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Formulation And Evaluation of Oral Micelles Carriers for Solubility Enhancement

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ABSTRACT

In the present study, oral micelles with a hydrophilic polymer and surfactant were developed using the hot homogenization technique process to improve the dissolution. The physicochemical properties of the lovastatin containing oral micelles were characterized using scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction, and a particle-size analyzer. The mean particle size of all Oral Micelles that were prepared was less than 500 nm. Polyethylene glycol (PEG) oral micelles significantly increased the maximum dissolution when compared with propylene glycol (PG), and polyvinylpyrrolidone (PVP) oral micelles. In this study, the oral micelles with a LO:PC:LC; 2:1:1.5 have rapid dissolution within 30 minutes, in addition to good oral bioavailability, with These results suggest that the preparation of lovastatin oral micelles using the hot homogenization process is a promising approach to improve the dissolution and absorption properties of drug.

Keywords: *Bioavailability, Lovastatin, Dissolution, Solvent evaporation method*

1. INTRODUCTION

Hyperlipidemia involves an imbalance of cholesterol levels, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the blood. LDL-C and HDL-C regulate the amount of cholesterol in the body and an imbalance can increase the risk of cardiovascular events, including myocardial infarction and stroke. Other forms of hyperlipidemia include hypertriglyceridemia as well as mixed hyperlipidemia, in which both cholesterol and triglyceride levels are elevated. Oral micelles have been recognized as alternative colloidal carriers that can substitute for conventional ones such as polymer nanoparticles, liposomes, nanoemulsions and microemulsions [1-3]. Oral micelles possess noticeable advantages, including skin occlusion, modulation of drug/cosmetic release, increased skin hydration and elasticity, UV blocking effects, drug targeting, and enhanced stability of chemically labile. Hot homogenisation is performed at elevated temperature and cold homogenization is done below room temperature. Active ingredient is dissolved or dispersed in the molten lipid before to the high-pressure homogenization, in both approaches. High pressure (100–2000 bar) moves the fluid in the narrow gap in homogenizer. approach homogenization is conducted at elevated temperature. The solid lipids are melted at a temperature above 5-10°C above their melting point [4-6]. A dispersion is obtained by adding liquid lipid and drug to be encapsulated. The mixture is dispersed in aqueous solution of surfactant (s) heated to same temperature by high shear mixing device and leads to formation of pre-emulsion. The pre-emulsion is introduced in high pressure homogenizer at controlled temperature. In this study, we developed a dual system that combines oral micelles and SD (SD- oral micelles) to modulate the skin release patterns of poorly water-soluble drugs. The proposed system would be expected to overcome the existing limitations and enable highly efficient treatments. Specifically, the solid lipid matrix is more hydrophilic due to the incorporation of the SD in the solid lipid core of the oral micelles, leading to a high penetration of drug into the skin, which is further facilitated by the nanoparticulate carrier [7-9]. The oral micelles play a role of the nanoparticulate system that can carry the drug highly soluble in the SD. The highly specific surface area of the nano-sized oral micelles facilitates the contact of drug with the stratum corneum and may favour accumulation for sustained drug release. Generally, the combination of these systems can facilitate the bioavailability enhancement of poorly water-soluble drugs through skin absorption and protects the drug molecules from degradation [10-14].

The complications associated with route of drug delivery and the physicochemical properties of drug, suggests that employment of strategies that are non-invasive and advanced technologies like nanotechnology, could be beneficial for the effective delivery of Nanoparticulate carrier systems (10–1000 nm), particularly below 200 nm, have shown to improve the bioavailability [15].

2. MATERIALS AND METHODS

Lovastatin was kindly donated by Alembic Life Sciences (Indore). Polyethylene glycol (PEG), propylene glycol (PG), and polyvinylpyrrolidone (PVP) were kindly obtained from S.D. fine Pvt. Ltd.

Optimization of formulation variables: The optimization of variables employed in the formulation was performed using 32 factorial designs. In the present study three independent variables were taken into consideration for the designing of formulation. The dependent variables for the selection of optimized process and batch were considered for the determination of particle size, zeta potential and polydispersity index. These were the parameters of importance for selection of appropriate combination of variables. The data obtained for the experimental design were fit to generate polynomial equation. The individual effect of these variables was investigated in development of oral micelles.

