

Preparation and Evaluation of Lipid-Based Liquid Crystalline Formulation of Fenofibrate

Abstract

Background: Many drugs have poor water solubility and so the oral delivery of such drugs is usually associated with limitation of low bioavailability and lack of dose proportionality. Lipid-based liquid crystal (LC) systems are excellent potential formulations for increasing dissolution and bioavailability of drugs. The aim of the present study was to formulate lipid-based LC containing fenofibrate (FFB) as a hydrophobic drug. **Materials and Methods:** The studied variables included lipid and stabilizer concentrations and the type of stabilizer. The LC formation was identified by the polarized optical microscopic method. The effects of variables on formulation characteristics such as particle size, drug release, and rheological behavior were evaluated. **Results:** The results showed that the prepared formulations had the particle size between 42 and 503 nm. The drug release profiles showed that FFB had the continuous release from the formulations and the highest dissolution efficiency was seen in formulation prepared by 1.5% of glyceryl monostearate and 0.5% of Pluronic F127 as the stabilizer. The change of stabilizer type from colloidal silica to Pluronic F127 increased the drug release, significantly. **Conclusions:** In the most formulations of FFB LCs, the DE% was more than the pure drug, and therefore, it seems that the liquid crystalline formulations can be effective for enhancing drug release. Furthermore, drug release rate depended on the stabilizer type so that the presence of colloidal silica caused slower drug release compared to Pluronic F127.

Keywords: Bioavailability, enhanced solubility, fenofibrate, liquid crystal

Introduction

Designing novel formulations to enhance the oral bioavailability of poorly water-soluble drugs has long been a key driver of the pharmaceutical industries. The poor intrinsic solubility of Biopharmaceutical Classification Scheme (BCS) class II compounds has stifled the development of many emerging therapeutic compounds. Considering that 75% of drug development candidates display poor aqueous solubility, their limited bioavailability is still an unmet challenge for pharmaceutical drug development.^[1] The absorption of these poorly water-soluble drugs is limited by their poor solubility and resultant slow dissolution rate in gastrointestinal fluids. In addition, these drugs can commonly display variable bioavailability affected by foods, with poor solubility being a strong predictor of positive food effects.^[2] Ingested lipids interact with bile salts and phospholipids in the postprandial intestinal milieu to solubilize poorly water-soluble drugs.

Although lipids can enhance absorption of these drugs, they may also lead to variable bioavailability during clinical use depending on the prandial state at the time of dose administration, potentially resulting in loss of efficacy.^[3]

Fenofibrate (FFB), a prodrug of fenofibric acid, has been used to treat hypertriglyceridemia because it reduces low-density lipoprotein (LDL) and very-LDL while increasing the level of high-density lipoprotein.^[4,5] It belongs to BCS II which means that it is lipophilic ($\log P = 5.575$)^[6] and practically insoluble in water,^[7] and its oral bioavailability is approximately 30% in humans.^[8,9] Orally administered agents possessing the aqueous solubility of 0.1 mg/ml usually demonstrate poor absorption due to impaired dissolution.^[10] Several techniques have been devised to amend solubility of drugs in the aqueous surroundings, thereby promoting their bioavailability.^[11] A number of solubilization methods have been

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engaged to significantly improve aqueous solubility and plasma titers of hydrophobic drugs. These approaches mostly involve particle-size diminution, incorporation of surface tension reducing substances, salt formation, pH modification, complexation, micronization, and development of solid dispersions.^[12,13] The Lipantil Micro is the capsule formulation of the micronized FFB which, displays food-dependent bioavailability, and therefore requires administration with food. A reformulated product, Lipantil Supra was developed using NanoCrystal technology, to overcome this limitation and allows food-independent administration and dose reduction.^[4,8,14] Furthermore, lipid-based formulations like self-emulsifying drug delivery systems can be more appropriate when the active substance is lipophilic. Lipid-based formulations have been widely investigated for their ability in enhancing solubilization within the gastrointestinal tract (GIT), generating supersaturation, and increasing drug absorption and have been shown to eliminate food effect *in vivo*.^[15] Solubilization of poorly water-soluble drugs within a lipid-based, liquid carrier allows delivery within a capsule which self-emulsifies on dispersion in GI fluids, maintaining drug solubilization. Coadministration of lipids as formulation excipients may promote the formation of mixed micelles enhancing solubilization and induce secretion of bile salts and phospholipids *in vivo*, mimicking the fed state environment.^[16-20]

