European Journal of Pharmaceutical Sciences 64 (2014) 26–36

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Proliposomes as a drug delivery system to decrease the hepatic first-pass metabolism: Case study using a model drug

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ARTICLE INFO

Article history:
Received 28 February 2014
Received in revised form 15 August 2014
Accepted 18 August 2014
Available online 23 August 2014

Keywords:
Proliposomes
Lovastatin
Bioavailability
First-pass metabolism
In vivo

ABSTRACT

Objective of the present study was to develop a proliposomal formulation to decrease the hepatic first-pass metabolism of a highly metabolized drug. Lovastatin was chosen as the model drug. Proliposomes were prepared by mixing different ratios of phospholipids such as soy phosphatidylcholine (SPC), hydrogenated egg phosphatidylcholine (HEPC) and dimyristoyl phosphatidylglycerol (DMPG) individually with drug and cholesterol in an organic solvent. Proliposomal powder was obtained following evaporation of the solvent. The proliposomal powder was either filled into capsules or compressed into tablets. Physical characterization, in vitro drug transport studies and in vitro dissolution of formulations and pure drug was carried out. In vitro transport across the membrane was evaluated using parallel artificial membrane permeability assay (PAMPA). The extent of drug released from various proliposomal formulations in the first 30 min was 85%, 87% and 96% with DMPG, SPC and HEPC containing formulations respectively, while the pure drug formulation showed 48% drug release in the same period. In vivo studies were carried out in male Sprague–Dawley rats. Following single oral administration of the selected formulation (F9), a relative bioavailability of 162% was achieved compared to pure lovastatin. The study demonstrated that proliposomes can be used as a drug delivery system to decrease the hepatic first-pass metabolism.

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1. Introduction

Oral route is the most preferred route of administration. Efficacy of an orally administered drug is dependent on its oral bioavailability, which in turn is dependent on the dissolution, extent of absorption and first-pass metabolism (Custodio et al., 2008). Oral absorption of a drug is fundamentally dependent on that drug's aqueous solubility or intestinal drug solubilization and gastrointestinal permeability (Amidon et al., 1995).

Amidon et al. first proposed the biopharmaceutical classification system (BCS) in 1995 that classified drug substances based on their aqueous solubility and intestinal permeability into four classes (Amidon et al., 1995). Any factor impacting the dissolution characteristics of these drugs would have a profound impact on their bioavailability, for example drugs such as carabamazepine, ketoprofen and verapamil. The inability of a drug to go into solution is sometimes a more important limitation to its overall rate of absorption than its ability to permeate the intestinal mucosa (Horter and Dressman, 2001). For drugs that cross the intestinal mucosa easily, the onset of drug levels is dictated by the time taken by the dosage form to release the drug content. Thus, poor bioavailability of poorly water soluble molecules that are not permeation-rate limited can be attributed to dissolution-rate kinetics (Merisko-Liversidge and Liversidge, 2008). Solubility issues affect the delivery of many existing drugs. Compared to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences that include decreased bioavailability, increased chance of food effect, incomplete release from the dosage form and higher inter-patient variability (Williams et al., 2013).

Classical approach to deal with the solubility issue is to generate salts of poorly soluble drugs or pro-drugs to improve the solubility while retaining the biological activity (Fiese and Hagen, 1986). Other strategies to resolve the solubility problems of drugs include formulation approaches such as pH adjustment (Williams et al., 2013), use of cosolvents (Zhao et al., 2013), use of surfactants

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http://dx.doi.org/10.1016/j.ejps.2014.08.008
0928-0987/© 2014 Published by Elsevier B.V.

(Li et al., 2013), complexation (Patel and Rajput, 2009), micronization (Han et al., 2013) and novel drug delivery approaches like liposomes (Kaluderovic et al., 2012), microspheres (Hu et al., 2011), nanoparticles (Tran et al., 2013) etc. In our study, we followed the approach of using proliposomes as a carrier for the delivery of a BCS class II drug. Proliposomes are dry, free flowing powder formulations which upon reconstitution in aqueous environment forms liposomes (Payne et al., 1986). The objectives of our present study were to (a) develop and characterize the proliposomal formulation (b) investigate the effectiveness of proliposomes as a delivery system to improve oral bioavailability by decreasing hepatic first-pass metabolism. Lovastatin a BCS class II drug which has low solubility and high permeability with extensive first-pass metabolism was selected as a model drug for this study (Henwood and Heel, 1988; Suresh et al., 2007). Lovastatin, an inactive lactone, upon oral ingestion is hydrolyzed to the active metabolite β-hydroxyacid (lovastatin acid). The conversion of lovastatin to its active metabolite takes place in the liver. This makes it an ideal candidate to see if the drug upon formulating into proliposomes can reduce the first-pass metabolism. This can be determined by measuring the increased levels of lovastatin and decreased levels of the active metabolite in the blood.

