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Enhanced oral bioavailability of an antipsychotic drug through nanostructured lipid carriers

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ABSTRACT

Olanzapine is an atypical antipsychotic, undergoes extensive first pass metabolism, also has poor aqueous solubility and belongs to BCS (Biopharmaceutical Classification System) Class II drug) exhibit low oral bioavailability. To overcome this and to enhance the bioavailability, intestinal lymphatic transport of drugs can be exploited through Nano structured lipid carriers (NLCs). The NLCs were formulated by solvent diffusion method using solid lipid (glyceryl tripalmitate), liquid lipid (castor oil) and surfactants (Pluronic F-68, Soylecithin). The formulated NLCs were characterized for physico-chemical properties, *in-vitro* release studies and *in-vivo* oral bioavailability. F6 has shown average particle size of 158.5 nm with PI of 0.115 indicating narrow particle size distribution and follows uni modal distribution. It was found that the batch with stearyl amine has a zeta potential of 28.39 mV which confers stability to the dispersion. Bioavailability studies indicate that there was more than 5½-fold increase in oral bioavailability in case of NLCs (F6) compared to olanzapine suspension which indicates that NLCs provided sustained release of the drugs, and these systems can be the preferred as drug carriers for lipophilic drugs in long term disease conditions such as schizophrenia for enhanced bioavailability.

1. Introduction

Oral route is the most accepted and preferable way of drug administration, due to low cost and easy administration which in turn high patient compliance. Now a day, lipophilic drugs show low oral bioavailability due to various reasons like poor aqueous solubility, high first pass metabolism [1]. Lipids have been used for a long time as a carrier for lipophilic drugs to improve their oral bioavailability.

Lipid emulsions are biphasic systems composed of oil phase dispersed as fine droplets in the aqueous phase and stabilized by phospholipids resulting in oil in water (O/W) emulsions [2]. The first safe intravenous lipid emulsion introduced as Intralipid® in the 1960′s consisted of an O/W emulsion of 10 or 20% soybean oil droplets (70–400 nm in size) stabilized by a monolayer of 1.2% egg yolk mixed phospholipids and 2.25% glycerol [3]. Lipid emulsion systems are more potential as drug carriers for highly lipophilic molecules solubilized in the core oil. Drug delivery and targeting research using lipid emulsions as carriers of poorly water soluble drugs have been explored [4]. However, due to the liquid state of the oil droplets, a prolonged drug release cannot be achieved. The use of solid lipid, which remains in solid state at room temperature and body temperature, instead of liquid oils is very attractive to achieve controlled drug release, leading to the formation of solid lipid nanoparticles (SLN) at the beginning of the1990′s.

The SLN combined the advantages of solid particles, emulsions and liposomes. The advantages of liposomes and emulsions are that they are composed of well tolerated excipients and they can easily be produced on a large scale, the pre- requisite for a carrier to be introduced to the market. SLN had different advantages, Mader and Mehnert showed various limitations of SLN such as poor drug loading, high water content, drug expulsion during storage due to the formation of more stable lipid structure [5]. To overcome the above problems, a third generation of lipid matrix was designed as Nanostructured Lipid Carrier – NLC [6].

Olanzapine is an atypical antipsychotic that belongs to thioenobenzodiazepine class used orally in treatment of Schizophrenia undergoes extensive first pass metabolism with

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over 40% of the drug being metabolized before reaching the systemic circulation. Also, it has poor aqueous solubility (BCS Class II drug). It is associated with severe dose related side effects which include drug-induced Parkinsonism, acute dystonic reaction, akathisia, tardive dyskinesia, and tardive dystonia. These side effects are seen at dosages that yield a beneficial effect on the symptoms of the disease. The severity of adverse events and/or lack of efficacy in considerable number of patients frequently results in poor patient compliance or termination of treatment. Many of patients are not in full control of their mental faculties. A dosage form of olanzapine having prolonged activity, and therefore requiring less frequent administration is highly desirable. This is because such a dosage form would minimize complications caused due to patients missing or failing to take a dose. Recently, solid lipid nanoparticles (SLNs) have been exploited as probable possibilities as carriers for oral intestinal lymphatic delivery [7]. The most promising mechanism is transcellular absorption, which operates for dietary lipids. The co-administration of lipid vehicle along with bioactives enhances absorption of water insoluble drugs into intestinal lymphatics and organs.

Based on the above background, the present work has been aimed to formulate and characterize NLCs containing Olanzapine (BCS class II drug) to improve the oral bioavailability by transporting the drug through the lymphatics via thoracic lymph duct to systemic circulation. The NLCs were formulated by solvent diffusion method using solid lipid (glyceryl tripalmitate), liquid lipid (castor oil), surfactants (Pluronic F-68, Soylecithin). The formulated NLCs were characterized for physico-chemical properties, *in-vitro* release studies and *in-vivo* oral bioavailability.

