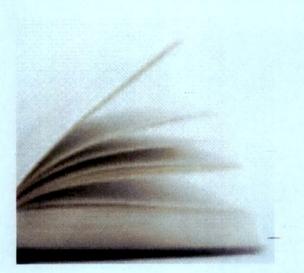
chapter 9





Conclusion

Under this investigation, mucoadhesive microemulsion of clobazam was successfully prepared, characterized and assessed pharmacokinetically through biodistribution in mice using radio tracer and pharmacodynamically for delaying the PTZ induced seizures in mice. Clobazam is a synthetic, small lipophilic molecule which satisfies the prerequisites for intranasal brain targeting, the development of microemulsion based mucoadhesive delivery system showed the added benefits in term of higher brain uptake which is reflected in the pharmacokinetic studies. It was found that the intranasal administration of mucoadhesive microemulsion protected the animals against convulsion within 15 minutes of administration. It is beneficial in acute status epilepticus to facilitate the patient for the safe hospitalization for further treatment and as a supplementary therapy. According to the results of this investigation, intranasal administration of clobazam provides an effective targeted delivery to brain with minimal systemic exposure resulting in reduction of dose and dosing frequency. In the treatment of anxiety and schizophrenia also, the intranasal clobazam mucoadhesive microemulsion administration may reduce the dose dependent tolerance and withdrawal symptoms associated with the chronic use of benzodiazepines.

Similarly, mucoadhesive microemulsion of clopidogrel bisulphate was successfully prepared and was assessed for brain uptake by using radio tracer and pharmacodynamically for control of damage to the ischemic brain. The brain uptake studies showed that the mucoadhesive microemulsions can effectively deliver the drug at the target site. In the pharmacodynamic study, the brain glutathione level of clopidogrel bisulphate mucoadhesive microemulsion treated group clearly indicated the restoration of antioxidant system in the animals and the protection against ischemic events. Hence, the neuroprotective effect of clopidogrel on hippocampal region of the brain can be selectively achieved by intranasal administration. It is also expected to minimize the side effects associated with the systemic exposure of clopidogrel bisulphate either by IV or oral route wherein the bleeding time increases which restores slowly within 7-14 days even after withdrawal of the drug.

Mucoadhesive nasal gel of insulin like growth factor-1 was successfully prepared. Biodistribution studies were carried out in mice using radiolabeling technique. Assessment of radiolabeled IGF-1 concentrations in the brain after IN administration of IGF-1 mucoadhesive gel demonstrated that the concentration achieved in brain in 30 minutes was two fold to that of simple IGF-1 solution by IN; thereby it shows the effectiveness of the delivery system in brain targeting. These results were further supported by the elevated brain levels of IGF-1 and glutathione in IGF-1 gel treated animal groups after transient forebrain ischemia. The animal studies under this investigation showed the potential of nasally administered IGF-1 mucoadhesive gel in protection of mice against cerebral ischemic events. Apart from poor permeability through BBB, systemic administration of IGF-1 not only carries the inherent risk of causing acute hypoglycemia, but also results in unwanted side effects due to the complexities of the relationship between IGF-1, growth hormone and somatostatin. Subcutaneous administration is used to deliver IGF-1 to motor neuron axons and terminals via the blood stream. However for the effective delivery of IGF-1 to pathology occurring within the brain in cases of cerebral ischemia, Alzheimer's diseases and central manifestations of amyotropic lateral sclerosis and multiple sclerosis, the intranasal route of administration would be beneficial. The studies demonstrate that intranasal administration of IGF-1 can be an effective, simpler, safer method of delivery as compared to IM and intracerebral ventricular injections. We achieved higher IGF-1 concentration in brain following intranasal administration of mucoadhesive gel of IGF-1 and protection against cerebral ischemia in animals. These findings may lead to a possible product for otherwise challenging clinical emergency of cerebral ischemia after extensive animal and clinical studies.

To conclude, mucoadhesive based drug delivery systems of different class of drugs were successfully prepared and assessed pharmacokinetically and pharamcodynamically in suitable animal models. The mucoadhesive delivery systems demonstrated their potential in effective brain targeting through intranasal route. Hence, these studies suggest potential application of intranasal clobazam, clopidogrel bisulphate and insulin like growth factor-1 in treating CNS disorders possibly by reducing dose and dose dependent tolerance of clobazam, minimizing side effects associated with the systemic exposure of clopidogrel bisulphate and BBB

circumvented enhanced delivery of insulin like growth factor-1. However, role of intranasal formulations developed in this investigation can only be realized after animal studies on atleast two more animal species followed by clinical studies with focus on toxicological evaluation on chronic use.

BOOK CHAPTERS

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PRESENTATIONS

- 1. Evaluation of Tc- ^{99m}-labeled IGF-1 for Brain targeting through intranasal route-Preliminary studies, at 9th Asian Oceanic congress of Nuclear medicine and biology, (2008) Abstract RP26. 31st Oct. 08 to 4th Nov. 08. New Delhi, India.
- 2. Intranasal delivery of clobazam mucoadhesive microemulsion for brain targeting, at Second Winter School: Nanotechnology, 24th -28th February 2009, National Institute of Pharamceutical Education and Research, (NIPER), Mohali.
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Intellectual growth should commence at birth and cease only at death.

- Albert Einstein

