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Spray dried glyceryl monooleate–magnesium trisilicate dry powder as cubic phase precursor

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Abstract

Glyceryl monooleate (GMO) is a polar amphiphilic lipid, which forms different sequential lyotropic liquid crystals upon hydration. GMO has been utilized for various delivery systems and routes of administrations. Owing to sticky and waxy nature of GMO, preparation of oral solid dosage form utilizing GMO is still a challenge for pharmaceutical researchers. Therefore, the objective of the present work was to fabricate dry powder precursors using GMO, which upon hydration in situ forms cubic phase and can be wisely used for fabrication of oral solid dosage forms. In addition to this, dry powder precursor was evaluated for drug loading, in vitro release behavior and in vivo performance of model drug diclofenac sodium (DiNa). The dry powder precursor was obtained by spray-drying GMO with DiNa using magnesium trisilicate (MTS) as adsorbent. The percent drug entrapment of various batches of powder precursor was in the range of 84–93% indicating high content uniformity. SEM and image analysis showed that as the amount of MTS in powder precursor was increased, the particle size decreased. Furthermore, the viscosity of powder precursor was function of amount of MTS. The rate of water uptake of powder precursor was higher due to uniform layer of GMO on the MTS surface, which led to faster transformation of lamellar phase into cubic phase. The polarizing light microscopy confirmed that cubic phase was formed upon hydration of powder precursor. The drug released from powder precursor was initially governed by the cubic phase formed and in later stage it depends upon dynamic swelling behavior of hexagonally packed cylindrical aggregates. The drug loaded powder precursor was found to have more effective and prolonged anti-inflammatory and analgesic activity as compared to pure drug. Thus the dry powder precursor of cubic phase was prepared in which drug release was entirely governed by the mesophases formed.

Keywords: Glyceryl monooleate; Cubic phase precursor; Spray-drying; Anti-inflammatory activity; Analgesic activity

1. Introduction

Glyceryl monooleate (GMO), an amphiphilic lipid self-associate to form sequential liquid crystalline mesophases, viz., lamellar, cubic and hexagonal when placed in an aqueous media (Shah et al., 2001; Kumar et al., 2004). Being non-toxic, biodegradable and biocompatible it has found its utility in various delivery systems and routes of administrations (Ganem-Quintanar et al., 2000). Delivery system based on partially hydrated lamellar phase (Farkus et al., 2000; Makai et al., 2003), hydrated cubic gel (Sallam et al., 2002), cubic phase dispersions (Siekmann et al., 2002; Spicer et al., 2002) and matrix (Kumar et al., 2004; Shah and Paradkar, 2005) have been explored by many researchers.

Cubic phase coexists in equilibrium with the excess water and being highly viscous has gained much attention for sustained release. The sustained release may be due to slow drug diffusion or increased residence time in its solublized form. Further, its isotropic nature, relative insensitivity to salts and solvents, robustness and resistance to physical degradation make it most preferred candidate for sustained drug delivery.

However, design and development of cubic phase based palatable solid dosage form of GMO has limitations due to its intrinsic properties like stickiness and stiffness. Preparation of dry powder precursors, which can be quickly transformed into cubic phase *in situ,* will promote industrial application of the system.

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Recently, Spicer et al. (2002) developed spray dried dry powder cubosomes by encapsulating monoolein using ternary (starch–monoolein–water) and quaternary (dextran–monoolein –ethanol–water) systems. The water based ternary system hydrates monoolein and generate highly viscous cubic phase. This require additional dispersion step to minimize sticking of powder to drying chamber. The quaternary system was processed without high shear dispersion; however, the final product has fairly high solvent content (13% water and 3% ethanol) exceeding the permissible ICH and regulatory guideline limits for residual solvents. Kim et al. (2000) has developed freeze-dried powder that can form a dispersed cubic phase in water. Cost effective production of this dosage form in a stipulated time limits its commercial application. Szoka et al. (1998) has prepared dry powder formulation of polynucleotidase complexes for inhalation using freeze-drying. However, the vesicles formed were spherical lamellar liquid crystal shells that have lower bilayer area per volume and were more shear sensitive.

