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Comparative evaluation of proliposomes and self micro-emulsifying drug delivery system for improved oral bioavailability of nisoldipine

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ABSTRACT

The objective of this study was to develop proliposomal formulation and self micro-emulsifying drug delivery system (SMEDDS) for a poorly bioavailable drug, nisoldipine and to compare their *in vivo* pharmacokinetics. Proliposomes were prepared by thin film hydration method using different lipids such as Soy phosphatidylcholine (SPC), Hydrogenated Soy phosphatidylcholine (HSPC), Dimyristoylphosphatidylcholine (DMPC) and Dimyristoyl phosphatidylglycerol sodium (DMPG), Distearyl phosphatidylcholine (DSPC), and Cholesterol in various ratios. SMEDDS formulations were prepared using varying concentrations of Capmul MCM, Labrasol, Cremophor EL and Tween 80. Both proliposomes and SMEDDS were evaluated for particle size, zeta potential, *in vitro* drug release, *in vitro* permeability and *in vivo* pharmacokinetics. *In vitro* drug release was carried out in purified water using USP type II dissolution apparatus. *In vitro* drug permeation was studied using parallel artificial membrane permeation assay (PAMPA) and everted rat intestinal perfusion techniques. *In vivo* pharmacokinetic studies were conducted in male Sprague-Dawley rats. Among the different formulations, proliposomes with drug: DMPC:cholesterol in the ratio of 1:2:0.5 and SMEDDS with Capmul MCM (13.04% w/w), Labrasol (36.96% w/w), Cremophor EL (34.78% w/w) and Tween 80 (15.22% w/w) demonstrated the desired particle size and zeta potential. Enhanced drug release was observed with proliposomes and SMEDDS compared to pure nisoldipine in purified water after 1 h. Nisoldipine permeability across PAMPA and everted rat intestinal perfusion models was significantly higher with proliposomes and SMEDDS. Following single oral administration of proliposomes and SMEDDS, a relative bioavailability of 301.11% and 239.87% respectively, was achieved compared to pure nisoldipine suspension.

1. Introduction

Oral route is the most common and preferred route of drug administration because of its convenience, and patient compliance. However, delivery of the drug by this route may often result in suboptimal therapeutic response because of the drug's poor solubility in gastrointestinal (GI) fluids, insufficient permeation across the GI membrane, and extensive first-pass effect. Proliposomes and SMEDDS are reported as drug delivery carriers for enhancing the oral bioavailability of drugs with poor bioavailability (Basalious et al., 2010; Potluri and Betageri, 2006). Proliposomes are dry, free flowing powders that can form multilamellar vesicles upon hydration (Nekkanti et al., 2014). Due to structural similarity between phospholipid bilayers and biological membranes, liposomes play an imperative role in facilitating the oral absorption of the poorly soluble drugs. SMEDDS is an isotropic mixture of oil(s), surfactant(s), and co-surfactant(s) that forms fine oil in water emulsion upon mild agitation. In the presence of GI fluids these systems undergo rapid self-emulsification producing nano sized globules of high surface area resulting in enhanced rate and extent of absorption with consistent plasma concentration time profiles (Porter et al., 2008). In addition, proliposomes and SMEDDS offer several benefits such as reduction in inter/intra subject pharmacokinetic variability, improvement in lymphatic transport and GI permeability and inhibition of P-glycoprotein (P-gp) efflux, all of which help in improving the oral bioavailability of hydrophobic drugs (Pouton, 2000). Both proliposomes and SMEDDS are emerging platform technologies for improving the oral delivery of drugs with poor bioavailability. In this study we made an effort

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to improve the oral bioavailability of nisoldipine by formulating into proliposomes and SMEDDS.

Nisoldipine is an orally administered calcium channel blocker used in the treatment of cardio vascular disorders such as hypertension, congestive heart failure and angina pectoris. Nisoldipine exhibits poor aqueous solubility and extensive pre-systemic metabolism resulting in low bioavailability following oral administration (Zannad, 1995). The reported mean bioavailability is approximately 5% with inter subject variability. The half-life of nisoldipine is 7–12 h and the mean time to achieve the peak plasma concentrations was reported as 9.2 ± 5.1 h. Nisoldipine is a known P-gp and P450 3A4 (CYP3A4) substrate, therefore any P-gp or CYP3A4 modulator can alter the pharmacokinetic properties of nisoldipine (Soldner et al., 1999).

Several formulation approaches have been reported to improve the oral bioavailability of nisoldipine. Most of these techniques have been focused on improving the solubility and absorption of nisoldipine from GI tract and/or to reduce P-gp efflux and CYP-450 mediated metabolism. The reported approaches include, extended release tablet (Schaefer et al., 1997), cyclodextrin complexes (Bayomi et al., 2002), solid dispersions (ul Hassnain et al., 2012), proniosomes for transdermal delivery (El Maghraby et al., 2015), self-nano emulsifying drug delivery system (Krishnamoorthy et al., 2015), nanosuspension (Sandhya et al., 2014), solid lipid nanoparticles (Dudhipala and Veerabrahma, 2015), sublingual tablets (Chatap et al., 2013), and lipid bearing pellets. However these investigational findings have not effectively translated into human clinical trials except film coated, extended release tablet (Sular®). The commercial tablet formulation consists of external coat and internal core portions of drug. The external coat provides an immediate release and internal core releases the drug over extended periods of time. It was reported that intake of food with high fat showed pronounced effect on the release of drug from the coat-core formulation leading to variability in systemic exposure (Heinig et al., 1997). Therefore, there is a requisite for a versatile drug delivery system that can improve pharmacokinetic performance of nisoldipine. To the best of our knowledge, there is no study reported comparing the *in vivo* pharmacokinetic performance of nisoldipine drug product developed using proliposomes and SMEDDS formulation technology. Our present investigation was primarily focused on developing an improved formulation for nisoldipine using proliposomes and SMEDDS. In this study, the prepared formulations (proliposomes and SMEDDS) containing nisoldipine were measured for particle size, zeta potential, *in vitro* drug release, *in vitro* permeability and *in vivo* pharmacokinetics.

