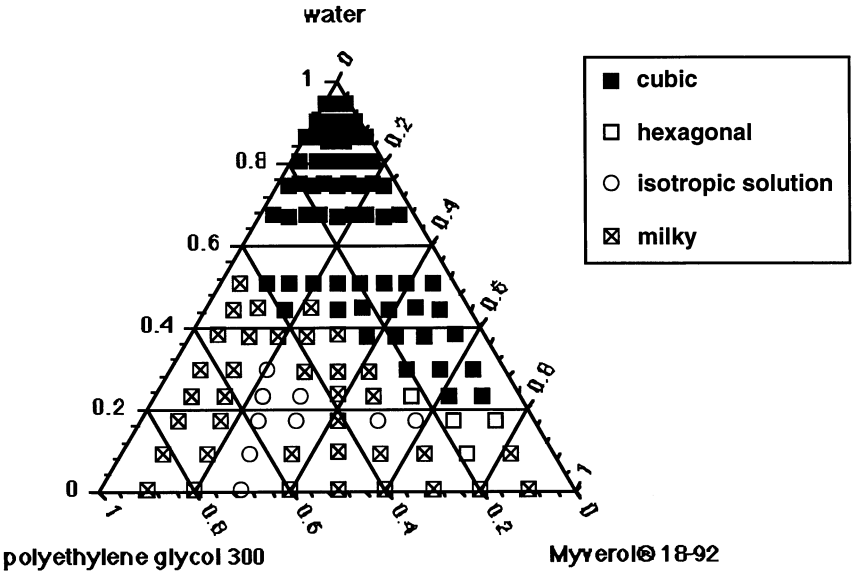

Fig. 11. Triangular phase diagram of polyethylene glycol 300–Myverol® 18-92–water system.

phase was obtained (Fig. 9); an isotropic solution phase was present at the center of the phase diagram. As with the 2-pyrrolidone system, the cubic phase was located in the low organic solvent content region and the area expanded as the water content increased. The hexagonal phase region was smaller than that of the 2-pyrrolidone system. The phase diagram of propylene glycol is shown in Fig. 10. No lamellar and clear solution phases were observed. The hexagonal phase was located in the high GML and low water content region. A similar phase diagram was obtained for polyethylene glycol 300 (Fig. 11). In addition to a hexagonal phase, a clear isotropic solution phase was observed. From these phase diagrams, it could be concluded that the cubic phase always occurred at high monoglyceride contents and the cubic phase area expanded with increasing water content. The hexagonal phase was observed in the high monoglyceride and low water content region. Some solvents also formed a lamellar or isotropic solution phase; these phases were usually located in the center of the phase diagram or in the high solvent content regions. The lamellar phase had a lower viscosity compared to the hexagonal and the cubic phase. The isotropic solution phase showed liquid-like viscosity. Since these low viscosity phases were located at the high solvent content regions, the diffusion of solvent into surrounding dissolution media, or, in the case of in vivo studies, into body fluids could transform them into the desired cubic phase after injection.

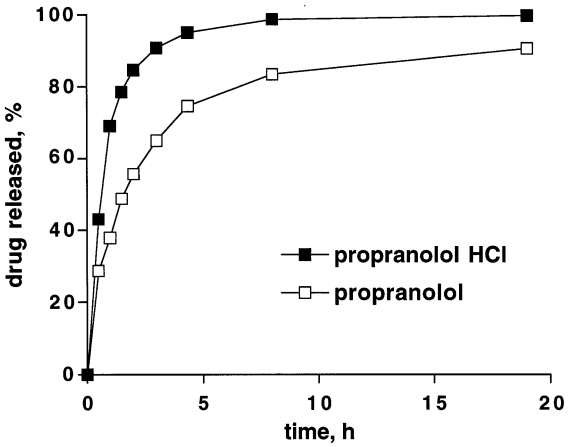

Fig. 12. Release of propranolol and propranolol HCl from an ethanol-induced low viscosity formulation with a ratio of ethanol–water–Myverol® 18-92 of 20:16:64 in 0.1 M pH 7.4 buffer.

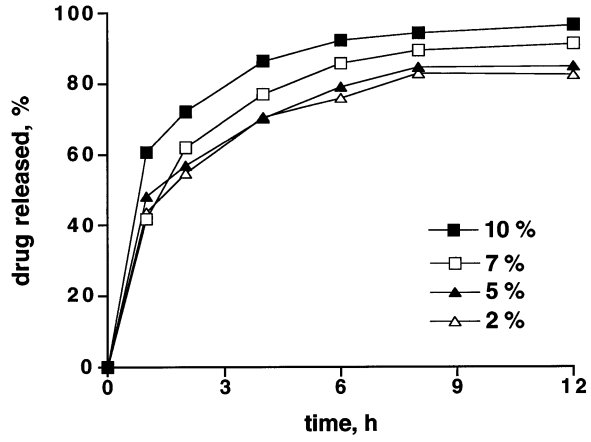

Fig. 13. Effect of propranolol HCl loading on the drug release from ethanol-induced low viscosity formulations with a ratio of ethanol–water–Myverol® 18-92 of 20:16:64 in 0.1 M pH 7.4 buffer.

An isotropic liquid formulation with a composition of ethanol–water–monolinoleate of 20:16:64 was selected for the drug release study. Fig. 12 shows the release of PPL HCl and PPL from the system. A fast initial burst release occurred and the drug was almost completely released within 12 h. In a realistic situation, there is much less water available after, for example, intramuscular or subcutaneous injection than in this in vitro release study. The diffusion of the solvent into the surrounding aqueous media should be much slower in vivo; slower drug release rates could therefore be expected in vivo. The slower release of the free propranolol base could be explained by its lower water solubility when compared to the salt. The results indicate that both the hydrophilic salt and the lipophilic base could be delivered from this formulation since both drugs were soluble and not dispersed in the formulation. The PPL HCl release was only slightly affected by the drug loading (Fig. 13), with the drug being released faster from formulations with the higher drug loading. The drug was not completely released from the lower drug content formulations. This incomplete release was due to the binding of the drug to the monoglyceride as described in a previous publication (Chang and Bodmeier, 1997b).

In conclusion, low viscosity monoglyceride-based injectable sustained formulations could be developed by drug- or solvent-induced phase transformation. These systems transform into the highly viscous cubic phase upon contact with aqueous media.

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