ABSTRACT

Scientific literature of preclinical animal and human clinical investigations has revealed that nasal drug delivery is an excellent route of administration for challenging clinical situations where common routes of administration like oral, intravenous offer sub-optimal therapeutic efficacy. Drugs, with significantly high first pass metabolism and where inonset of action is critical for disease management, thenasal route is non-invasive and does not require trained hospital staff for dosage administration. Howsoever, not all drugs can be administered via nasal route due to their limited instillation volume as well as potential to cause irritation of nasal mucosa.

Opioids are typically used for the management of moderate to severe acute pain, but opioid use is limited by the occurrence of a range of side effects. Unrelieved acute pain may cause anxiety, sleep disturbances, and demoralization and may interfere with mental activity and social interactions. In addition to these, more severe adverse effects likeuncontrolled acute pain are also associated with gastrointestinal effects, including development of ileus, nausea, and vomiting. Hence, there is a need for an alternative drug delivery system which can provide immediate pain relief with minimum side effects.

Tapentadol (TAP) is the first orally US FDA approved centrally acting analgesic having both μ-opioid receptor agonist and noradrenaline (norepinephrine) reuptake inhibition activity with minimal serotonin reuptake inhibition. This dual mode of action of Tapentadolis particularly useful in the treatment of both nociceptive pain and neuropathic pain. When Tapentadol is given orally, it undergoes extensive first pass metabolism, hence low bioavailability (32%). About 97% of the parent compound is metabolized. None of the metabolites contribute to the analgesic activity.Tapentadol has limited protein binding affinity, exhibits no active metabolites or significant microsomal enzyme induction or inhibition, thus, has a limited potential for drug-drug interactions. Clinical trials outcome in acute,chronic or cancer pain and neuropathic pain demonstratedsignificant reduction in opioid-sparing effect that reduces some of the typical opioid-related adverse effects. Specifically, the reduction in treatment-emergent gastrointestinal adverse effects for Tapentadol compared with equianalgesic pure μ-opioid receptor agonist resulted in improved tolerability and adherence to therapy.

Present thesis enumerates the design rationale of nasal formulation which is primarily a gellangum based formulation and drug encapsulated in solid lipid nanoparticles with an objective to attain higher or comparable C_{max} and early T_{max} with enhanced concentrations in the brain with limited nasal irritation profile when compared to oral formulation.

To ascertain the nasal irritation potential, multiple doses of Tapentadol formulation was instilledat 5 mg/kg of rabbitatevery 6 hours upto 3 days. Total Protein(TP) and Lactose Dehydrogenase (LDH) was used as biomarkers to assess the irritation potential. Trends in biomarker analysis, as well as the absence of clinical signs,indicate that Tapentadol is non-irritant to the nasal mucosa. Multiple dosePK studies revealed no nasal irritation as well as drug accumulation potential,which indicates it can be safely administered for human studies.

PK studies were performed to evaluate the characteristics of the dosage form designed by administeringasingle dose of oral solution, and intranasal formulations comprising ofthedrug in gellangum as well as encapsulated in solid lipid nanoparticles whereinsignificant reduction in T_{max} is observed. Plasma concentration over time profiles in blood was extrapolated to estimate the concentrations in the brain.Simulations were carried out for multiple instillations to assess the accumulation potential at a dosing frequency of four hours and six hours respectively. The overall study results indicate that the developed formulation has immense potential for management of pain flares as well as for the recurrence of pain episodes in acute pain management like accidental injuries and breakthrough cancer pain.

Based on the unmet clinical needs and hypothesis to address acute pain management, technical findings from this work indicate that with earlyT_{max} and higher C_{max}in both plasma and brain,and long plasma exposure of the two formulations designed offers anadvantage over the oral marketedformulation.Thefindings indicate that the designed drug delivery system with drug encapsulated in solid lipid nanoparticles has a great potential as a nasal delivery system for acute and chronic pain management.

The present work of the thesis is patented as “SolidLipid Nanoparticles of Tapentadol" Application Number : 201621034343, published on 13.04.2018.