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Formulation and evaluation of Pravastatin –loaded microemulsions for Transdermal delivery-pharmacokinetic and pharmacodynamic evaluation in rat model

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Abstract: Pravastatin is an antihyperlipidemic drug available as oral tablets. They have low bioavailabiity (18%) due to first pass metabolism. The chronic use of statins is associated with side effects like gastrointestinal disorders (0.5%), myalgia (0.1%), arthralgia (0.1%), induction of type II diabetes, liver damage. The objective of present study was to improve bioavailability of Pravastatin and reduction of adverse effects by formulating in to transdermal microemulsions. Microemulsions (ME) were prepared by using water titration method. Optimization of ME was done by employing central composite experimental design. Solubility studies in various oils, surfactants, co- surfactants were performed by using equilibrium solubility method. Based on solubility studies Capmul MCM, Tween 80 and Transcutol P were selected as oil phase, surfactant and co- surfactant. To determine the Smix ratio and microemulsion region pseudoternary phase diagrams were constructed by using CHEMIX software. Compositions of all formulations were obtained from central composite design. All prepared formulations were evaluated for physicochemical parameters like size, zeta potential, pH, viscosity, drug content, PDI, % of transmittance and *Ex- vivo* permeation on excised rat abdominal skin mounted on franz diffusion cells. Oil, Smix and water were selected as independent variables; size, zeta potential and flux of the formulations were selected as dependent variables for the optimization of formulation. The optimized formulation (ME21D) was further converted into gel (ME21DG) form by adding HPMC or Carbopol as gelling agents. Pravastatin solution was used as control for comparison purpose in Ex-vivo permeation studies. Pharmacokinetic and Pharmacodynamic studies were performed on male Wistar rats. Pharmacodynamic study was conducted by using Triton X-100 induced hyperlipidemia model. The optimized formulation (ME18D) was further evaluated for its surface morphology, skin irritation and stability studies.

The size and zeta potential of optimized formulation were 43 nm and -33.95 mV. The flux of ME21D was 8.1 folds higher than drug solution and 4.7 times higher to gel (ME21DG). $AUC_{0-\infty}$ of ME21D was significantly high compared with marketed oral formulation and gel. The bioavailability of microemulsion (ME21D) was 3.2 times higher than marketed formulation given orally. There was significant reduction in lipid profiles of rats treated with ME21D compared to oral preparation and gel. Skin irritation studies proved the safety of the ME21D. The present investigation proved the efficiency of transdermal microemulsion compared oral roué and transdermal gels.

***Key words**: Microemulsion, Transdermal delivery, Hyperlipidemia, Statins, Central composite design*