Liquid crystals (LCs) are semisolids with crystalline structures combining the properties of both solid and liquid states.^[21] Commonly encountered phases in LCs include the lamellar, bicontinuous cubic, and inverse hexagonal phases.^[22] LCs are easily formed by various amphipathic lipids such as glyceryl monooleate (GMO) and phytantriol in excess amounts of water. Many studies reported that the oral administration of LCs enhanced the bioavailability of poorly water-soluble drugs.^[23] In the pharmaceutical arena, viscous lipid-based systems, such as bicontinuous cubic and hexagonal liquid crystalline phases offer considerable scope for application as drug delivery systems.^[24] They have the potential for control over release rates, low toxicity, and versatility in application across a range of administration regimes, including oral,^[25] transdermal,^[26] and parenteral delivery.^[27] Lipid-based liquid crystalline systems are also mucoadhesive.^[28] An important attribute of a limited number of lipid-based liquid crystalline systems is that they are thermodynamically stable in excess water, thereby providing a persistent matrix on exposure to liquids such as GI and interstitial fluids. This property also allows for the predispersion of liquid crystalline systems in aqueous vehicles in the form of submicron particles suitable for intravenous drug delivery.^[29]

Materials known to exhibit such phase behaviour include phospholipids, alkyl glycerides such as GMO,^[30] amphiphiles with phytanyl chains such as phytantriol^[31] and glycolipids,^[32] and alkyl glycerates.^[27] The ability

of drug delivery systems based on lipids such as GMO which enhances the bioavailability of FFB as a poorly water-soluble drug after oral administration, is well known, and is thought to reflect the ability of lipids and their digestion products to interact with endogenous bile-salt phospholipid micelles in the GIT, resulting in an increase in the solubilization capacity of the GI fluids.^[33] The aim of the present study was to improve the solubility of FFB by lipid-based LC formulation. Considering the advantages of this pharmaceutical technology that provides the large membrane surface area, LCs can increase the solubility of FFB, thereby improve its bioavailability.

Materials and Methods

Materials

FFB was provided by Faraby Pharmaceutical Company (Iran). Glyceryl monostearate (GMS), Pluronic F127, and Tween 20 were purchased from Merck Chemical Company (Germany), colloidal silica was from Sigma-Aldrich Company (USA). Dialysis bag was obtained from the Armaghane Kali Gavan Co (Iran). All chemicals and solvents were of analytical grade. Minitab Software (Version 16, USA) was used for experimental design and the evaluation of the effect of variables on responses.

Fenofibrate assay

The quantitative determination of FFB was performed by ultraviolet (UV) spectrophotometer (Biochrom WPA BioWave II, England) at $\lambda_{\max} = 288$ nm in 0.1 N of hydrochloric acid containing 1% of Tween 20. The validity of the assay method involving linearity, repeatability, accuracy, and limit of quantification were calculated.^[34]

Preparation of fenofibrate liquid crystal formulations

For the preparation of FFB LC formulations, FFB was dissolved in GMS (as the lipid phase), then aqueous solution of stabilizer (Pluronic F127 or colloidal silica) was added to the lipid phase. The final mixture was heated at 50°C with sonication in a bath sonicator (POWER-SONIC 505, Korea) at power of 500 W. Independent variables in this study included; concentration of the lipid (1, 1.5, 2 w/w%), concentration of the stabilizer (0.5, 5, and 10 w/w%), and the type of stabilizer (Pluronic F127 or colloidal silica). The concentration of the drug in all formulations was kept constant at 1 w/w%.^[35] The composition of different formulations is illustrated in Table 1.

