FORMULATION DEVELOPMENT, *IN-VITRO* AND *IN-VIVO* CHARACTERIZATION OF PALIPERIDONE LOADED SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM TO IMPROVE ORAL BIOAVAILABILITY

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ABSTRACT:

Introduction: Oral route is preferred route for formulators and has dominated over other routes of drug administrations. This route may be limited for drugs with poor aqueous solubility which leads to low and erratic bioavailability. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. In order to overcome this problem much attention was focused on lipid –based formulations to improve bioavailability of poorly water soluble drug. Recently, much attention has been paid to lipid based formulations with particular emphasis on self-micro emulsifying drug delivery systems (SMEDDS) is the one of the method for the improvement of oral bioavailability. SMEDDS are the isotropic mixtures of oils, surfactants, solvents and co-solvents. Paliperidone is a poorly water soluble drug with low oral bioavailability hence selected for the formulation of SMEEDS.

Aim & objective: The aim of investigation is to develop Self Micro Emulsifying Drug Delivery System of Paliperidone, with an objective is to enhance the oral bioavailability of paliperidone and evaluate the same by performing *in -vivo* studies.

Materials and Methods: Capmul MCM, Cremophor EL and Labrafil M1944CS were selected as oil, surfactant, co-surfactant and Aerosil, neusilin US2 as carriers respectively.

Methods: Ternary Phase diagram of surfactant, Co-surfactant and oil was constructed using TRIPLOT VI-4 software. Five formulations were prepared using varying concentrations of above mentioned excipients. The formulation design was optimized by Solubility assays, compatiabilty tests by Differential Scanning Calorimeter(DSC) and Fourier Transform Infrared Spectroscopy(FTIR), *in-vitro* evaluation (self-emulsification time, Phase separation and stability of microemulsion Droplet size analysis and determination of zeta potential, Physical stability and *in-vitro* drug release studies for liquid SMEDDS, and Flow properties, Compressibility Index, Hausner Ratio and SEM and PXRD studies for Optimized Solid-SMEDDS. *in-vivo* studies for bioavailability of Optimized formulation of Paliperidone was performed by HPLC method for a pharmacokinetic study in rat plasma.

Results and Discussion: Based on the droplet size analysis, self-emulsification time and *in-vitro* drug release studies "formulation F9" (Capmul MCM 25% w/w, Cremophor EL 47.5% w/w and Labrafil M1944 27.5% w/w) was chosen as the optimized formulation. L-SMEDDS-F9 adsorbed on to neusilin showed better flow properties was optimized. DSC thermogram showed no hint of presence of drug in crystalline form of S-SMEDDS. SEM study indicates the transformation of drug to amorphous or molecular state of S-SMEDDS-N. S-SMEDDS were tested for the release profile in comparison to liquid SMEDDS no significant difference was observed. *in-vivo* pharmacokinetic studies revealed that Paliperidone in S-SMEDDS formulation showed improved

pharmacokinetic profile with increase in AUC, C_{max} and bioavailability was increased by 2.6 times compared to a paliperidone suspension.
Conclusion: S-SMEDDS were prepared by physically adsorbing liquid on to neusilinUS2 with high surface area. Improved rate and extent of absorption of paliperidone from SMEDDS unravels their potential as suitable carriers for improving the oral bioavailability of paliperidone.