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Original article

Development and evaluation of Desvenlafaxine loaded PLGA-chitosan nanoparticles for brain delivery

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ABSTRACT

Depression is a debilitating psychiatric condition that remains the second most common cause of disability worldwide. Currently, depression affects more than 4 per cent of the world's population. Most of the drugs intended for clinical management of depression augment the availability of neurotransmitters at the synapse by inhibiting their neuronal reuptake. However, the therapeutic efficacy of antidepressants is often compromised as they are unable to reach brain by the conventional routes of administration. The purpose of the present study was to reconnoiter the potential of mucoadhesive PLGA-chitosan nanoparticles for the delivery of encapsulated Desvenlafaxine to the brain by nose to brain delivery route for superior pharmacokinetic and pharmacodynamic profile of Desvenlafaxine. Desvenlafaxine loaded PLGA-chitosan nanoparticles were prepared by solvent emulsion evaporation technique and optimized for various physiochemical characteristics. The antidepressant efficacy of optimized Desvenlafaxine was evaluated in various rodent depression models together with the biochemical estimation of monoamines in their brain. Further, the levels of Desvenlafaxine in brain and blood plasma were determined at various time intervals for calculation of different pharmacokinetic parameters. The optimized Desvenlafaxine loaded PLGA-chitosan nanoparticles (~172 nm/+35 mV) on intranasal administration significantly reduced the symptoms of depression and enhanced the level of monoamines in the brain in comparison with orally administered Desvenlafaxine. Nose to brain delivery of Desvenlafaxine PLGA-chitosan nanoparticles also enhanced the pharmacokinetic profile of Desvenlafaxine in brain together with their brain/blood ratio at different time points. Thus, intranasal mucoadhesive Desvenlafaxine PLGA-chitosan nanoparticles could be potentially used for the treatment of depression.

1. Introduction

Depression is a debilitating mental disorder, characterized by low mood, hopelessness, sadness, low self-esteem, disturbed sleep and often with suicidal thoughts (Kircanski et al., 2012; Lenox and Frazer, 2010). As per current WHO report, depression is one of the leading causes of disability affecting more than 350 million people worldwide (Marcus et al., 2012). The World Mental Health Survey conducted in 17 countries reported that on average 1 in 20 people have suffered an episode of depression (WHO, 2015). Depression has also been held responsible for suicides which translate to 1 million lives per year (Marcus et al., 2012). The primary cause of depression is the disturbances in the monoaminergic i.e. norepinephrine, serotonin, dopamine transmission in brain due to complex interaction of several social, psychological and biological factors (Kircanski et al., 2012; Lenox and Frazer, 2010). Therefore,

Abbreviations: CNS, central nervous system; FST, forced swim test; BBB, blood brain barrier; BSF, blood-cerebrospinal fluid barrier; i.n., intranasal; 5 HT, 5-hydroxytryptamine; HCl, hydrochloric acid; PDI, poly dispersity index; PLGA, poly (lactic-co-glycolic acid); DVF, Desvenlafaxine; CN, chitosan; PVA, polyvinyl alcohol.

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most of the drugs intended for treatment of depression enhance the availability of monoamines at the synapse by various mechanisms. Nevertheless, the therapeutic efficacy of these antidepressants is dependent on their continuous prolonged presence at the site of action in brain (Kircanski et al., 2012; Lenox and Frazer, 2010; Nutt, 2008). Currently antidepressants are mainly delivered by oral route due to chronic nature of treatment across several days. However, the efficacy of oral antidepressants is limited due to their inability to reach the brain effectively from systemic circulation as the blood brain barrier (BBB) and blood-cerebrospinal fluid (BSF) barrier restrict the transport of drugs from systemic circulation into the central nervous system (CNS) (Kilts, 2003). Also, the variation in plasma drug concentration following oral delivery leads to adverse effects, loss of efficacy and intolerability (Kilts, 2003). For many decades, different types of antidepressants such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), and serotonin and norepinephrine reuptake inhibitors (SNRI) have been used for treatment of depression but the remission rate after the first trial of an antidepressant is <30%, that continues to decline after a first antidepressant failure (Kircanski et al., 2012; http://mentalhealthdaily.com). Therefore, scientists and pharmaceutical companies have been competing to develop effective antidepressant drug capable of providing quick and prolonged remission. This is reflected by a series of new antidepressant drugs approved by FDA in the past 3 years such as vilazodone, levomilnacipran, vortioxetine and 20 more currently under clinical trials (http://mentalhealthdaily.com). These facts provide a strong rationale for the development of intranasal nanoformulation that can transport the antidepressant drug to the brain non-invasively and increase its brain concentration reducing the dosage, side effects and intolerability. In past few years intranasal (i.n.) nose to brain delivery has emerged as a novel technique for transporting therapeutic agents to the CNS (Kumar et al., 2008a,b). Nose to brain drug delivery is possible due to unique connection provided by the olfactory and/or trigeminal nerve system present between the olfactory epithelium and the CNS, bypassing the BBB (Kumar et al., 2008a,b). Recently, a large number of publications have reported the nose to brain delivery of many drugs due to its obvious benefits e.g. avoidance of BBB and hepatic first pass metabolism, non-invasiveness and ease of administration (Kumar et al., 2008ab; Al-Ghananeem et al., 2010; Md et al., 2012).

