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Research paper

Effect of HLB of additives on the properties and drug release from the glyceryl monooleate matrices

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Abstract

Glyceryl monooleate (GMO) is an amphiphilic surfactant, which as such can solubilize hydrophilic, lipophilic and amphiphilic drug molecules in its different polarity regions. Addition of additives with different polarities in GMO leads to change in phase behavior and related properties of GMO. Effect of the additives with different hydrophilic lipophilic balance (HLB; 1.5, 3, 4, 5, 7, 10 and 11) in GMO matrices on its phase transformation, rheological properties, mechanical properties, wetting and release behavior was investigated. Polarizing light microscopy showed that the GMO matrices incorporated with lower HLB additive (1.5, 3, 4 and 5) form cubic phase at higher rate while lamellar phase was prominent for matrices with additive of HLB 7, 10 and 11. The diametrical crushing strength and viscosity was decreased with increased HLB of additive. Lower HLB additives enhanced contact angle as compared to plain matrices and high HLB additives induced change in solid–liquid interface from hydrophobic to hydrophilic leading to decline in contact angle. Percent swelling of matrices was increased linearly with increase in HLB of additives. Tensiometric method was used for determination of bioadhesive strength of hydrated matrices and it was observed that matrices with additives of HLB 10 presented highest bioadhesion due to higher rate of hydration and formation of lamellar phase. As the HLB of additives in matrix increased, release was shifted from anomalous (non-Fickian) diffusion and/or partially erosion-controlled release to Fickian diffusion. Initial lag was observed for drug released from matrices with additive of HLB 1.5, 3, 4 and 5. Thus incorporation of the additives of different HLB changed molecular packing, which significantly affected drug release pattern.

Keywords: Glyceryl monooleate; Glyceryl mono-stearate; Phase transformation; Diametrical crushing strength; Contact angle; Rheological behavior

1. Introduction

Glyceryl monooleate (GMO) is a water insoluble (HLB = 3) synthetic amphiphilic surfactant. Being non-toxic, biocompatible and biodegradable, it has emerged as a potential candidate for various drug delivery systems especially controlled ones [1–5].

Upon contact with water GMO forms different sequential liquid crystalline phases viz. lamellar, cubic and hexagonal phase. These phases are highly ordered microheterogeneous systems, capable of being transformed into each other in definite sequence under certain circumstances [6–8]. Phase transformation was mainly determined by water content, temperature and polarity of additives. With increase in water content, system forms most complex cubic phase via reverse micellar and lamellar phase [9–11]. Cubic phase is most favored for sustained delivery system as it is highly viscous, robust and insensitive to salts and solvents. It is highly stable phase being in equilibrium with excess of water. It is lipid and water continuous phase, where the lipid forms curved, non-intersecting bilayers containing hydrophobic and hydrophilic domains. These bilayers are organized in such a way that two unconnected continuous systems of water channel are formed. Such a 'honeycombed' structure can simultaneously accommodate hydrophilic, lipophilic

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and amphiphilic molecules [12,13]. Incorporation of additives with different polarities may lead to phase transformation due to change in packing parameter resulting from interaction of the additives with curved bicontinuous lipid bilayer. Packing parameter can be used to describe local constraint upon the curvature of the interface that can attribute to the geometric features of the lipid and is given by the following equation [14].

$$v = al \quad (1)$$

where 'v' is the hydrophobic chain volume, 'a' is the group area and 'l' is the chain length.

The phase transformation of GMO can be predicted by the packing parameter as it connects molecular shapes and properties to the favored curvature of the polar–non-polar interface and therefore topology and shape of aggregates [15].