2. Materials and methods

2.1. Materials

Dimyristoyl phosphatidylglycerol (DMPG) was obtained from Genzyme pharmaceuticals (Cambridge, MA, USA). Soy phosphatidylcholine (SPC) was obtained from Avanti polar lipids (Alabaster, AL, USA), hydrogenated egg phosphatidylcholine (HEPC) from NOF Corporation (Tokyo, Japan). Cholesterol and magnesium stearate were obtained from Spectrum chemical and laboratory products (Los Angeles, CA, USA). Silicified microcrystalline cellulose (SMCC), microcrystalline cellulose (MCC) and sodium starch glycolate were gifted by JRS Pharma (Patterson, NY, USA). Lovastatin was obtained from TCI America (Portland, OR, USA), lovastatin hydroxy acid and simavastatin hydroxy acid was obtained from Toronto Research Chemicals Inc. (Toronto, Ontario, Canada), simvastatin was obtained from Sigma Aldrich (Munich, Germany). PAMPA plates were obtained from Millipore (Billerica, MA, USA). Sprague–Dawley rats were obtained from Harlan Incorporated (Indianapolis, IN, USA) and rat plasma was obtained from Valley Biomedical (Winchester, VA, USA). All other materials and solvents used in the study were of HPLC grade and were obtained from EMD (Billerica, MA, USA).

2.2. Methods

2.2.1. Preparation of proliposomes

Proliposomal formulations containing lovastatin were prepared using lipids such as DMPG, SPC, HEPC and cholesterol. The details of the formulation composition are summarized in Table 1. Solvent evaporation method was used to prepare proliposomes. Briefly, to prepare DMPG proliposomes, lipid, cholesterol and lovastatin were dissolved in chloroform. In the case of SPC and HEPC formulations, lipid and cholesterol were dissolved in ethanol followed by the addition of the lovastatin and the resultant dispersion was adsorbed onto SMCC. Solvent was removed under a stream of nitrogen to obtain a proliposomal powder. This proliposomal powder was then subjected to vacuum desiccation to remove any residual solvent and passed through the sieve (250 μm; 60 mesh) to obtain free flowing proliposomal powder. The prepared formulation was either filled into capsules or compressed into tablets for further evaluation.

Table 1
Formulation composition of proliposomes.

Formulation code	Lipid	Drug (in parts)	Lipid (in parts)	Cholesterol (in parts)
F1	DMPG	1	0.45	0.05
F2	DMPG	1	0.9	0.1
F3	SPC	1	2	0
F4	SPC	1	1	0
F5	SPC	1	0.5	0
F6	HEPC	1	2	0
F7	HEPC	1	1	0
F8	HEPC	1	0.5	0
F9	SPC	1	0.45	0.05
F10	HEPC	1	0.45	0.05

2.2.2. Physical characterization of proliposomes

The proliposomal powder was dispersed in nanopure water and hydrated by mixing gently for 5 min at room temperature. The liposomes formed after hydration was observed through an optical microscope (Nikon Eclipse Ti-Series, Nikon instruments Inc., Melville, NY, USA). The sample was also subjected to Cryo-TEM analysis. Proliposomal tablet formulation was hydrated using 10 ml of distilled water (37 °C) for about 20 min. The sample was then centrifuged at 10,000 rpm for 5 min to separate the excipients from the liposomes (supernatant). The liposomal dispersion was transferred to an eppendorf tube. A drop of the liposomal dispersion was placed onto a carbon with copper grid (Lacey Formvar®). The samples were then frozen using Vitrobot Mark IV (FEI Company, Eindhoven, Netherlands). The prepared samples were observed under a Cryo-TEM (JEOL-JEM 1230 Electron Microscope; JEOL, Tokyo, Japan).

Proliposomes were hydrated in nanopure water as described above to obtain liposomes. The resultant dispersion was then analyzed for size distribution using Malvern Zetasizer ZS90 (Malvern Instruments, Worcestershire, UK).

2.2.3. Compression of proliposomal powder into tablets

The proliposomal powder formulations containing different compositions were compressed into tablets using Cadmach mini rotary tablet press (Cadmach Machinery Co. Pvt. Ltd., Gujarat, India). Sodium starch glycolate (3% of the weight of proliposome powder in each tablet) and magnesium stearate (0.5% of the weight of proliposome powder in each tablet) were used as tablet excipients. Tablets containing pure drug without any lipids were also compressed using the same composition and quantity of tablet excipients as used in the proliposomal tablets.

2.2.4. Tablet weight variation, breaking force and disintegration time

Weight variation of the prepared tablets was carried out on 20 tablets. Tablet breaking force was determined using a tablet hardness tester (Varian-VK200, Cary, NC, USA). Disintegration time was determined using a tablet disintegrating apparatus (Electrolab, Mumbai, India).

2.2.5. Analysis of lovastatin

A reversed phase HPLC method as reported in the United States Pharmacopoeia (USP) monograph for lovastatin tablets (USP, 2007) was used with slight modification. A Waters HPLC system (2487/600/717) with UV–visible detector was used for the analysis (Waters, San Diego, CA, USA). The mobile phase consisted of acetonitrile:phosphate buffer (pH 4.0):methanol (5:3:1), set at a flow rate of 1.2 ml/min with a sample injection volume of 50 μl. The chromatographic separation was performed on a Symmetry C-18 column (3.5 μm, 75 × 4.6 mm) preceded by a pre-column of similar material. The column assembly was enclosed within a column oven whose temperature was maintained at 45 °C. The column

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