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Review

Glycerol monooleate liquid crystalline phases used in drug delivery systems

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ABSTRACT

During the last few decades, both scientific and applied research communities have shown increased attention to self-assembled lyotropic liquid crystalline phases of polar lipids, due to their remarkable structural complexity and usefulness in diverse applications.

Amphiphilic properties of polar lipids in relation to water are the driving force for self-assemblies following an extraordinary polymorphism. This polymorphism is an interesting phenomenon in which lipids combine short-range disorder and long-range order. The most widely investigated liquid crystalline phases are the lamellar, the cubic and the hexagonal.

Such phases have high solubilization capacity for hydrophilic, lipophilic and amphiphilic guest molecules and the ability to protect molecules against hydrolysis or oxidation. So, they can be used as an interesting drug delivery matrix for drugs, amino acids, peptides, proteins and vitamins in various food, pharmaceutical and biotechnical applications.

This review presents recent progress in glycerol monooleate liquid crystalline phases used as drug delivery vehicles.

Contents

Abbreviations: SAXS, small-angle X-ray scattering; DSC, differential scanning calorimetry; NMR, nuclear magnetic resonance; FTIR, Fourier transform infrared spectroscopy; MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-dyphenyl tetrazolium bromide; TGA, thermogravimetry analysis; PEG, polyethylene glycol; M, molar; mM, millimolar; Mr, molecular mass.

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1. Introduction

Liquid crystalline phases are frequently encountered in everyday life. For example, the cell membranes in the body are the result of the lyotropic liquid crystalline phase that is generated from the dissolution of phospholipids in water (Collings and Hird, 1997; Seddon and Templer, 1995). Probably, microsomes' membranes, mitochondria and tight junctions between cells are formed from non-lamellar liquid crystalline structures. Etiolated chloroplasts, which consists of six-fold or four-fold interconnected tubular membrane structures, are strikingly similar to the structure elements of the inverse bicontinuous cubic phases. The structures of certain membranous organelles in cells, for example in endoplasmic reticulum, bear a quite striking similarity to the sponge phase.

It has been assumed that liquid crystalline phases, possibly including cubic phases, play a role in the process of fat digestion *in vivo* (Collings and Hird, 1997; Lynch and Spicer, 2005; Seddon and Templer, 1995). During this process, triglyceride is hydrolyzed first to diacylglycerol plus fatty acid, then to monoacylglycerol plus two fatty acid molecules. Research on phase equilibria of lipid mixtures similar to those found in the intestine showed that liquid crystalline phases, as well as an inverse micellar solution, were formed and it was suggested that the latter phase may coexist with mixed micelles in the human intestine. These phases have an important property that all reactants and products, whether polar, non-polar or amphiphilic can diffuse freely across the structure. Accordingly, life itself critically depends upon liquid crystalline phases.

Liquid crystals show properties between those of conventional liquid and solid crystals (Seddon and Templer, 1995). For instance, a liquid crystal may flow like a liquid but have the molecules in the liquid arranged and oriented in a crystal-like way.

The type of molecular structure that generates liquid crystalline phases is amphiphilic (Collings and Hird, 1997; Seddon and Templer, 1995). The amphiphilicity implies the dualistic properties of the molecules in relation to water, with flexible hydrocarbon chains avoiding water contact and a polar head group that tends to orient towards water. Amphiphilic molecules form aggregates through a self-assembly process that is driven by the "hydrophobic effect" when they are mixed with a solvent (usually water). The aggregates formed by amphiphilic molecules are characterized by structures in which the hydrophilic head-groups shield the hydrophobic chains from contact with water. For most lyotropic systems aggregation occurs only when the concentration of the amphiphile exceeds a CMC (critical micelle concentration) or the CAC (critical aggregation concentration). Above the CMC the self-assembled amphiphile aggregates exist as independent entities, in equilibrium with monomeric amphiphiles in solution, and with no long ranged orientational or positional (translational) order. These dispersions are micellar solutions (its constituent aggregates are micelles, generating isotropic phases). The lyotropic liquid crystalline phases are formed as the concentration of amphiphile in water is increased beyond the point where the micellar aggregates are forced to be disposed regularly in space. For amphiphiles that consist of a single hydrocarbon chain the concentration at which the first liquid crystalline phases are formed is typically in the range 25–30 w/w%.

In the same way, polar lipids, as amphiphilic molecules, have a remarkable ability to self-assembly in water to form different structures. In the solid state, the general structure of lipids is a stack of planar molecular bilayers. The hydrocarbon chains are close-packed in these bilayers, and the polar heads form the outer surfaces. The hydrogen-bond system in the sheets formed by the polar head groups is strong compared to the weak van der Waals interaction between the hydrocarbon chains (Collings and Hird, 1997; Larsson, 1989, 2000; Seddon and Templer, 1995). During the melting of this structure, first the hydrocarbon chains become disordered into a liquid-like structure, with the overlying gross structure remaining intact, then, at a higher temperature the complete melting occurs. In solids, planar zigzag conformations of the carbon–carbon bonds exist (all-*trans*), whereas in disordered states, occurring in liquid crystals and in melts, *gauche* conformations form dynamically along the chain. The combination of disorder on the atomic scale with the long-range order in layers is the characteristic property of liquid crystalline phases of lipids.

Several review articles about lipid liquid crystalline phases have been published to give insights into their structure and the diversity of applications. The purpose of this review is to summarize the data about drug delivery systems based on glycerol monooleate liquid crystalline phases (Amar-Yuli et al., 2009; Caboi et al., 2001; Chernik, 1999; Drummond and Fong, 1999; Engström, 1990; Fong et al., 2012; Garti et al., 2012; Guo et al., 2010; Hitesh et al., 2011; Kaasgaard and Drummond, 2006; Kulkarni et al., 2011; Larsson, 2009; Leser et al., 2006,b; Sagalowicz et al., 2006a,b; Shah et al., 2001).

2. Glycerol monooleate

Glycerol monooleate is one of the most widely studied amphiphilic lipid used in the formation of various liquid crystalline drug formulations (Ganem-Quintanar et al., 2000).

Glycerol monooleate (Fig. 1) is a glycerol fatty acid ester. It has a *cis* double bond at C9. From the molecular point of view, glycerol monooleate has the acyl chain which is by an ester bond attached to the glycerol backbone (Ganem-Quintanar et al., 2000; Kulkarni et al., 2011). The two remaining carbons of the glycerol moiety are free, giving polar characteristics to this part of the molecule. This hydrophilic part can form hydrogen bonds with water in an aqueous environment (the headgroup). The hydrocarbon chain (the tail) gives hydrophobic properties to glycerol monooleate.

Glycerol monooleate is a lipophilic substance, HLB = 3–4, almost insoluble in an aqueous phase. Its solubility in water is $\cong 10^{-6}$ M and it forms micellar solution with water above its critical aggregation concentration, approx. 4×10^{-6} M (Barauskas et al., 2010).

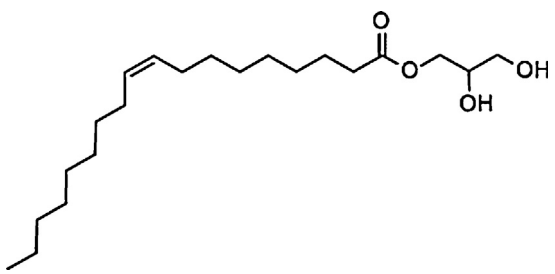

Fig. 1. Chemical structure of glycerol monooleate.