Recognition of anisotropy of liquid crystals by polarized microscopy

Polarized microscopy method was used as a quick and easy inspection method to show the birefringence behavior of the LCs. The texture of the samples was observed by the polarizing microscope (HUND, Germany). A small quantity of the sample was placed on a clean glass slide. The existence of birefringence was verified by observation

The region marked in points shows the limits of LCs formation region. Eight samples marked in the phase diagram were selected to study. The contents of each component are listed in Table 1. LCs were formed in 1%–2% of the lipid and 0.5%–10% of the stabilizer with both types of the stabilizers (Pluronic F127 and colloidal silica).

Figure 2 shows the polarized microscopy micrograph that demonstrates birefringence behavior of the LCs.

Particle size distribution

Particle size and poly dispersity index (PDI) of different LC formulations are demonstrated in Table 1. The results of this table indicate that the particle size of formulations was between 42 and 503 nm with PDI was <0.7 . The minimum and maximum values of particle size relate to formulations $P_{0.5}G_{1.5}$ and P_5G_2 , respectively. The effects of the studied independent variables were also studied on the mean particle size of LC formulations. The following equation demonstrates the regression between the independent variables and the particle size:

$$\text{Particle size} = 57.303 (X_1) + 0.172 (X_2) + 188.011 (X_3) - 56.157 \quad (\text{eq. 1})$$

Where X_1 is the type of stabilizer, X_2 is the percentage of stabilizer, and X_3 is the percentage of lipid. Regression analysis showed there was a significant relationship between the mean particle size and the percentage of the stabilizer and the lipid ($P < 0.05$). Thus, the particle size was affected by formulation parameters and considering the positive sign of all variables in eq. 1.

Drug loading

Table 1 shows the drug loading efficiency in different LC formulations of FFB. Based on the results, the drug loading efficiency was more than 95% in all of the formulations. The minimum and maximum drug loading efficiency was seen in formulations $P_{0.5}G_1$ and $P_{0.5}G_{1.5}$, respectively. The following equation demonstrates the regression between the studied independent variables and the drug loading efficiency (LE%):

$$\text{LE\%} = 0.553 (X_1) + 0.177 (X_2) + 1.321 (X_3) + 95.544 \quad \text{eq. 2}$$

Regression analysis showed that there was a significant relationship between LE% and the percent of stabilizer (X_2) and lipid (X_3). So that, with increasing in lipid percent from 1 to 2, and increasing in stabilizer percent from 0.5 to 5 and 0.5 to 10, the LE% increased and all of the this variables had a positive effect on the LE%.

Rheological properties of the liquid crystal formulations

The stable flow behavior curves of the LC phases are shown in Figure 3. All of the samples behaved as shear thinning fluids. The only significant parameter affecting on

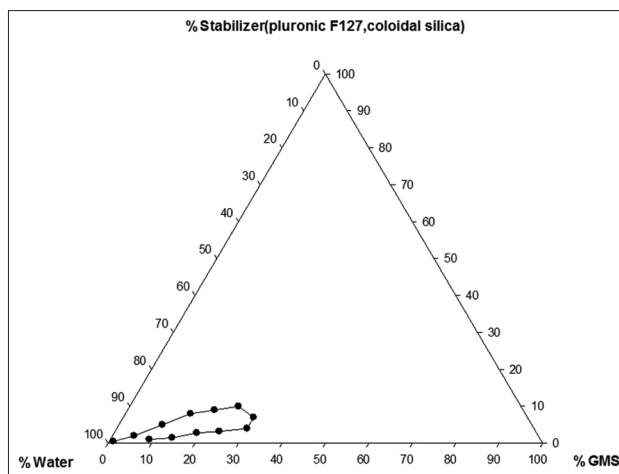


Figure 1: The ternary phase diagram of lipid/stabilizer/water system used for the production of fenofibrate liquid crystals