Table 1: 32 study of optimization for the oral micelles (LOM)

Levels	Lipid content (X1)		
	Linseed oil (LO) (mg) Xa	Phosphatidylcholine (PC) (mg) Xb	Lecithin (LC) (mg) Xc
-1	10	10	10
0	15	15	15
1	20	20	20

Preparation of Oral Micelles (OM): The oral micelles in the current research utilized hot homogenization technique for preparation. The drug was intended to be encapsulated in the lipid matrix with the help of surfactant. The use of stabilizer in the formulation was for improvement in the stability of developed oral micelles [16].

Table 2: Variability in combination of OM on the basis of lipid content (LO: PC: LC) concentration of surfactant and sonication time

Formulation Code	Lipid content (X1)			Amount of surfactant (X2) (%) (Tween 80)	Addition of sonication time (X3) (Min.)
	Linseed oil (LO) (mg) Xa	Phosphatidylcholine (PC) (mg) Xb	Lecithin (LC) (mg) Xc		
LOM1	20	10	15	10	10
LOM2	10	20	15	10	10
LOM3	20	15	10	10	10
LOM4	10	15	20	10	10
LOM5	15	20	10	10	10
LOM6	15	10	20	10	10

Characterization of oral micelles (OM): The oral micelles in the current research employed three techniques for the fabrication of oral micelles. The technique was optimized based on the particles size of the resultant nano lipid particles with poly dispersity index (PDI). The technique through which lower particle size with high entrapment efficiency derived was

selected for further progress in formulation development [17-18].

Particle size distribution: The particle analysis in oral micelles was investigated by photon correlation spectroscopy method. For this study, the dispersion of oral micelles was diluted with purified water in 1:2 ratios and final dispersion was filtered using membrane filter of 0.45µm. The angle for light scattering study was fixed at 90°C. The study was carried out at room temperature (25°C). Three reading were taken for calculating average mean to avoid any errors [19].

Determination of yield of OM: Yield of the formulation indicates the quantity of oral micelles achieved after the preparation. The yield is derived from gravimetric analysis. In this process a 10 mL suspension of drug was dried until the weight was constant to express the ratio of lipid present after drying and used initially. The yield was calculated in percentage [20].

Zeta potential measurement: The zeta potential studies for prepared formulations were carried out utilizing zeta sizer instrument. For the preparation of sample, the drug loaded oral micelles were diluted with purified water in the ratio of 1:2. The sample were analyzed three times and average mean was taken into consideration [21].

Table 3: Determination of various parameters of prepared LOM

Formulation Code	Particle size (nm)	Layers	Zeta potential (mV)	PDI
LOM1	122.01±1.12	Single	-21.12±1.02	0.206±0.08
LOM2	124.03±1.14	Single	-23.12±1.05	0.211±0.02
LOM3	129.21±1.01	Double	-24.21±1.09	0.226±0.05
LOM4	130.12±1.06	Single	-22.12±1.08	0.224±0.07
LOM5	128.21±1.02	Single	-23.01±1.03	0.219±0.05
LOM6	123.03±1.04	Single	-20.18±1.05	0.215±0.02

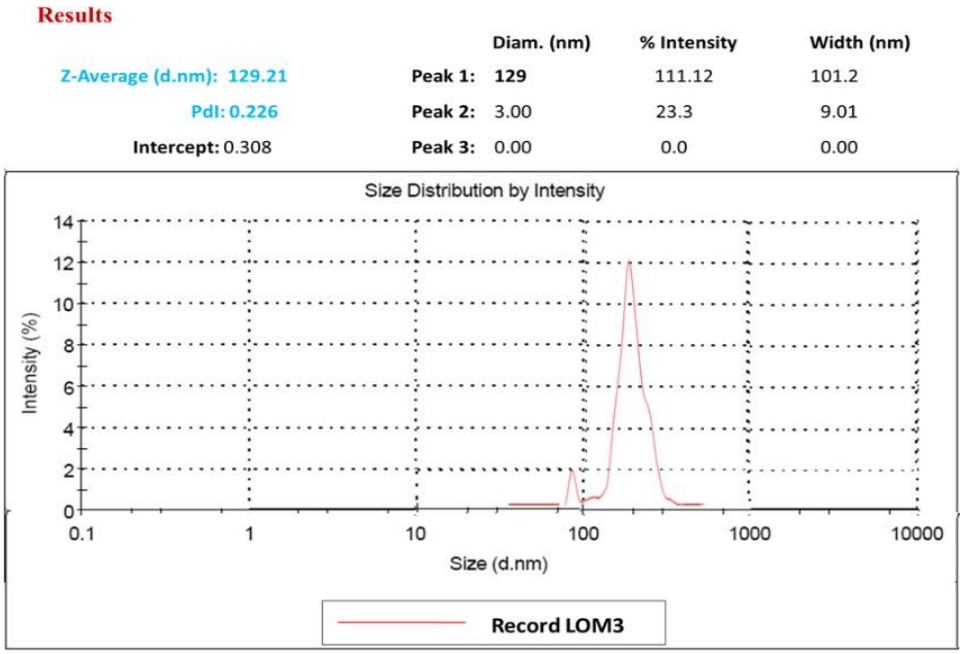

Figure 1: Particle size distribution & Polydispersity Index (PDI) of oral micelles (LOM3)

