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Designing and Development of Sublingual Dosage Forms of Poorly-Soluble Drugs with High Hepatic First-Pass Metabolism

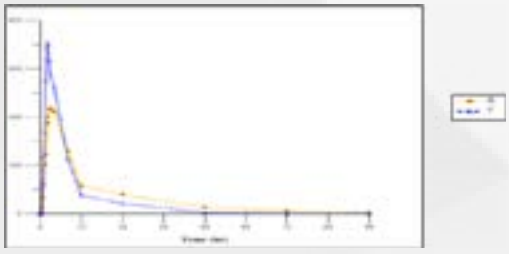
Statement of Problem: Poor solubility and first-pass metabolism are major concerns for formulation scientists during development of oral dosage forms. To overcome these challenges, many drugs are formulated in parenteral forms, which require special infrastructure, skilled medical professionals, and specialized storage/packaging. Sublingual route is an alternative route however, the same is challenging for drugs having low solubility, bitter taste, stability, physicochemical and clinical challenges.

Objective: Aim of present study was to successfully design, optimize and develop sublingual tablet formulation (STF) of Drug JG002, which can overcome challenges associated with presently approved injectable dosage form.

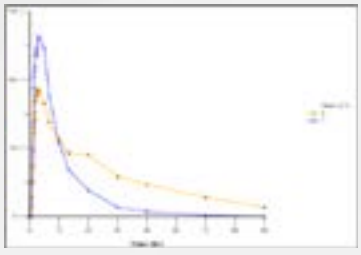
Methodology: STF successfully designed and developed by using suitable excipients like diluent, disintegrant, pH modifiers, solubilizing, taste masking and flavoring agent. STF was prepared after carrying out diligent scientific experimentations and optimization of formulation and process variables to achieve desired technical attributes like disintegration, dissolution, pH, assay, stability and pre-clinical/clinical studies.

Findings: The prepared STF was evaluated for therapeutic effect through animal and human studies. The STF exhibited improved drug release, pleasant mouth-feel without any unpleasant taste in mouth. STF was physically and chemically stable under accelerated stability conditions. Comparative pharmacokinetic studies were conducted in beagle dogs to assess in-vivo performance in comparison to standard IV administration. The peak concentration of active metabolite was observed to be higher with STF compared to IV administration (Cmax Test/Reference ratio:~139%), relative bioavailability from sublingual route was~70% based on AUCt data and ~69% based on AUCinf parameter. STF exhibited a good pharmacokinetic profile in humans, peak concentration of active metabolite was observed higher compared to IV administration (Cmax Test/Reference ratio:~162%). No undesirable safety/tolerability concerns identified.

Conclusion: These findings confirm feasibility of Drug JG002 delivery via sublingual route with desired formulation and clinical technical attributes.



Mean Plasma Concentration-Time Curve obtained after administration of Test (T) and Reference (R) in Beagle Dogs



Mean Plasma Concentration-Time Curve obtained after administration of Test (T) and Reference (R) in Humans

Biography

Indranil Nandi is former Senior Vice President & Head R&D, Jubilant Pharma Limited, USA. Dr. Nandi received an MBA from Rutgers State University of New Jersey, a doctorate from St. John's University and a graduate degree from Birla Institute of Technology & Science.