In the present study Desvenlafaxine succinate (DVF), a second generation SNRI, was selected as the drug candidate for nose to brain delivery. Desvenlafaxine is an active metabolite of venlafaxine with an oral bioavailability of 80% and plasma half life of 11 h. Although Desvenlafaxine has better serotonin:norepinephrine ratio (10:1) than Venlafaxine (30:1), oral therapy is associated with a number of side effects such as increased blood pressure and heart rate, constipation, agitation, tremor, sweating, nausea, headache, and sleep disturbances (Mann, 2005; Perry and Cassagnol, 2009). For development of drug delivery system, biodegradable polymeric nanoparticles composed of polylactide-co-glycolide (PLGA) and chitosan (CN) were optimized. PLGA-CN nanoparticles are biodegradable, biocompatible and bioadhesive in nature to extend the residence time of drug in the nasal cavity and limit its nasal mucociliary clearance for better absorption across nasal epithelium including the olfactory regions for nose to brain delivery (Pawar et al., 2010).

The purpose of the present study was to optimize a nano-sized drug delivery system using PLGA and CN for intranasal nose to brain delivery of DVF and evaluate its antidepressant efficacy by pharmacodynamic and biochemical studies in rodents. The other objective of the present work was to evaluate the pharmacokinetics of DVF loaded PLGA-CN nanoparticles in brain and plasma, respectively for correlation with the outcomes of pharmacodynamic and biochemical studies.

2. Materials and methods

2.1. Materials

Poly (D,L-lactic-co-glycolic) (50:50, MW 9–12 KDa, carboxylic acid terminated) was purchased from Shandong Institute of Medical Instrument (Jinan, Shandong, China). DVF succinate was obtained from Chengdu-Kaijie Biopharm Co. Ltd (Chengdu, China). Polyvinyl alcohol (PVA, Av. MW 30–70 KDa), low MW Chitosan (CN, ~75–85% degree of deacetylation, MW 50–190 KDa) and crude pig mucin (PM) were purchased from Sigma Chemical Co. All the other chemicals and reagents used were of the analytical grade.

2.2. Animals

Adult male Wistar rats (aged 6–8 weeks) weighing ~250 g were selected for pharmacodynamic, biochemical and brain pharmacokinetic studies. The current study was approved by the Research review and ethics board (RREB), Tianjin Huanhu Hospital, P.R. China. All animal experiments were carried out as per the obligation of the national act for the use of experimental animals (People's Republic of China).

2.3. Preparation of PLGA-CN nanoparticles

PLGA-CN nanoparticles were prepared by emulsion solvent evaporation method (Wang et al., 2013). Briefly 100 mg of PLGA was dissolved in 2.5 mL of chloroform with or without DVF (30% w/w) and added to 10 ml aqueous phase (0.5% acetic acid solution with pH range of 4.6–4.8) containing 0.5% PVA and 0.5% CN. The primary emulsion was vortexed for 90 s and then sonicated by a probe sonicator at 50 W (Q700 Sonicator, CT USA) for 60 s on ice. The chloroform was removed by rotary evaporator under partial vacuum. The nanoparticles were obtained by ultracentrifugation (23,000*g*, 18 min at 4 °C, Beckmann coulter, USA). The concentrated nanoparticles were freeze-dried using mannitol as cryoprotectant (2.5% w/w).

2.4. Characterization of PLGA-CN

PLGA-CN nanoparticles were characterized for particle size and size distribution, zeta potential entrapment efficiency (EE) and drug loading (DL). The particle size, size distribution and zeta potential were measured by Zetasizer (model: Nano ZS, Malvern Instruments, UK). The particle size of the optimized formulation was also determined using transmission electron microscopy (TEM, Morgagni 268D, USA). The EE and DL were determined by the separation of free DVF from the DVF associated with PLGA-CN nanoparticles by ultracentrifugation at 45,000*g* for 30 min. The entrapment efficiency and drug loading were calculated using equations as given below:

$$\text{Entrapment efficiency}(EE\%) = (\text{Total DVF} - \text{free DVF})/\text{Total DVF} \times 100$$

$$\text{Drug loading}(DL\%) = (\text{Total DVF} - \text{free DVF})/\text{Total weight of Nanoparticles} \times 100$$

The *in vitro* release of DVF from optimized formulation was determined by dialysis bag (MWCO 12 KDa; Sigma-Aldrich) dipped in a dissolution apparatus filled with phosphate buffer at pH 7.4 and pH 6.0 (at 37 °C ± 0.5 °C). At predetermined sampling time points, a 2 mL aliquot was withdrawn for analysis and replaced with equal amount of fresh phosphate buffer till 24 h. DVF was determined in the samples by reverse-phase HPLC with UV