CHAPTER 5

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The aim of the present investigation was to develop and evaluate intranasal microemulsion for treatment of epilepsy. Widely used antiepileptic drugs having poor solubility, such as carbamazepine and Phenytoin, were selected to prepare microemulsion based delivery system. Currently these drugs are available as tablets, capsules, suspensions and injectable. Oral therapy releases drugs in peripheral circulation, which limits the drug uptake across the brain barrier and results in to delayed onset of action and result in drug distribution to non targeted sites. Although injectable preparation provides rapid onset of action but it requires presence of trained person. Hence, an alternative route of drug delivery is needed since oral and injectable routes for delivering drugs are sometimes impractical and inconvenient.

Stable oil in water intranasal microemulsions of carbamazepine was successfully prepared and evaluated in this study. Microemulsion was prepared by water titration method. Microemulsion base was selected on the basis of solubility data. The solubility data showed that carbamazepine having highest solubility in oleic acid and thus oleic acid was selected as oil to formulate microemulsion. Surfactant and cosurfactant were selected on the basis of solubility data, literature review and safety profile. Tween 80 and Transcutol® were selected as surfactant and cosurfactant. 1:1 ratio was selected as optimum Smix ratio from microemulsion regions obtained from pseudoternary phase diagrams. The microemulsions were prepared with optimized Smix ratio and evaluated for various physicochemical parameters. The In vitro diffusion through sheep nasal mucosa suggested higher carbamazepine (70%) diffused through sheep nasal mucosa in comparison to carbamazepine diffused from carbamazepine solution (40%). The optimized microemulsion did not show any toxicity on rat nasal mucosa during In vivo study. Pharmacodynamic study suggested faster recovery and lesser intensity of seizures in rats treated with intranasal optimized carbamazepine microemulsion in comparison with rats treated with oral carbamazepine microemulsion and intranasal carbamazepine solution. In-vivo brain uptake study in rats showed that at 10 min, the ratio of brain/plasma concentration of carbamazepine obtained by nasal route was about 14 times higher than that obtained by IP route. Similarly, after 30 min of administration, 12.61 times higher ratio was obtained.
Pyridoxal phosphate, active form of pyridoxine (vitamin B6), plays important role in generation of one of the important inhibitory neurotransmitter GABA, deficiency of which can produce epilepsy. Hence vitamin B6 was loaded in aqueous phase of optimized carbamazepine microemulsion. Pharmacodynamic study revealed that no significant difference in intensity of epilepsy was observed in rats treated with carbamazepine microemulsion administered intranasally and microemulsion containing carbamazepine and vitamin B6 ME administered intranasally (p<0.05, n=6). Hence microemulsion containing carbamazepine coupled with vitamin B6 was not selected for further studies.

Phenytoin microemulsion was prepared by water titration method. Based on solubility study results Capmul MCM was selected as oil while Labrasol® and Transcutol® were selected as surfactant and cosurfactant based on solubility study, literature review and safety profile. Based on microemulsion area obtained in pseudoternary phase diagrams 1:1 ratio was selected for Labrasol®: Transcutol® mixture. Simpex centroid design was used to optimize composition of Phenytoin microemulsion. The concentration of oil (X₁), surfactant (X₂) and cosurfactant (X₃) were selected as independent variables and the globule size (Y₁) and cumulative phenytoin diffused at 60 minutes (Y₂) through sheep nasal mucosa were taken as dependent variables. The concentrations of independent variables were selected based on microemulsion region obtained from pseudoternary phase diagram. The results of dependent variables were determined experimentally. The model equation was generated and validity of mathematical model was established. The optimized phenytoin microemulsion was further evaluated for physicochemical parameters, In vitro nasal toxicity study, pharmacodynamic study and brain uptake study. Optimized PHN ME did not show any toxicity on sheep nasal mucosa and showed faster recovery from seizures in rats treated with intra nasal phenytoin microemulsion in comparison to the rats treated with oral microemulsion and nasal solution in pharmacodynamic evaluation. Four times higher concentration of phenytoin was found in rats treated with intranasal microemulsion in comparison to the rats treated with phenytoin solution administered intraperitonially. Localization of PHN was confirmed by gamma scientigraphy.
study. Gamma scietigrophy results also suggested faster localization of drug in brain after administration of intra nasal administration of PHN ME.

The findings of this study conclusively demonstrate that intranasal delivery of microemulsion rapidly and effectively delivers carbamazepine and phenytoin to brain. Higher brain uptake of drug confirms that these formulations could be more useful for the drugs like carbamazepine and phenytoin specifically during severe bouts of seizures when oral administrations of drugs are not possible. Noticeable advantages were observed for these intranasal microemulsions in comparison to conventional therapy and are expected to help in management of epilepsy patients in better way.

In these study two antiepileptic drugs, carbamazepine and phenytoin were selected for preparation of intranasal microemulsion. It was observed that Slightly higher concentration of PHN (0.060 mcg/gm) was obtained in rat brain after administration of intranasal PHN ME in comparison to CBZ concentration (0.05163 mcg/gm) obtained after administration of intranasal CBZ ME. The possible explanation for this phenomenon was smaller globule size of PHN ME in comparison to CBZ ME. In addition PHN (log P 2.48) is slightly more lipophilic than CBZ (log P 2.44) which may play synergistic role in higher absorption of PHN. The study also demonstrated that PHN loaded ME showed comparatively grater reduction in seizures activity during pharmacodynamic study. The results suggested that the rapid recovery in seizures can be obtained with intranasal PHN ME in comparison to CBZ ME. However, exact role of intranasal microemusions developed in this study for treatment of epilepsy can only be realized after through clinical evaluations.