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Preparation and Evaluation of Montelukast Sodium Loaded Solid Lipid Nanoparticles

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ABSTRACT

Solid lipid nanoparticles (SLNs) are an alternative carrier system used to load the drug for targeting, to improve the bioavailability by increasing its solubility, and protecting the drug from presystemic metabolism. The avoidance of presystemic metabolism is due to the nano-metric size range, so that the liver cannot uptake the drug from the delivery system and is not metabolized by the liver. Montelukast sodium is an anti-asthmatic drug, because of its poor oral bioavailability, presystemic metabolism, and decreased half-life; it was chosen to formulate as the solid lipid nanoparticle (SLN) system by hot homogenization followed by an ultrasonication method, to overcome the above. Compritol ATO 888, stearic acid, and glyceryl monostearate were used as a lipid matrix and polyvinyl alcohol as a surfactant. The prepared formulations have been evaluated for entrapment efficiency, drug content, *in vitro* drug release, particle size analysis, scanning electron microscopy, Fourier transform-infrared studies (FT-IR), differential scanning calorimetry (DSC), and stability. Particle size analysis revealed that the SLN prepared from the higher melting point lipid showed a larger particle size and with increased carbon chain length of the fatty acids. Entrapment efficiency (EE) was ranging from 42% to 92%. *In vitro* release studies showed maximum cumulative drug release was obtained for F 1 (59.1%) containing stearic acid, and the lowest was observed for F 18 (28.1%) containing compritol ATO 888 after 12 h and all the formulations followed first-order release kinetics. FT-IR and DSC studies revealed no interaction between drug and lipids. Studies showed that increase in lipid concentration, increased particle size, EE, and maintained the sustained release of drug. Among all, compritol ATO 888 was chosen as the best lipid for formulating SLN because it had high EE and sustained the drug release.

Key words: Entrapment efficiency, lipids, montelukast sodium, solid lipid nanoparticles, surfactant

INTRODUCTION

Solid lipid nanoparticles (SLNs) are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid. They have many advantages such as good biocompatibility, low toxicity, and lipophilic drugs are better delivered by as the solid lipid nanoparticle (SLN), and the system is physically stable. SLN may be a promising sustained release and a drug targeting system for lipophilic drugs.[1]

SLNs are composed of physiological and compatible lipids with a high melting point as the solid core, which is coated by nontoxic amphiphilic surfactants as the outer shell. The

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nanoparticles are in the submicron size range (50–1000 nm) and in the solid state at both body and room temperatures. Studies have shown that the physiochemical characteristics and stability of drug-loaded SLNs depend on the properties of drug and ingredients.

Appropriate choice of lipids, surfactants, and their composition affects the particle size, long-term stability during storage, drug loading, and release behavior. It means that there is an optimal SLN formulation for each drug that can be obtained by investigating the effect of process variables on the characteristics of desired carriers.[2]

Montelukast sodium is a potent, selective, and orally active leukotriene receptor antagonist that acts by inhibiting physiological actions of the cysteinyl leukotrienes. It is used in the prophylaxis and treatment of asthma exercise-induced bronchospasm, allergic rhinitis, urticaria, and to relieve the symptoms of seasonal allergies. The main drawback of conventional montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows biological half-life of 2.5–5.5 h, thereby decreasing the bioavailability up to 64%. The short half-life, poor solubility in water, and low bioavailability of montelukast sodium make a promising candidate for formulation of a sustained-release dosage form. SLNs are an alternative carrier system used to load the drug for targeting, to improve the bioavailability by increasing its solubility and protecting drug from first pass metabolism. The avoidance of presystemic metabolism is due to the nano-metric size range, so that the liver cannot uptake the drug from the delivery system and is not metabolized by the liver.[1] Therefore, when montelukast sodium is formulated as SLN the first pass metabolism may be avoided.

In this work, montelukast sodium-loaded SLNs were prepared by using stearic acid, glyceryl monostearate (GMS), and compritol ATO 888 as the lipid matrix and polyvinyl alcohol as the surfactant. The effects of lipid type and its concentration and surfactant concentration on the entrapment efficiency (EE), particle size, thermal characteristics, and drug release behavior of the resulting nano drug delivery systems were investigated.

MATERIALS AND METHODS

Materials

Montelukast sodium and glyceryl behenate were obtained as a gift sample from Microlabs, Hosur (TN) and Orchid Pharma, Chennai (TN), India. Glyceryl monostearate [GMS] (CDH Pvt. Ltd., Mumbai, India), stearic acid (Nice chemicals, Kerala, India), dialysis membrane 50-LA 387 (Himedia, Mumbai, India) were purchased from the local market. All the other reagents and solvents used were of analytical grade.

Formulation of montelukast sodium loaded solid lipid nanoparticles

Montelukast sodium loaded SLNs[3-6] were prepared by using the method of hot homogenization followed by ultrasonication. Montelukast sodium and lipid of various concentrations, i.e. 1, 2, 5, 10, 15, and 20% (composition of the formulations is shown in Tables 1 and 2) were weighed and dissolved in ethanol. Organic solvents were completely removed using a rotary flash evaporator (super fit rotary flash evaporator). The embedded lipid layer was melted by heating 5–10°C above the melting point of the lipid. The aqueous phase was prepared by dissolving polyvinyl alcohol in distilled water (sufficient to produce 30 ml of preparation) and heated to the same temperature as the oil phase. The hot aqueous phase was added to the organic phase and homogenization was performed (at 2000 rpm) by using a mechanical stirrer for 60 min. The obtained coarse

Table 1: Composition of SLN formulations

Ingredients	Formulations																	
	E 1	E 2	E 3	E 4	E 5	E 6	E 7	E 8	E 9	E 10	E 11	E 12	E 13	E 14	E 15	E 16	E 17	E 18
Surfactant (%)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Stearic acid (%)	1	2	5	10	15	20	–	–	–	–	–	–	–	–	–	–	–	–
Glyceryl monostearate (%)	–	–	–	–	–	–	1	2	5	10	15	20	–	–	–	–	–	–
Compritol ATO 888 (%)	–	–	–	–	–	–	–	–	–	–	–	–	1	2	5	10	15	20

Table 2: Composition of SLN formulations

Ingredients	Formulations																	
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12	F 13	F 14	F 15	F 16	F 17	F 18
Surfactant (%)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Stearic acid (%)	1	2	5	10	15	20	–	–	–	–	–	–	–	–	–	–	–	–
Glyceryl monostearate (%)	–	–	–	–	–	–	1	2	5	10	15	20	–	–	–	–	–	–
Compritol ATO 888 (%)	–	–	–	–	–	–	–	–	–	–	–	–	1	2	5	10	15	20