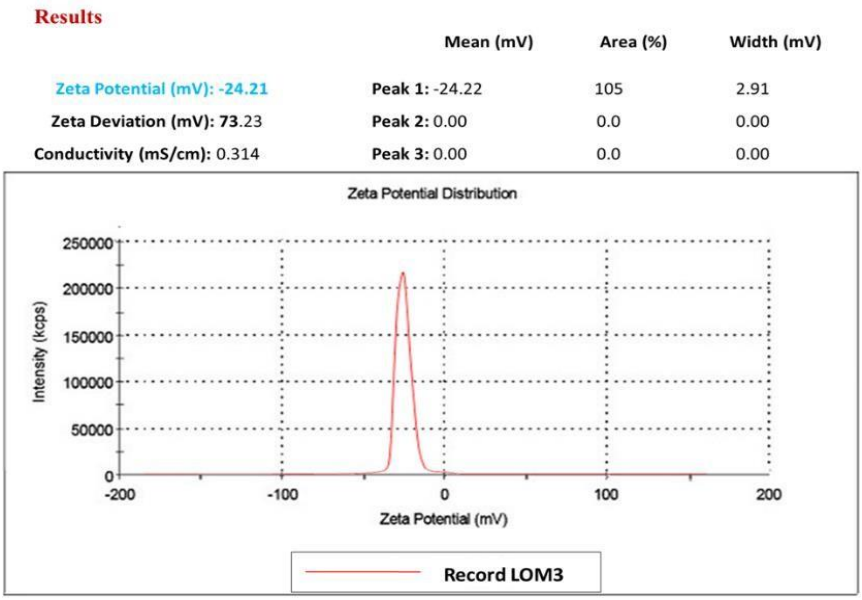

Figure 2: Zetapotential of oral micelles (LOM3)

3. RESULTS AND DISCUSSIONS

The optimization of lipid ratio over the oral micelles content on the result of dependent variables i.e. Particle size, Zeta potential, Poly dispersity index, prepared various formulations from LOM1 to LOM6. The content of lipid core linseed oil (LO) was coated with single layer of lipid content and double layer of combination of two layers of phosphetidylcholine (PC) and lecithin (LC). The various combinations of Linseed oil: Phosphatidylcholine: Lecithin optimize with constant concentration of surfactant as penetration enhancer of drug. The penetration enhancer affects the insertation of drug lovastatin amount inside the solid lipoid core through the single or double layer of lipid layers. The sonication time affect the multilaminar vesicles to unilaminar vesicles and the process also useful for overcome the problem of agglomeration of vesicles. The result of all dependent variables was evaluated and among all the formulations LOM3 has Linseed oil, Phosphatidylcholine, Lecithin was selected best formulation. The prepared LOMs layers ratio varying from 0.5 to 1.5 in with lipid oil provides a hydrophobic core. The result concluded that as the concentration of solid core varies and the amount of lipid content increase the particle size increase, thus increase the PDI and zetapotential action. The variations of result of all parameters also showed between the optimization of single or double layer. The optimization of sonication time was improving the particle size of LOM1 and LOM2, because of single layer of oral micelles and showed smaller size than the other formulations. The formulation LOM3 has more effect to identify the penetration rate or drug entrapment efficiency inside the solid lipid core. The optimization of sonication time also evaluated for identification of effect vesicular size and shape. The in- vitro Release profile of tablets was characterized for release percentage and release rate k. Release data within the linear range were selected and fitted to a zero-order mathematical model.

Conclusion: In the present study, lovastatin oral micelles were developed using the solvent evaporation method with a hydrophilic polymer and a surfactant. The polymer-drug ratio was also an important factor affecting the particle size of the LOM and the drug release rate. Elucidation of drug release mechanism using surfactant, particle size measurement showed the effectiveness of the established formulations in enhancing the skin absorption of lovastatin by altering the drug particle size and drug crystallinity without any molecular interaction changes. The study introduced a new technique by modifying the LOM structure using formulation to combine the advantages of LOM to promote potential applications of poorly water-soluble drugs in skin products.

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