2. Materials and methods

2.1. Materials

Olanzapine was obtained from Ind Swift Pvt. Ltd., Chandigarh, Glyceryl monostearate was purchased from Kemphasol, and Tripalmitate was obtained from Sigma Aldrich. Pluronic F-68, Methanol HPLC grade, Acetone HPLC grade were purchased from Sisco. Potassium dihydrogen ortho-phosphate, Sodium hydroxide pellets, Triethylamine were obtained from Qualigen Fine Chemicals, Mumbai. Ethanol and Potassium bromide IR grade were purchased from S.D Fine Chemicals. Acetonitrile HPLC grade and Ortho-phosphoric acid were purchased from Rankem, New Delhi. Hydrochloric acid and Dialysis bag were obtained from Fisher Chemicals Ltd and HiMedia Labs, Mumbai respectively.

2.2. Preparation of nanostructured lipid carrier (NLC)

NLC were prepared based on the principle of 'Solvent diffusion method' technique [8–10]. Briefly the organic phase – consisted of Olanzapine, soy lecithin, stearyl amine, glyceryl tripalmitate and castor oil which were solubilized in the mixture of ethanol and acetone(1:1). Multiple batches where prepared at different concentration of ingredients by keeping Soy lecithin and stearyl amine as constant (Table 1). The organic phase was heated to 60–70 °C and added drop wise to aqueous phase under continuous stirring at 3000 rpm. The aqueous phase consisted of pluronic F-68(surfactant) which was dissolved in 50 mL of distilled water. The NLCs formed were centrifuged at 10000 rpm and freeze dried by addition of 2% mannitol (cryoprotectant) and used for further characterization.

2.3. Evaluation of nanostructured lipid carriers

2.3.1. Particle size and zeta potential [11]

Particle size and zeta potential of the solid lipid nanoparticles were measured by photon correlation spectroscopy using a Malvern Zetasizer Nano ZS90 (Malvern Instruments, Worcestershire, UK), which works on the Mie theory. All size and zeta potential measurements were carried out at 25 °C using disposable polystyrene cells and disposable plain folded capillary zeta cells, respectively, after appropriate dilution with original dispersion preparation medium. In order to investigate the effect of stearylamin e on zeta potential two batches were prepared with and without stearylamine and their zeta potential were measured.

2.3.2. Polydispersity index

Polydispersity was determined for the prepared batches to get clear estimation regarding the distribution of particle size by applying standard polydispersity index formula, and thus optimized trail can be considered for study.

2.3.3. Entrapment efficiency and scanning electron microscopy (SEM)

Weighed quantities of NLCs (5 mg) were dissolved in 0.1 N HCl under water bath at 70oC for 30 min and then cooled to room temperature to preferentially precipitate the lipid. Drug content in the supernatant after centrifugation (4000 rpm for 15 min) was determined by UV visible spectroscopy at 258 nm using 0.1N HCl as blank [12].

$$\text{Drug entrapment efficiency } (\%) = \frac{\text{Analyzed weight of drug in NLCs}}{\text{Theoritical weight of drug loaded in NLCs}} \times 100$$

External surface morphology of drug loaded NLCs was recorded using SEM at 20 kV as an accelerating voltage [13]. Weighed amount of samples (5–7 mg) were mounted on an aluminium stub with double sided adhesive tape. The tape was firmly attached to the stub and sample was scattered carefully over its surface. The stub with the sample was then sputter coated with a thin layer of gold to make the sample conductive. Processed sample was subjected to SEM analysis. The images were captured under magnification of 10,000- 15,000 x and recorded.

2.3.4. Differential scanning calorimetry

Differential scanning calorimetry DSC Q200 V24.4 Build 116, Mettler Toledo was used. The instrument was calibrated with indium for melting point and heat of infusion. A heating rate of 20 °C/min was employed throughout the analysis in the 25–200 °C. Standard aluminium sample pans were used for the sample F6; an empty pan was used as reference. The thermal behaviour was studied under a nitrogen purge; triplicate run were carried out on sample to check reproducibility.

2.3.5. In-vitro release studies

The release of Olanzapine from the NLCs was studied under sink conditions. F6 and F8 showing higher drug content and entrapment efficiency were evaluated for *in-vitro* release. 5 mL of NLCs equivalent to 1 mg were put in dialysis bags (MWCO 12000 kDa, HiMedia). The dialysis bags were placed in 50 mL of pH 7.4 phosphate buffer dissolution medium and stirred under magnetic stirring at 37 °C. Aliquots of the dissolution medium were withdrawn at each time interval and the same volume of fresh dissolution medium was added to maintain a constant volume. Samples withdrawn from pH 7.4 phosphate buffer saline were analyzed for Olanzapine content spectrophotometrically at 258 nm against solvent blank [14].

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