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ORIGINAL ARTICLE

Direct and enhanced delivery of nanoliposomes of anti schizophrenic agent to the brain through nasal route

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Abstract The problem of inadequate oral bioavailability of Quetiapine Fumarate, a lipophilic drug used for schizophrenia, due to hepatic metabolism and repulsion by brain barrier was attempted in this study. Combination of two approaches, viz. Quetiapine inclusion into the liposomal carrier for better diffusion and administration through nasal route to avoid hepatic metabolism and barrier elimination was applied. Thin film hydration followed by sonication method was employed in liposome preparation and the formulation was optimized using 3^2 full factorial design. The number of sonication cycles (X_1) of 2 min and 80% amplitude and molar ratio of constructional components such as cholesterol to egg phosphatidylcholine (X_2) as independent variables and a % of entrapment efficiency (Y_1) and cumulative *in vitro* drug release (Y_2) at 6 h as dependent variables was selected. Batch F7 prepared by 2 cycles of sonication and 1:3 M ratio of cholesterol: egg phosphatidylcholine was optimized as a consequence of substantial entrapment efficiency of 75.63 ± 3.77%, and 99.92 ± 1.88% drug release and 32.33 ± 1.53% drug diffusion, which was optimum among all other batches at 6 h. Diffusion study was done for all the batches of liposomal formulation by using sheep nasal mucosa and good amount with better diffusion rate was measured which proved liposomal dispersion a virtuous delivery system for brain drug delivery through nasal route. Results of *in vivo*, ciliotoxicity and gamma scintigraphy studies on mice supported the above inference.

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1. Introduction

Schizophrenia is a disorder of brain and characterized by the sudden breakdown of thought processes and by poor emotional responses. In contrast to other tissues, brain endothelial cells are more intimately associated and that prevent access of any potentially toxic substances into the brain (Pardridge, 1999). Any molecule enters through the blood into the brain is restricted by this barrier made up of endothelial cells' "Tight Junctions" or "*Zonula Occludens*" or also called as blood brain barrier (BBB) (Misra et al., 2003). Owing to its stringent penetrability, it is presumed to be the key obstacle in the development of central nervous system (CNS) targeted drug delivery (Pathan et al., 2009). Various strategies to use different routes of drug administration than oral or parenteral route such as intranasal and olfactory route and like to use drug nanocarriers have been applied to cope with the problem of the transportation across the blood brain barrier (Abbott and Romero, 1996).

The historical backdrop of nasal drug transportation goes once again to prior topical applications of medications proposed for local effects (Alsarra et al., 2010). Intranasal drug delivery has numerous focal compensation over other routes of drug administration (Behl et al., 1998; Costantino et al., 2007; Illum, 2000). Late improvements in nasal drug delivery have recommended intranasal administration as a safe and adequate course for brain targeting, especially for drugs with biological consequences on the CNS and constrained BBB permeability (Watts et al., 2002). The Olfactory region is of significant interest toward medication conveyance in light of the fact that it evades the BBB, conveying restorative drugs to the CNS (Frey, 2002). Nasal delivery is easily accessible, convenient, and a dependable system, with a porous endothelial membrane, and a profoundly vascularized epithelium that provides a quick assimilation of the compound into the systemic circulation, circumventing the hepatic first pass disposal (Parmar et al., 2011; Türker et al., 2004). In addition to that, intranasal drug delivery enables reduction in the dose, quick therapeutic level attainment of the drug into the blood, speedier onset of pharmacological activity, and fewer side effects (Arora et al., 2002; Ugwoke et al., 2001). It is reported that lipophilic drugs are by and large, well absorbed from the nasal cavity with pharmacokinetic profiles, which are frequently indistinguishable to those acquired after an intravenous infusion with a bioavailability approaching 100% (Aacharya et al., 2015). Strategy of delivering the drug by intranasal route could be effective in the delivery of therapeutic proteins such as brain delivered neurotropic factor (BDNF) to the olfactory bulb as a treatment for Alzheimer's disease (Thorne et al., 1995).

Colloidal drug transporters resembling micelles, emulsions, liposomes and nanoparticles have been largely accounted for brain drug delivery because methods of preparation are generally simple and easy to scale-up (Garcia et al., 2005; Woensel et al., 2013). Liposomes are self-assembling colloidal structures comprising of lipid bilayers encompassing an aqueous compartment, and can typify the wide range of hydrophilic drugs within this compartment (Pathan et al., 2009). Liposomes have been demonstrated to provide stable epitome to different drugs and offer unique focal points over un-encapsulated agents (Lasic and Papahadjopoulos, 1995).

Thus, liposomes have been proposed for utilization in an assortment of applications in research, industry, and medicine, especially for the utilization as transporters of symptomatic and therapeutic compounds (Fang et al., 2009). The unique ability of liposomes to entrap drugs, in both an aqueous and a lipid phase makes such delivery systems attractive for hydrophobic and hydrophilic drugs, such encapsulation proved to reduce drug toxicity while retaining or improving the therapeutic adequacy (Fielding, 1991). Liposomes are most commonly used carrier of mixes for brain delivery *in vivo* (Afergan et al., 2008; Schnyder et al., 2005; Shi et al., 2001; Xie et al., 2005) and proved to enhance bioavailability of numerous deprived agents into the brain (Alsarra et al., 2008; Arumugam et al., 2008; Hamed et al., 2012; Vyas et al., 1995).

Quetiapine Fumarate (QTF) is indicated for the treatment of schizophrenia and also for the acute manic episodes associated with bipolar I disorder. QTF is an antipsychotic drug with limited oral bioavailability (7–9%) due to hepatic metabolism and excision by the blood brain barrier (Brayfield and Sweetman, 2007). Albeit numerous endeavors have been made to attain brain entry of QTF, it doesn't efficiently infiltrate into the BBB (Kararli et al., 1992; Lohan et al., 2015).

It was hypothesized that if saline liposomal suspension of QTF administered through nasal route, it would avoid hepatic first pass metabolism and BBB crossover, and hence could achieve improved bioavailability and brain targeted drug delivery. The objective of the present study was to formulate different factorial batches of QTF liposomes by varying the molar ratio of constructional components and optimize by comparison for % entrapment efficiency and % drug release with time. The applied factorial design was validated and all the batches were further evaluated for diffusion through the sheep nasal mucosa by *ex vivo*. The optimized batch was then radiolabeled and compared with the simple solution of ^{99m}Tc in simulated nasal fluid (SNF) using a gamma scintigraphy study, which is then sustained by comparison of liposomal dispersion with the simple dispersion of QTF by *in vivo* study in mice.

2. Materials and method

2.1. Materials

QTF was a generous gift from Elite pharmaceuticals, Ahmedabad. Egg Phosphatidylcholine (EPC) was obtained as a gift sample from Vav Life sciences Pvt. Ltd., Mumbai, and Cholesterol (CH) was purchased from Astron Chemicals, Ahmedabad.

2.2. Analytical method

QTF is analyzed for %EE, %CDR and % diffusion study by Uv double beam spectrophotometer (Shimadzu-1800, Japan) in SNF, pH 6.8 by generating standard curve for the entire range from 5 to 25 μg/ml at 242 nm (Sahu and Rana, 2011; Vincenzo et al., 2003). The method used for estimation of QTF in brain homogenate and plasma involves high performance liquid chromatography (HPLC) analysis (Model LC) using a C18 column with Uv detector. Mobile phase consists of phosphate buffer (pH 3): Acetonitrile: Methanol