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Mixed Hydrotropic Zaleplon Oral Tablets: Formulation and Neuropharmacological Effect on Plasma GABA Level

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Abstract : Zaleplon (ZP) is a non-benzodiazepine poorly soluble hypnotic drug indicated for the short term treatment of insomnia having a bioavailability of about 30%. The aim of the present study is to enhance the solubility and consequently the bioavailability of ZP using hydrotropic agents (HA). Phase solubility diagrams of ZP in presence of different molar concentrations of HA (Sodium benzoate, Urea, Ascorbic acid, Resorcinol, Nicotinamide, and Piperazine) were constructed. ZP/Sodium benzoate and Resorcinol microparticles were prepared adopting melt, solvent evaporation and melt-evaporation techniques followed by XRD. Directly compressed mixed hydrotropic ZP tablets of Sodium benzoate and Resorcinol in different weight ratios were prepared and evaluated compared to the commercially available tablets (Sleep aid® 5 mg). The effect of shelf and accelerated stability storage (40°C ± 2°C/75%RH ± 5%RH) on the optimum tablet formula (F5) for six months were studied. The enhancement of ZP solubility follows the order of: Resorcinol > Sodium benzoate > Ascorbic acid > Piperazine > Urea > Nicotinamide with about 350 and 2000 fold increase using 1M of Sodium benzoate and Resorcinol respectively. ZP/HA microparticles exhibit the order of: Solvent evaporation > melt-solvent evaporation > melt > physical mixture which was further confirmed by the complete conversion of ZP into amorphous form. Mixed hydrotropic tablet formula (F5) composed of ZP/(Resorcinol: Sodium benzoate 4:1w/w) microparticles prepared by solvent evaporation exhibits in-vitro dissolution of 31.7±0.11% after five minutes (Q5min) compared to 10.0±0.10% for Sleep aid® (5 mg) respectively. F5 showed significantly higher GABA concentration of 122.5±5.5mg/mL in plasma compared to 118±1.00 and 27.8±1.5 mg/mL in case of Sleep aid® (5 mg) and control taking only saline respectively suggesting a higher neuropharmacological effect of ZP following hydrotropic solubilization.

Keywords : zaleplon, hydrotropic solubilization, plasma GABA level, mixed hydrotropy
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