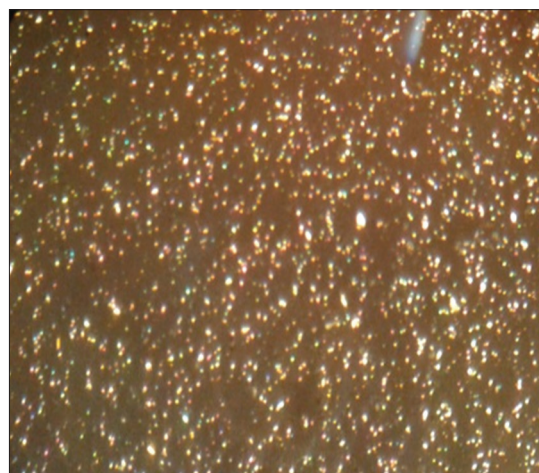


Figure 2: The birefringent behavior of the prepared formulations of fenofibrate liquid crystals

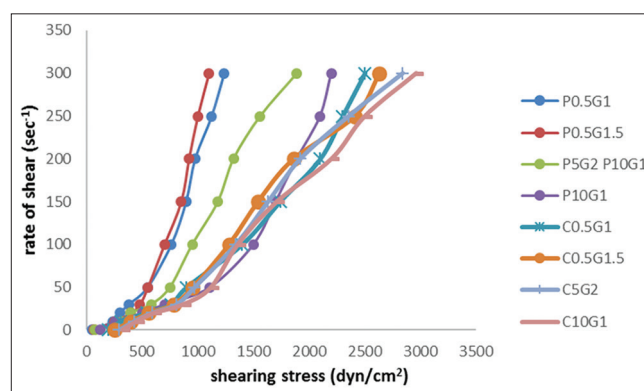


Figure 3: Rheograms of the liquid crystalline formulations of fenofibrate

the shearing stress of formulations was the stabilizer type, in which by changing the stabilizer type from Pluronic F127 to colloidal silica the shearing stress increased significantly ($P < 0.05$). The other studied variables had no significant effect on the shearing stress of the formulations ($P > 0.05$).

Drug release

The dissolution efficiency (DE%) of different formulations varied between 16.58% and 35.83%. The minimum and maximum of DE belonged to formulations C_5G_2 and $P_{0.5}G_{1.5}$, respectively [Figure 4]. All formulations except two ($C_{0.5}G_{1.5}$ and C_5G_2) showed more DE% than pure drug [Figure 4]. In formulations $P_{0.5}G_{1.5}$, P_5G_2 , and $P_{10}G_1$, this difference was statistically significant ($P < 0.05$). The following equation demonstrates the regression between independent studied variables and DE%:

$$DE\% = -8.12(X_1) - 0.13(X_2) - 3.53(X_3) + 43.1 \quad \text{eq. 3}$$

The only significant effective parameter on the DE% was the stabilizer type. So that, by changing in stabilizer from colloidal silica to Pluronic F127, DE% was increased.

Discussion

Particle size distribution

According to the results, the particle size was affected by formulation parameters and considering the positive sign of all variables in eq. 1, it may be concluded that all of them had an increasing or synergistic effect on the particle size of the LCs. This has been suggested to be the result of stabilizer incorporated into the GMS bilayer, causing swelling and ultimately a transformation of nanostructure resulting to increase in particle size. When the stabilizer content was kept constant and the concentration of GMS used in dispersion was increased, the particle size of the LCs increased. The increase in GMS was expected to manifest proportionally increase in surface area while stabilizer content was held constant. Considering the surface area of the system has increased, but equal amounts of stabilizer associated per unit surface area was constant, it may be concluded that the stabilizer was changing its conformation at the interface, thereby allowing the polymer to occupy the greater surface area at the same concentration. These results are in accordance with the results obtained in previous studies.^[37-39]

