ABSTRACT

The project was undertaken with an aim to develop oil in water microemulsion based intranasal delivery system for brain targeting for treatment of epilepsy. Carbamazepine and Phenytoin, widely used antiepileptic drugs, were selected for this study. These drugs are currently available in the form of oral and injectable dosage forms. Oral therapy results in slower brain uptake and systemic side effects while injectable therapy requires need of trained person which may not be available at the time of seizures. Hence novel patient friendly intranasal formulation was proposed to provide faster on set of action during seizures.

Carbamazepine is widely preferred therapy for the treatment of epilepsy. However, oral therapy results in slower brain uptake and systemic side effects. Intranasal route can achieve faster brain uptake, but poor aqueous solubility of carbamazepine is the main obstacle for administration by nasal route. Thus, intranasal microemulsion of carbamazepine was prepared by water titration method using oleic acid as oil, Tween 80 as surfactant and Transcutol® as cosurfactant. Different pseudoternary phase diagrams were prepared and depending on area of microemulsion region, 1:1 ratio of Tween 80: Transcutol® was selected for preparation of carbamazepine microemulsion. Carbamazepine microemulsions were evaluated for various physical parameters including globule size, viscosity, pH, conductivity and pharmacodynamic study. Toxicity study of optimized carbamazepine microemulsion was carried out by employing sheep nasal mucosa. The results suggested that the optimized microemulsion contains 8% oleic acid, 39% Tween 80, 39% Transcutol and 14 % water. The optimized microemulsion, thus obtained, was stable and transparent with average globule size of 21.03 nm and did not show any toxic symptoms. It was observed that comparatively faster recovery was observed in rats treated with intra nasal carbamazepine microemulsion in comparison to rats treated with oral carbamazepine solution and oral carbamazepine microemulsion. Higher brain/plasma ratio for drug was obtained with nasal microemulsion in comparison to ratio obtained after intraperitoneal injection of carbamazepine solution.

Pyridoxal phosphate, active form of pyridoxine (vitamin B6), is the important factor in treatment of epilepsy and hence vitamin B6 was loaded in aqueous phase of optimized carbamazepine microemulsion. The carbamazepine microemulsion and microemulsion
containing carbamazepine and vitamin B6 were evaluated by pharmacodynamic study. No significant difference in the Hind limb Extension phase 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 is widely used antiepileptic drug having poor solubility and absorption by oral route hence intranasal microemulsion of phenytoin was prepared to achieve faster onset of action in treatment of epilepsy. Phenytoin microemulsion was prepared by water titration method. The concentration of oil (X₁), surfactant (X₂) and cosurfactant (X₃) were selected as independent variables, in a simplex centroid design, from microemulsion region obtained from pseudoternary phase diagram while the globule size (Y₁) and cumulative phenytoin diffused at 60 minutes (Y₂) through sheep nasal mucosa were taken as dependent variables. Total ten batches were prepared and constraints were laid to identify the optimum batch. It was found that optimized microemulsion contains 10% oil, 33.33 % Labrasol®, 33.33% Transcutol® and 23.34% water. Ex-vivo toxicity study of optimum microemulsion was carried out by employing sheep nasal mucosa. The optimized phenytoin microemulsion did not show any toxicity on sheep nasal mucosa. It was found that faster recovery from seizures was obtained in rats treated with intranasal phenytoin microemulsion in comparison to the rats treated with oral microemulsion and nasal solution. Higher concentration of phenytoin was found in rats treated with intranasal microemulsion in comparison to the rats treated with phenytoin solution administered intraperitoneally. Gamma scintigraphy results also suggested faster availability of drug in to brain when formulation was administered intranasally. The optimized microemulsion remains stable for 3 months with average globule size of 16 nm and 52% PHN diffusion.

Keywords: Carbamazepine, Epilepsy, Intranasal, Microemulsion, Phenytoin