In this study dry powder precursors were produced by spray-drying. The drug and magnesium trisilicate (MTS; as a carrier) were dispersed whereas GMO was dissolved in isopropyl alcohol. During spray-drying GMO coats MTS and drug surfaces. The resulting powder has advantage of increased surface area and residual solvent content within standard ICH and regulatory limits. The dry powder precursors obtained by this modified method can directly be used for capsule or tablet preparations; the most popular dosage forms. Further, spray-drying technique, offers flexibility to alter and control powder properties as particle size distribution, bulk density, flowability, solid-state properties and moisture content (Broadhead et al., 1992; Cornigan, 1995), making it suitable method for preparation of pharmaceutical powder. Diclofenac sodium (DiNa) was selected as model drug and the powder precursors were evaluated for percent yield, drug content, image analysis, surface topography, residual solvent content, phase behavior, physical interactions, rheology, *in vitro* drug release, *in vivo* anti-inflammatory and analgesic activity.

2. Materials and methods

2.1. Materials

Glyceryl mono-oleate (Rylo^{TM} MG Pharma19) was generous gift from Danisco Cultor, (Copenhagen, Denmark). Licaps® capsules (size 0, hard gelatin capsule specially designed for lipid formulations) were obtained as gift sample from Capsugel (India). Magnesium trisilicate was purchased from Loba Chemicals, Mumbai, India. MTS has average particle size of 5.7 μm (d 0.5) determined by Laser Diffractometer, Mastersizer 2000 with distilled water as dispersant (Mastersizer Ver. 2, Malvern Instruments, Malvern, UK). Diclofenac sodium was gift from Bluecross Laboratories Ltd., Nasik (India). Subsyde®-CR capsules (Raptakos Brett and Co. Ltd., Roha, India.) containing controlled release beads of DiNa were purchased from local pharmacy shop. All other chemicals used were of analytical grade.

Table 1
Composition of powder precursor

Batch code	Composition of powder precursor (parts by weight)		
	GMO	MTS	DiNa
A	1	0.5	0.5
B	1	1	0.5
C	1	1.5	0.5
D	1	2	0.5
E	1	2.5	0.5

2.2. Preparation of powder precursor

GMO was dissolved in sufficient amount of isopropyl alcohol and then dispersed MTS and DiNa in it (proportions are shown in Table 1). Total solid content of dispersion of all batches was 5.0%. Spray-drying was carried out using laboratory scale spray dryer (Jay Instruments and Systems Pvt. Ltd., Mumbai, India) consisting of a cylindrical chamber with two cyclone collector at the air exit. Dispersions to be spray dried was kept under stirring on magnetic stirrer and fed into a twin-fluid nozzle at the top of the spray dryer body with a liquid orifice size of 0.1 cm using peristaltic pump. Aspiration air at a pressure of 300 mm WC (mm of water column) was pumped through 0.25 cm annular air orifice. The inlet temperature of drying air was 95 °C (outlet temperature 85 °C). The dispersion consisting of GMO, MTS and DiNa was pumped through the liquid side of the twin-fluid atomizer at a rate 10-ml/min with atomization air pressure of 1,96,133 Pa (2 kg/cm^2). Samples of powder precursor were kept in desiccator at room temperature over silica gel for 12–24 h before being subjected to any further evaluation.

2.3. Evaluation of powder precursor

2.3.1. Percent yield

The weight of powder precursor obtained after spray-drying was considered as observed yield and percent yield was calculated by using following formula:

$$\text{percent yield} = \left(\frac{\text{observed yield}}{\text{theoretical yield}}\right) \times 100 \quad (1)$$

2.3.2. Drug content

Powder precursor equivalent to 60 mg of DiNa was weighed accurately and dissolved in suitable quantity of methanol. This solution was filtered through 0.45 μm filter and absorbance was determined at 276 nm by UV spectrophotometer (V-530, JASCO, Japan) after appropriate dilution. The DiNa content was calculated using the absorbance obtained by repeating the same procedure for 60 mg of pure DiNa.

2.3.3. Image analysis

For image analysis, the images were captured using a stereomicroscope (Carl Zeiss, Germany) attached with a digital camera (Watec, Wat-202, Japan). The captured images were analyzed using Biovis Image Plus software (Expert Tech Vision,