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CHAPTER - 7

CONCLUSIONS

7.0 CONCLUSION

Pain management is complex and devoid of a variety of efficacious treatment options. Pain is not managed by its etiology or origin, but by its intensity and duration. Physicians seek a broad array of pharmacological agents to target different types of pain and symptoms, but almost none are indicated for specific types and the underlying diseases that cause the pain. Treatment requires active ingredients to be delivered to the required site of action in a controlled manner to produce maximum relief with minimum side effects. The objective of the research project undertaken was to design drug delivery technologies can that offer a solution. Hence, a new route i.e., intranasal administration of Tapentadol with two distinctly different formulations, Gellan gum& SLN formulation was scientifically explored over conventional oral drug delivery.

Development of analytical methods are extremely important for evaluation, characterization, stability assessment, release rate studies in-vitro and in-vivo. It was imperative to design suitable methods. In this project UV spectrophotometric and liquid chromatographic methods were developed and validated for the selected drug TAP. The developed method was highly selective, sensitive, accurate, precise &robust ,for estimation of TAP in various pre-formulation and formulation studies. The bioanalytical method was highly selective and sensitive and devoid of interferences of the matrix was ruled out for estimation of TAP in plasma of rabbits.

Pre-formulation studies of TAP indicate that the excipients selected for designing the dosage form were not incompatible. SLNs were prepared by the modified hot homogenization and emulsification technique, lyophilization cycle was developed to stabilize the particles for long term stability. SLNs produced was adequately characterized using numerous tests like particlemorphology, particle size distribution (PDI), zeta potential, entrapment efficiency, & in vitro release rates. SLN prepared with Glyceryl behenate andpolysorbate80 as surfactant and sucrose as cryoprotectant using Hot homogenization, followed by probe sonication or high shear homogenization followed by lyophilization demonstrated unimodal particle size distribution ranging from 245.5 ± 6.12 nm to 300 ± 8.1 nm with 0.345 PDI and negative (-43.5 mV) zeta potential which indicates good dispersibility and physical stability. Loading efficiency (LE %) was found to be maximum 15% and Encapsulation efficiency (EE%) around ~1%.The marginal increase in particle size growth was observed after lyophilization and the concentration of sucrose was optimized to 7.5 % to produce consistent particles in the

size range of 300 to 400nm.In vitro drug release was found to be 99.48% over 48 h with initial cumulative control 15 %/ hour average upto6hours, indicating a controlled and sustained release profile of TAP-SLNs.

Nasal irritation profile of Tapentadol was evaluated on rabbits with Benzalkonium chloride as a positive control and was found to be non-irritant. The clinical effectiveness and side effects of a drug delivery system are highly dependent on the rates at which the drug is released from the dosage form, site and route of absorption, its bio-distribution, and elimination kinetics.

Pharmacokinetics studies were performed on New Zealand rabbits, in which there was the slow and sustained absorption of TAP SLN from i.n. the route with shortest T_{max}, less than 15 mins, as compared to an oral solution which is close to 90 mins but AUC and C_{max}similar to the oral solution, thus minimizing any potential risks of adverse effects. The TAP Gellan gum system produced significantly higher AUC almost 2.5 fold with a time of T_{max} less than 25 mins as compared to oral formulation. TAP Gellan gum system has immense potential for dose reduction at least three to four fold in human as clearance rate of the drug is higher in human than rabbits. The extrapolated brain concentration by simulation it was found that time to achieve peak concentrations is around 7.5 minutes with SLN particles followed by 15 minutes in Gellan gum formulation against 60 mins by the oral route. The time to achieveC_{max} in the brain as low as 7.5 mins and slow elimination rate with early T_{max} less than 15 mins in plasma of the SLN particles suggest that the drug delivery system can offer a potential solution for breakthrough cancer pain or pain management in a sports injury or accidental injury without the risk of adverse effects.

Thus, it is concluded that TAP-SLNs could be an effective drug delivery system for acute pain management with minimum adverse effects. TAP Gellan gum offers an opportunity for dose reduction which may be useful for chronic pain management.

7.1 FUTURE SCOPE OF WORK

Since achieving high drug loading in SLN is a challenge for highly water soluble drugs, further optimization from bench scale to larger scale using standardized scalable equipment may be required to increase both encapsulation efficiency and loading efficiency. With enhanced encapsulation efficiency and loading efficiency, the total

amount of lipids and the total mass for administration can be decreased by virtue of which mucociliary clearance can be further decreased.

