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Nanostructured lipid carrier versus solid lipid nanoparticles of simvastatin: Comparative analysis of characteristics, pharmacokinetics and tissue uptake

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ABSTRACT

Nanostructured lipid carrier (NLC) system of simvastatin was investigated for improvement in release, pharmacokinetics and biodistribution over its solid lipid nanoparticles (SLN). The NLC formulations prepared by solvent injection technique were optimized by 2^3 full factorial design. Optimized NLC was deduced on the basis of dependent variables that were analyzed using Design expert 8.0.2® software (Stat Ease, Inc., USA). Pareto charts and response surface plots were utilized to study the effect of variables on the response parameters. The optimized NLC was a suspension of nanosized homogeneous particles with significantly higher entrapment efficiency (>90%) and lower recrystallization properties ($p < 0.01$) than SLNs. The pharmacokinetic parameters of Tc^{99} labeled optimized NLC in mice, obtained using Quickcal software (Plexus, India) revealed 4.8 folds increase in bioavailability as compared to simvastatin suspension and 2.29 folds as compared to SLNs. Biodistribution study revealed preferential accumulation of NLC in the liver and this is advantageous because liver is the target organ for simvastatin. IVIVC studies demonstrated level A correlation between *in vitro* release and percent drug absorbed. This investigation demonstrated the superiority of NLC over SLN for improved oral delivery and it was deduced that the liquid lipid, oleic acid was the principal formulation factor responsible for the improvement in characteristics, pharmacokinetics and biodistribution of NLCs.

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1. Introduction

Attention is being focused on nanotechnology-based drug delivery systems including biodegradable polymeric nanoparticles, smart polymeric micelles, nanocrystals, nanosuspension, nanoemulsions and lipid nanoparticles with the aim to improve low aqueous solubility or oral bioavailability to bring about satisfactory therapeutic efficacy. Over the past few years lipid nanoparticles have been especially considered, because these are composed of natural or synthetic lipids, show good biocompatibility and have potential to exhibit controlled release of drugs (Li et al., 2009). Lipid-based nanoparticle formulations may also enhance drug absorption via improvement in dissolution and solubilization within the intestinal milieu, a reduction in gastric emptying rate and increase in mucosal permeability. Lipids are known to enhance lymph formation and simultaneously promote lymph flow rate (Suresh et al., 2007). Therefore, lipid nanoparticles have the potential to enhance the overall extent of absorption as well as increase the proportion of what is absorbed and transported to the systemic circulation via intestinal lymph (Humberstone and Charman, 1997; Aungst, 2000).

Simvastatin (SV), a lipophilic active constituent derived from fungi, is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor with beneficial effects on coronary diseases and mortality rate in patients with hypercholesterolemia. It is administered as an inactive lactone prodrug and has two separate metabolic pathways. Oxidative biotransformation is one of the pathway mediated primarily by cytochrome P3A (Christains et al., 1998), and hydrolyzation of simvastatin acid by carboxylesterase is another pathway leading to non-enzymatic metabolism into an active competitive statin. The SV then reduces the amount of mevalonic acid, a precursor of cholesterol, thereby inhibiting *de novo* synthesis of cholesterol. Consequently, the synthesis of low density lipoproteins receptors increases while cholesterol synthesis decreases; resulting in the increased clearance of low density lipoproteins from the bloodstream (Lilja et al., 2004).

Most of the available statins, including simvastatin, have been developed as immediate-release formulations. However, SV is a poorly water soluble drug (aqueous solubility ≈ 0.03 g/L) with a short half-life time of about 2 h, and is cleared by extensive metabolism in the intestinal gut and liver by cytochrome P 3A (Mahley and Bersot, 2006). Due to the slow dissolution rate in the intestinal tract and significant first-pass effect, the oral bioavailability of SV in humans is as low as 5%. Recently number of

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strategies have been employed to address the issues related to low bioavailability and poor aqueous solubility of SV. These include self microemulsifying drug delivery system (Kang et al., 2004; Patil et al., 2007), self nanoemulsifying granules (Dixit and Nagarsenker, 2008), solid dispersion (Silva et al., 2010), cubic nanoparticles (Lai et al., 2009), and Polyring device (Vishwanathan, 2008).

In a series of investigations carried out in our lab, SV loaded SLN formulations have been worked out as a potential oral therapeutic carrier system. SLNs were formulated and optimized using two lipids, glyceryl monostearate (GMS) and Compitrol 888 ATO. The optimized SLN formulation made with GMS exhibited a particle size of 258.5 nm, %entrapment efficiency of 75.81%, with 82.67% cumulative drug release after 55 h and its recrystallization index was found to be 65.51% (Shah and Pathak, 2010). A 1.87 folds increase in bioavailability was recorded with SV SLN made using glyceryl monostearate with respect to SV suspension in. On the other hand, the optimized formulation of Compitrol based SLN with a mean particle size of 271.18 nm, %EE of 68.16% and %CDR of 76.23% after 55 h documented a relative bioavailability of 220%, substantiating the protective action of SLNs against liver metabolism. On comparison, it was concluded that the SLNs made with Compitrol 888 ATO demonstrated higher bioavailability than SLNs made with GMS because of higher lipophilic nature of the former that was responsible for more sustained release of drug (Shah et al., 2010). Though these formulations provided sustained release of SV with potential for improved therapeutic efficacy, SLNs suffer from two major limitations that are limited drug loading and expulsion of drug during storage.