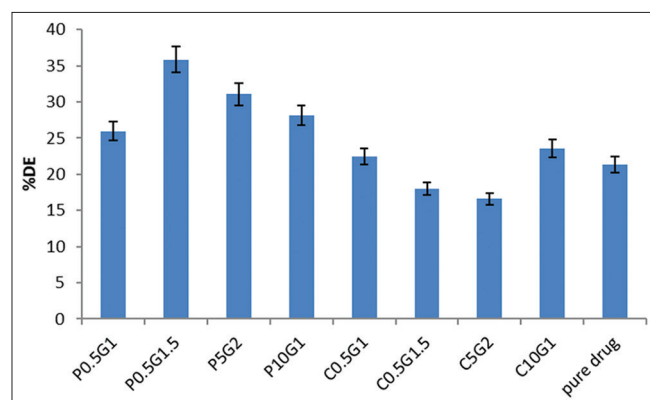


Figure 4: Dissolution efficiency percent of fenofibrate in the different studied formulation of liquid crystals ($n = 3$)

Drug loading

According to the results of Table 1, increasing in lipid content caused to increase of LE%. This may be related to hydrophobic properties of the encapsulated drug in LCs. Increasing in lipid content makes the LCs more lipophilic and more capable to entrap and solubilize the lipophilic drugs. Furthermore, increasing in stabilizer percentage makes the LCs be more stable and help to solubilize more drug.

Rheological properties of the liquid crystal formulations

Based on regression analysis, the only significant parameter affecting on the shearing stress of formulations was the stabilizer type, in which by changing the stabilizer type from Pluronic F127 to colloidal silica the shearing stress increased. The micellar phase or hexagonal phase (H_1) could be found in a less hydrophilic surfactant system on the solubilization of the oil.^[40] Since the Pluronic is not a very hydrophilic surfactant, it appears in the micellar phase up to a certain concentration. Beyond this concentration, the hexagonal phase (H_1) appears. In contrast, colloidal silica is not amphiphilic; therefore, it appears in the cubic phase. The cubic phases are even more viscous than the hexagonal phases. Some reports are available on the rheological behavior of different phases of LCs which are related to this phenomenon.

Drug release

According to the results, the only significant effective parameter on the DE% was the stabilizer type. So that, by changing in stabilizer from colloidal silica to Pluronic F127, DE% was increased. This may be related to the viscosity of LCs formulation. According to the results of section 3.5, LCs formulations which contained colloidal silica as a stabilizer showed more viscosity than formulation prepared with Pluronic. The reason may be related to the increase in LCs matrix viscosity, which caused slower diffusion of the aqueous release media to the matrix, and consequently, decrease in drug release rate. Furthermore, previous studies showed that addition of Pluronic to LCs formulation accelerated drug release.^[41] According to the results, LC formulations have been successful to improving solubility and bioavailability of FFB, which is consistent with the results of previous studies.^[42] In addition, this study has addressed the disadvantages and problems of previous studies including the method of preparing LCs. Despite previous studies in this study, LC formulations are easily made at a lower temperature without any need for high pressure, which makes it possible to industrial scale-up.

Conclusions

Dissolution property of FFB, a poorly soluble drug, was improved by preparing LC formulations using rapid and simple method with two different stabilizers, Pluronic F127 and colloidal silica. LCs could increase the solubility and

in vitro releasing of this poorly soluble drug, thus expecting to improve its bioavailability. Drug release profiles showed that in the most formulations of FFB LCs, the DE% was more than the pure FFB, and therefore, it seems that the liquid crystalline formulations would be effective for enhancing drug release. Furthermore, drug release rate depended on the stabilizer type, so that the presence of colloidal silica caused slower drug release compared to Pluronic F127.

Increasing in lipid content caused increasing in LE%. On the other hands, lipid component in LC formulations had a critical role in hydrophobic drug encapsulation. Particle size distribution was affected by the percentage of the stabilizer and the lipid. Considering that GMS formed the bilayer structure in LCs, increasing of stabilizer content led to swelling and increasing in particle size. Altogether, LC formulations, especially formulations containing Pluronic F127 as a stabilizer, are suitable for increasing the dissolution rate of FFB.

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Conflicts of interest

There are no conflicts of interest.

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