To optimize drug release pattern from GMO based formulation, it is suggested to evaluate the effect of polarity of formulation additives on phase transformation of GMO. Chang and Bodmeier [16] investigated the effect of varying amounts of oleic acid on the release from GMO matrices. It was observed that cubic phase was transformed to reverse hexagonal phase with solubilization of oleic acid in lipophilic domain of matrix system. This inherently increased hydrocarbon chain space and altered molecular packing, presenting different release pattern. Recently, Shah and Paradkar [17] prepared *in situ* cubic phase transforming system of GMO by utilizing hydrophobic nature of magnesium trisilicate and Gelucire® 43/01. Increased drug release was observed due to transformation of cubic phase into hexagonal phase with these hydrophobic additives. Very few researchers have focused on the degree of freedom in cubic phase system with respect to phase transformation, rheological and mechanical properties and their impact on the drug release pattern.

A model study was carried out here to explore the effect of polarities of formulation additives on phase transformation of GMO. This study signifies the importance of additives' polarity for effective and optimum formulation development of the GMO based formulations. Therefore, in the present study, the effect of HLB of additives on phase transformation of GMO, crushing strength, rheological behavior, contact angle, swelling, bioadhesion and drug release of such formulations was studied. As drug properties can affect the formation of mesophases and release from the GMO matrices, the amphiphilic drug melatonin was selected as model drug.

2. Materials and methods

2.1. Materials

Glyceryl monooleate (Rylo™ MG Pharma19) was obtained as a gift sample from Danisco Cultor (Copenhagen, Denmark). Glyceryl mono-stearate and PEG monostearate were gift samples from Nikko Chemical Co. Ltd. (Seoul, Korea) (see Table 1). Melatonin was a gift sample from Aristo Pharma (Bhopal, India). All other chemicals used were of analytical grade.

2.2. Methods

2.2.1. Preparation of matrices

Plain GMO matrices were prepared by melting GMO (300 mg) at 55 °C on a water bath followed by addition of melatonin (5 mg) to it under continuous stirring. This molten mixture was then poured in fabricated stainless steel cylindrical moulds (inner diameter of 8.5 mm, height of 10 mm) and allowed to solidify at −15 °C for 10 min. These matrices were trimmed in order to obtain the uniform cylinders. Matrices with the additives were prepared in a similar manner as described above with an additional step of individual addition of the additives of different HLB (1.5, 3, 4, 5, 7, 10 and 11) (50 mg each) to molten mixture of GMO and melatonin. The matrices thus prepared were kept in desiccator at room temperature over silica gel for 12–24 h before being subjected to further evaluation.

2.2.2. Polarizing light microscopy

The matrices were placed in a dissolution test apparatus (USP 24 type II) (Electrolab TDT-08L, Mumbai, India) containing 0.1 N HCl (900 ml) maintained at 37 ± 0.5 °C and allowed to hydrate under stirring at 100 rpm. The hydrated samples were examined under polarizing light microscope (Nikon, Kanagawa, Japan) using λ 1/4 compensator in order to study the texture of structure indicative anisotropic phases. The phase boundaries were examined at a magnification of 200×. Photomicrographs of these samples were taken at room temperature after hydration of 1 and 8 h.

2.2.3. Diametrical crushing strength

Diametrical crushing strength of the matrix was determined using diametrical crushing tester (Incorp., Hyderabad, India). The force required for diametrical deformation of the matrices was determined. This study was performed in six replicates.

2.2.4. Rheological behavior

The rheological examination was carried out using Brookfield LV-DV III programmable rheometer equipped with spindle CP40 (Brookfield Engineering Laboratories, Inc. Middleboro). A cone and plate sensor having a diameter of 2.4 cm and the cone angle of 0.8° was used. The thickness of sample in the middle of sensor was 0.0127 mm. The matrices were hydrated for 1 h in 0.1 N HCl (900 ml) contained in dissolution vessel (USP 24 type II; Electrolab TDT-08L, Mumbai, India) maintained at 37 ± 0.5 °C under stirring at 100 rpm. The hydrated sample was loaded on rheometer plate at temperature 25 ± 0.3 °C and the initial linear viscoelastic region of the samples was determined and 100 rpm was chosen as a suitable shear rate (corresponding calculated shear rate was 13,333 s^{-1}) for all