Among the lipid-based formulations, the nanostructured lipid carriers (NLCs), regarded as the second-generation of lipid nanoparticles, are attracting foremost consideration as alternative colloidal drug carriers. NLCs have evolved from solid lipid nanoparticles (SLN) and are composed of a mixture of spatially different lipid molecules, i.e., solid lipid is blended with liquid lipid to overcome the disadvantages of SLNs such as limited drug loading, larger particle size, risk of gelation and drug leakage during storage caused by lipid polymorphism. In view of this NLC may be regarded as an alternative to SLN and can be exploited as a novel approach for improving the delivery of SV. Lipid formulations loaded with poorly water-soluble drugs for oral route have been investigated and reported to improve the oral bioavailability by many research teams (Mohamed et al., 1998; Paliwal et al., 2009) but there are few reports on NLC system for oral administration. In this study we have made efforts to investigate the feasibility of improving oral bioavailability of SV through NLC.

Thus the objective of present study was to develop and optimize NLC suspension of SV using solid lipid and liquid lipid agents, in order to increase the drug entrapment efficiency and to further reduce the particle size; the major limitations of SLNs and thereby increase bioavailability by preventing hepatic first pass metabolism up to some extent along with comparison with the SLN and drug suspension. Thus, the SV-loaded NLCs were developed and screened and the physicochemical characteristics, *in vitro* drug release properties, pharmacokinetics and biodistribution were investigated in detail. Then all the parameters of NLCs were compared with the SLNs. Finally, the possible absorption mechanism of NLC formulation is discussed.

2. Materials and methods

2.1. Materials

Simvastatin was a kind gift from Ranbaxy Laboratories, India. Glycerol monostearate (M.P. 52–54 °C; molecular weight 358.63) was purchased from CDH, India. Poloxamer 407 (molecular weight 12.5) was purchased from BASF, USA. Oleic acid was purchased from Ranbaxy fine chemicals limited, India. Dialysis bag (molecular weight cut off 12–14 kDa; pore size 2.4 nm) was supplied by Hi Media, Mumbai, India. Other chemicals were of analytical grade.

2.2. Experimental design

In this study, a 2^3 full-factorial design was used to optimize NLCs. In order to optimize, the amount of GMS (X_1), amount of OA (X_2) and concentration of poloxamer 407 (X_3) were selected as independent variables. Each factor was set at a high level and low level. The actual values and coded values of different variables are given in Table 1. Eight formulations of simvastatin NLCs (F1–F8) were prepared according to the factorial design. The particle size, %entrapment efficiency and %cumulative drug release at 55 h were taken as response parameters. The statistical analysis of responses was made by Design expert 8.0.2. (Stat-Ease Inc., USA) that has been detailed in Section 2.7.

2.3. Preparation of simvastatin loaded NLCs

Nanostructured lipid carriers were prepared by solvent injection technique. Simvastatin (SV) (15 mg) and specified amount of GMS and OA as given in Table 1 were dissolved in 2 ml of isopropyl alcohol (boiling point 81–83 °C) with heating at the melting temperature of GMS. Though GMS is soluble in IPA it requires some heat for ease of solubilization. The resulting solution was rapidly injected into the 10 ml of aqueous phase containing specified amount of poloxamer 407 as given in Table 1 that was continuously stirred at 400 rpm for 30 min on a magnetic stirrer. 0.1 N HCl (4 ml) was added to the dispersion to decrease the pH around 1.5–2 for causing aggregation of NLCs for the ease of separation. Thereafter, the dispersion was centrifuged at 10,000 rpm (5590 × *g*) for 30 min at 10 °C in REMI cooling centrifuge (Model C-24BL, VACO-779, Vasai, India), and aggregates were re-suspended in 10 ml double distilled water containing 4% poloxamer 407 (by weight) as stabilizer with stirring at 1000 rpm for 10 min.

2.4. Purification of SV-loaded NLCs

Purification of SV-loaded NLCs was done by dialysis technique. Re-suspended suspension was taken in the dialysis bag and sealed at both ends. The dialysis bag then immersed into 100 ml of double distilled water containing 0.2% (w/v) sodium lauryl sulphate and stirred at 100 rpm for 20 min. Five milliliter of sample was withdrawn at time intervals of 5, 10, 15, and 20 min, diluted appropriately and analyzed for amount of drug by HPLC. Paired *t*-test was used to check any significant difference between the percent free drug removed at 15 and at 20 min.

2.5. HPLC assay for SV

The SV content was assayed using ADEPT HPLC systems – Cecil CE 4201, equipped with a Rheodyne injector Hamilton 702 NR, Adept 4100 dual piston pump and detector CE 4200 set at 239 nm, with a microsorb C18 analytical column (RP-18, 250 mm × 4.6 mm, 5 μm). The mobile phase was a mixture of acetonitrile:0.01 M ammonium acetate buffer (35:65, v/v), eluted at a flow rate of 1.0 ml/min and a sample injection volume of 20 μl. The limit of detection and the limit of quantification of this analytical method were 0.163 μg/ml and 0.493 μg/ml respectively. Linear calibration curve was obtained for SV with $r^2 = 0.9998$ in the range 5–25 μg/ml.

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