DESIGN AND EVALUATION OF NASAL DELIVERY SYSTEMS OF ANTIPSYCHOTIC DRUGS FOR TARGETING TO THE BRAIN

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Abstract: The mental and behavioural disorders are chronic, severe and disabling brain disorders affecting people throughout life history. In India, it is estimated that 6-7% population suffer from common mental disorders and 1-2% severe mental disorders (National Mental Health Programme-2011).The economic burden of schizophrenia is particularly great (approximately, the treatment consumes a total of $ 63 billion per year).The conventional dosage forms (oral and intravenous) of clozapine are unable to reach brain in sufficient concentration for its therapeutic action due to blood brain barrier, degradation in GI harsh environment and extensive hepatic first pass metabolism. Many patients (69-82%) discontinue medication due to invasiveness and intolerable side effects.

In the present research work, formulations for nasal delivery of Clozapine were developed and their brain targeting efficiency was evaluated. This approach can bypass the Blood Brain Barrier (BBB) and provides a practical, non-invasive, rapid and efficient method to deliver clozapine to the brain. This method works because of the unique connection between the nose and the brain through olfactory nerve pathway.

The main objective behind the research was to formulate and evaluate thermosensitive *in situ* gels of Clozapine (CZP) to increase efficacy for targeting to brain. Two types, aqueous based and oily based *in situ* gel systems were developed by using water and oleic acid as solvents respectively. All the *in situ* gel formulations were prepared by cold method using Pluronic F127 & F68 as thermosensitive gelling agents, Labrasol, Transcutol P, Tween 80 and ethanol as co solvents. The prepared *in situ* gels were evaluated for clarity, gelation temperature ($T_{sol-gel}$), gelation time, gel strength, pH, viscosity, and mucoadhesive strength and ex vivo drug permeation studies. The effect of mucoadhesive agents like HPMCK4M, Chitosan, Sodium-β- glycerophosphate and Polyox WSR303 also evaluated. The optimized formulation F4 (the aqueous CZP *in situ* gel composed of Tween 80 and ethanol (1:1) with 0.5 % Polyox WSR303 as mucoadhesive agent and 0.5% Sodium glycocholate as permeation enhancer) showed viscosity 253±5.2cP at 25^{o}C, 582.6±5.03 cP at 32^{o}C; mucoadhesive strength 5069.6±21.5 dynes/cm^2 and the flux was found to be 198.77 µg/cm^2/hr with optimum gelling properties such as gelation temperature (Tsol-gel) 32.3^{o}C±0.5; gelation time 64±1.5sec. The enhancement ratio(ER) of optimized formulation was found to be 2.16 folds higher than the plain drug solution. The results revealed that aqueous based *in situ* gels are more efficient than oil based gels. From the results, it can be concluded that formulation of intranasal *in situ* gels of clozapine could increase the brain targeting efficacy and enhances the bioavailability.

Keywords: Clozapine, *in situ* gels, Nasal Drug Delivery, Olfactory pathway, Brain targeting,