2. Materials and methods

2.1. Materials

Nisoldipine was purchased from Lusochimica S.P.A (Milan, Italy). Soyphosphatidylcholine (SPC), Distearoyl-phosphatidylcholine (DSPC), hydrogenated Soyphosphatidylcholine (HSPC), Dimyristoylphosphatidylcholine (DMPC) and Dimyristoylphosphatidylglycerol sodium (DMPG) were purchased from Avanti Polar Lipids (Alabaster, AL, USA); Avicel PH 102 was purchased from FMC BioPolymers (Philadelphia, PA), Capmul MCM was purchased from Abitech Corporation (Janesville, WI, USA), Labrasol and Cremophor EL was purchased from Alfa chemicals (Binfield, Berkshire, UK) and Tween 80 was purchased from EMD (Billerica, Massachussetts, USA), cholesterol and Krebs-Hensleit Buffer (pH 7.4) was purchased from Sigma Aldrich, (St. Louis, MO, USA), 96 well plates were purchased from Millipore (Millipore, Billerica, USA). Cannulated Sprague-Dawley (SD) rats were purchased from Harlan laboratories (Indianapolis, IN, USA). Blank rat plasma was purchased from Valley Biomedical (Winchester, VA, USA). Hard gelatin capsules (Size 0) were purchased from Capsugel Inc. (Morristown, NJ, USA) and all reagents used were of analytical grade.

2.2. Preparation of formulations

2.2.1. Proliposomes

Nisoldipine proliposomes were formulated using SPC, HSPC, DSPC, DMPG, DMPC and cholesterol in various ratios. The composition details of respective formulations are summarized in Table 1. Briefly, the required amounts of nisoldipine, phospholipid and cholesterol were weighed and dissolved in ethyl alcohol. The resultant solution was adsorbed onto microcrystalline cellulose (Avicel PH 102). The excess solvent from the preparation was removed using a rotavapor (Buchi R-210, Buchi Corporation, New Castle, DE, USA) to obtain dry proliposomes (Nekkanti et al., 2015). The proliposomal formulations were then passed through a sieve (#50 mesh) to obtain free flowing powders. The proliposomal formulations were filled into glass scintillation vials and stored at 5 ± 3 °C for further studies. The prepared formulations were filled into size 0, hard gelatin capsules for *in vitro* dissolution studies.

2.2.2. SMEDDS

To determine the concentration of oil, surfactant and co-surfactant for SMEDDS, a pseudo ternary phase diagram was plotted using the water titration method at room temperature (25 °C). The selection of these formulation excipients is based on the solubility of nisoldipine (Fig. 1). The selected surfactant (Labrasol & Cremophor EL) and co-surfactant (Tween-80) were mixed in different ratios (1:1, 1:2, 1:3, 1:4 and 2:1) and titrated with purified water by a drop-wise addition under gentle agitation. The appropriate ratios of oil, surfactant and co-surfactant in the SMEDDS formulation were analyzed for the formation of self-emulsifying regions by constructing a pseudo ternary plot using CHEMIX® ternary plot software. All the studies were carried-out in triplicate.

Based on the self-emulsifying region, the formulations of SMEDDS were prepared by dissolving the drug in the optimized concentrations of oil, surfactant, and co-surfactant (Table 2). Required amounts of Labrasol, Cremophor EL and Tween 80 were added to the glass vial and mixed well with gentle heating until the drug is completely dissolved. The concentration of nisoldipine for all formulations was kept constant (i.e., 8%, w/w) to enable filling of a therapeutic dose of 20 mg into a size "0" capsule (hard gelatin).

Table 1
Formula composition, particle size and zeta potential of proliposomal formulations.

Formula code	Lipid Used	Drug:Lipid:Chol. Ratio	Mean vesicle size (nm ± SD)	PDI (mean ± SD)	Zeta potential (mV ± SD)
F-I	SPC	1:2:0.5	962.3 ± 72.5	0.322 ± 0.031	−15.2 ± 3.1
F-II	DSPC	1:2:0.5	958.7 ± 51.3	0.724 ± 0.028	−18.6 ± 2.8
F-III	HSPC	1:2:0.5	1647.5 ± 68.6	0.625 ± 0.018	−13.2 ± 3.5
F-IV	DMPC	1:2:0.5	846.2 ± 55.4	0.711 ± 0.025	−19.3 ± 3.2
F-V	DMPG	1:2:0.5	1525.2 ± 85.2	0.651 ± 0.029	−16.2 ± 3.2