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Pharmacoscintigraphic evaluation of potential of lipid nanocarriers for nose-to-brain delivery of antidepressant drug

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ABSTRACT

Efficacy of antidepressants relies upon their continued presence at the site of action (brain) over a prolonged period of time. The BBB restricts the access of antidepressants to the brain on oral as well as intravenous administration. Direct delivery (by-passing the BBB) of antidepressant drugs can increase the CSF concentration with concomitant reduction in dose and side effects. Intranasal administration of nanostructured lipid carriers (NLC) containing antidepressant drug circumvent the BBB and maintain the prolonged release at the site of action. The aim of the present study was to evaluate the enhancement in brain uptake of NLC containing duloxetine (DLX) after intranasal administration. Duloxetine loaded NLC (DLX-NLC) was evaluated pharmacoscintigraphically for drug targeting potential (DTP), drug targeting efficiency (DTE) and biodistribution studies in different organs including brain. The radiolabeling efficiency of DLX and DLX-NLC was found to be 98.41 ± 0.96 and 98.87 ± 0.82 after 30 min, respectively. The biodistribution studies exhibited higher percentage of radioactivity/g for DLX-NLC formulations in brain as compared with the DLX. The higher DTP (86.80%) and DTE (757.74%) suggested that DLX-NLC formulation has a better brain targeting efficiency than DLX solution (DTP = 65.12%; DTE = 287.34%) when administered intranasally. Moreover, the intranasal administration exhibited about 8-times higher concentration of DLX in brain when compared with the intravenous administration of DLX solution. The intranasal NLC containing DLX can be employed as an effective method for the treatment of depression.
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1. Introduction

Pharmacoscintigraphic technique has been widely used to study the *in vivo* behaviour of drug and drug delivery systems using emitted radiations from the radioactive materials. This technology has proven to be of great value in the assessment of a wide range of pharmaceutical formulations and new drug delivery systems. The radiometric detection of drugs labelled with a suitable radiotracer is the best technique for the detection and concentration of the drugs given through nasal route. Pharmacoscintigraphy study includes gamma-counts in different organs and gamma-imaging of intact animal after administering the calculated dose of drug. Gamma-counts of gamma-radiation emitted by the deposited radiolabelled DLX and NLC in different organs were done by the gamma-counter. Moreover, the gamma-imaging was done by the gamma-camera which gives images to provide the functional map of physiological processes. For scintigraphic studies the formulations are usually labelled with the gamma-ray emitting radionuclide ^{99m}Tc (technetium), which has ideal radiation energy (140 keV) for use with a gamma-camera (Newman and Wilding, 1998). The short half-life of ^{99m}Tc (6 h), coupled with a very clean and safe radiation emission profile which contains few beta-particles results in very low radiation doses, so that satisfactory scintigraphic data can be obtained using only a fraction of the radiation dose required for diagnostic X-ray procedures (Newman and Wilding, 1998).

Neurotransmitters (*e.g.*, serotonin) are chemical messengers within the brain that facilitate communication among nerve cells. Inadequate supplies lead to the symptoms that are known as depression. It is a serious medical condition and is associated with decrease in functioning and well-being, high levels of disability, and high work absenteeism and health care costs. According to WHO estimates, depression will become the second-largest cause of the global health burden by 2020. Yet, depression remains one of

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the most under diagnosed conditions. Over 60 percent of suicides are attributed to major depressive disorder. It is a common mental illness with lifetime occurrence rates close to 20% which is heritable as well (Glahn et al., 2012). Duloxetine (DLX), an SNRI is the first in the class of anti-depressants that ensures rapid and sustained efficacy in the treatment of both emotional and physical symptoms of depression. DLX promises treatment of physical symptoms that accompany major depressive disorder (MDD) such as aches, pains, and gastrointestinal disturbance as well. On oral administration DLX undergoes hepatic first pass metabolism and has a systemic bioavailability of 50% (Lantz et al., 2003). Moreover the drug is acid labile at gastric pH. Oral administration of the drug also causes side effects including nausea, dry mouth, headache, dizziness, orthostatic hypotension fatigue. Efficacy of antidepressants relies upon their continued presence at the site of action (brain) over a prolonged period of time (Kilts, 2003). On oral as well as intravenous administration the BBB restricts the access of antidepressant drugs to the brain. Brain targeting can increase the CSF concentration of the drug with concomitant reduction in dose and side effects (Misra et al., 2003).

Intranasal administration offers a non-invasive alternative route to the central nervous system (CNS) for drug delivery, effectively bypassing the BBB (Graff and Pollack, 2005). The nasal route is one of the most permeable and highly vascularized site for drug administration ensuring rapid absorption and onset of therapeutic action. The neural connections between the nasal mucosa and the brain provide a unique pathway for noninvasive delivery of therapeutic agents to the CNS (Thorne and Frey, 2001; Illum, 2000). The olfactory and trigeminal nerve components in the nasal epithelium provide pathways to deliver therapeutic agents to the olfactory bulb and brainstem, respectively, where dispersion to other CNS areas may be possible *via* pulsatile flow within the perivascular spaces of cerebral blood vessels (Thorne et al., 2004; Thorne et al., 2008).

