Thesis Title : Formulation of Slow Release Chloroquine Injection

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Abstract

Chloroquine is still the most prescribed antimalarial drug. Parenteral chloroquine absorption is very rapid. As a consequence, transiently very high blood concentration appeared followed by lethal hypotension in some individuals. Therefore, slow release chloroquine injection was formulated in this study. Three method had been taken. The first method was to prepare aqueous suspension of chloroquine base. The release rate may be controlled by varying particle sizes of chloroquine base in the suspension. It appeared that chloroquine base powder could not be prepared with this method. The second method was to prepare w/o/w multiple emulsion with chloroquine phosphate dissolved in the innermost phase. Initially, stable system for w/o emulsion was investigated by studying various factors affecting emulsion appearance and stability such as phase volume ratio, type and amount of emulsifiers, HLB values and emulsifying instruments. But suitable emulsifier in preparing stable

w/o emulsion was not found. The third method was to prepare viscous chloroquine phosphate solutions using methylcellulose (MC) 1500 as a viscosity-inducing agent. The influence of viscosity on the release rate of chloroquine *in vitro* and *in vivo* was studied. It revealed that the logarithm of chloroquine release rate was directly proportional to the logarithm of viscosity. In 2% w/v MC 1500 solution, drug release rate was about 2.6 times slower than in aqueous solution.

The *in vivo* release rate of chloroquine from Test preparation containing 2% w/v MC 1500 was compared to a commercial product, Resochin, whose viscosity was close to distilled water. A randomized crossover design was used in 8 rabbits, each receiving intramuscular chloroquine phosphate injection of both Test preparation and Resochin. Whole blood was periodically taken for analysis of chloroquine and the pharmacokinetic parameters were compared. It was found that the time to peak concentration from the Test preparation was about 3 times greater than from Resochin which is in agreement with the *in vitro* results. The C_{max} obtained from the Test preparation were significantly lower but AUC_{0-24} were essentially the same for both preparations. It might be concluded that increasing the viscosity of chloroquine phosphate solution with MC 1500 could significantly decrease drug release and absorption rates from dosage form. Hence, the toxicity of chloroquine due to high blood concentration could be reduced.