NLCs are particles produced from the blend of solid and liquid (oil) lipids. It possesses many "imperfections" increasing drug loading capacity and minimizing or avoiding drug expulsion during storage (Muchow et al., 2008). Being lipophilic in nature NLC has been expected for the transport of therapeutic substances to the brain. They are composed of physiological and biodegradable lipids exhibiting low toxicity that means an excellent tolerability. The lipid nanoparticles are able to enhance the chemical stability of compounds sensitive to light, oxidation and hydrolysis (Pardeike et al., 2009).

Thus, the present study was designed to deliver DLX, an antidepressant drug to the brain through nose to brain route of drug delivery using NLC as drug delivery system and the quantification and biodistribution studies were performed by pharmacoscintigraphic method.

2. Materials and method

2.1. Drugs and reagents

DLX was provided by Dr. Reddy's Laboratories (Hyderabad, India). Glyceryl monostearate (solid lipid) (Loba chemie Pvt. Ltd., Mumbai, India), pluronic F-68 (surfactant) and capryol PGMC (liquid lipid) (Sigma Chemical Company, MO, US), bile salt (sodium taurocholate) (co-surfactant) (Thomas Baker, chemicals, Ltd., Mumbai, India), and mannitol (cryoprotectant) (S.D. fine-chem Ltd., Mumbai, India) were used as received from suppliers. Sodium pertechnetate, separated from molybdenum-99 (^{99}Mo) by solvent extraction method, was provided by Regional Centre for Radiopharmaceutical Division (Northern Region), Board of Radiation and Isotope Technology (New Delhi, India). Stannous chloride dihydrate ($SnCl_2$ $2H_2O$) was purchased from Sigma–Aldrich (St. Louis, MO, USA). Instant thin layer chromatography (ITLC) silicic acid (ITLC-SA) strips were purchased from Gelman Sciences Inc. (Ann Arbor, MI, USA). All other chemicals and solvents were of analytical reagent grade and were used without further purification.

2.2. Animals

Swiss albino Wistar rats of either sex (200–250 g) were used for performing the gamma count in different organs. All animals were given free access to water and food and kept under standard laboratory conditions, temperature at $25 \pm 2\,^{\circ}C$ with a natural light–dark cycle and relative humidity of $55 \pm 5\%$. The animals were housed in polypropylene cages, six per cage with free access to standard laboratory diet (Lipton feed, Mumbai, India; providing 3630 kcal/g energy and containing 22.10% crude protein, 4.10% crude oil, 4.05% crude fiber, 10.05% ash, 0.75% sand silica) and water *ad libitum*. Ethical clearance for performing biodistribution studies was taken from the Institutional Animal Ethics Committee, Jamia Hamdard, New Delhi and the study was performed at INMAS (Delhi, India).

New Zealand rabbits weighing between 2.00 and 2.50 kg (female) were employed for performing the gamma-imaging studies. Animals were procured from the animal house of INMAS (Delhi, India). The guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) (Ministry of Culture, Govt. of India) were followed throughout the study and maximum care was taken to make certain that animals were treated in the most human and ethically acceptable method.

3. Experiments

3.1. Preparation of DLX-NLC and lyophilization

DLX-NLC was prepared by dissolving DLX (2 g/l) in a mixture of melted solid lipid (glyceryl monostearate) and liquid lipid (capryol PGMC). The lipid concentration and the ratio of liquid lipid to total lipid was optimized to 2 (% w/w of aqueous phase) and 0.94:1, respectively. The lipid mixture was homogenized (Heidolph, Diax 900, Schwabach, Germany) at 10,000 rpm for 20 min with hot aqueous solution (80 °C) of surfactants {pluronic F-68 = 1.5% w/w; and bile salt (sodium taurocholate) = 0.5% w/w} followed by ultrasonication (10 min) and lyophilization (at −70 °C) using mannitol (3% w/w) as cryoprotectant (Alam et al., 2011).

3.2. Procedure for radiolabeling

Radiolabeling was performed using sodium pertechnetate. Radioactivity was eluted out from Mo–Tc generator in saline. Ethanol was chosen as a solvent to extract out the radioactivity. A suitable method of radiolabeling was chosen by which DLX was labelled with ^{99m}Tc. The method of radiolablleing was standardized by gamma-imaging technique so as to visualize the distribution of radiolabelled drug in animal models. The selection of ^{99m}Tc was based on a number of properties including its short half-life of 6.02 h, cost effective, easily eluted from the generator, soluble in solvents like acetonitrile and methyl ethyl ketone (MEK) and the dried form of activity is easily leached out from the glass beaker with the help of acetonitrile.

3.3. Radiolabeling of DLX and DLX-NLC

Radiolabeling was done using ^{99m}Tc by a direct labelling method. DLX (5 mg) or DLX-NLC (equivalent to 5 mg of DLX) was accurately weighed in a vial and 1 ml of distilled water was added.

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