Gellan gum formulations can be further evaluated in different concentrations and different instillation volumes to further decrease dose as well as dosing frequency.

Both the formulations have the potential to be exploited for acute & chronic pain management by altering the pharmacokinetics.Further,direct confirmatory studies in appropriate animal model by estimation of drug in brain willbe direct evidence to the current scientific findings.

List of Publications from Thesis

International Publications

V. Nagpal, E. Joseph, J. Abraham and R.N. Saha. (2015). Three dimensional viewed validated diode array UV-LC method for estimating dopamine in liposomes. Journal of Analytical Chemistry, 70 (3), 1-9 (Accepted).

V. Nagpal, E. Joseph, J. Abraham and R.N. Saha. (2015). Ultra Micro Quantification of Dopamine using Solid Phase Extraction: A Simple and Rapid HPLC method for in-vivo pharmacokinetic and bio-distribution studies of the pure drug and LPs formulations in rats via i.n. and i.v administration. Plos one. (Communicated)

International Conferences

J. Abraham,R. N. Saha (April 2017). Drug delivery of intranasal Tapentadol.World Pharma Congress at Dusseldorf, Germany.

V. Nagpal, E. Joseph, J. Abraham, G. Balwani, S. Reddi, R.N. Saha. (2013). Development of controlled release liposome formulation for nasal delivery of candidate hydrophilic CNS active drug.

Annual Meeting and Exposition, American Association of Pharmaceutical Scientists, San Antonio, Texas, USA.

V. Nagpal, J. Abraham, E. Joseph, G. Balwani, R. N. Saha. (2013). Ultra micro quantification of Dopamine in rat Plasma using solid phase extraction: A simple and rapid 3D view method for higher recovery, selectivity, and sensitivity with UFLC diode array method. Annual Meeting and Exposition, AmericanAssociationof Pharmaceutical Scientists San Antonio, Texas.

Patents

Patent 201621034343 has been published on 13.04.2018titled as Solid Lipid Nanoparticles of Tapentadol,joint application between Torrent Pharmaceuticals and BITS, Pilani.

Biography of Chair Prof.Ranendra N. Saha

Prof.Ranendra N. Saha is Senior Professor of Pharmacy and Director of BITS Pilani, Dubai Campus. He has served BITS Pilani, Pilani campus as HOD, Dean and Deputy Director. He completed his Bachelor of pharmacy and Master of Pharmacy from Jadavpur University, Kolkata, and Ph.D. from BITS, Pilani. He was the recipient of *Shri B. K. Birla and Shrimati Sarala Birla Chair Professorship* at BITS Pilani for his excellence in teaching and research for the period of 2011 to 2016. He has vast experience in the field of Pharmacy especially in Pharmaceutics, novel drug delivery systems, and Pharmacokinetics. He received "*Pharmacy Professional of the Year 2013*"Award given by Indian Association of Pharmaceutical Scientists and Technologists. He is also the recipient of "*The Best Pharmacy Teacher Award*" for the year 2005, awarded by Association of Pharmaceuticals Teachers of India (APTI), in recognition of his contribution to teaching and research in the field of Pharmacy. He visited USA, Canada, Sweden, Syria, Nepal, Bangladesh and others on the invitation.

He is visiting Professor at Kathmandu University, Nepal. He delivered lectures at several International and National Conferences. Prof. R. N Saha has more than 36 years of teaching, research, and administrative experience. He has supervised a large number of doctoral, postgraduate and undergraduate students. He has published a book, several book chapters, research articles in renowned journals and presented papers at conferences in India and abroad. He has successfully completed several governments and industry sponsored projects.

Dr.Saha has developed commercial products for industries, transferred technologies to industries and granted patents. He is a member of advisory board and selection committee member of a number of Universities in India and abroad.

Biography of Jaya Abraham

Jaya has completed her Bachelors and Masters degree in Pharmaceutical Sciences from BITS, Pilani in 1993 and is currently pursuing her Ph.D. in Drug delivery from Birla Institute of Technology and Science (BITS), Pilani in India. Jaya has also completed a Diploma in Intellectual Property from National Law University, Hyderabad, India.

Jaya's area of expertise is drug delivery, where she has worked on different dosage form design for New Chemical Entities (NCE), Novel Drug Delivery Systems (NDDS) and value added generics from Lab to Commercial scale. She has filed over 50 patents internationally. She has gained strong expertise in the strategic evaluation of disease prevalence, identifying unmet clinical needs, understanding PK-PD and bridging the gap through innovative drug delivery systems to improve patient adherence to therapy.

In addition to the technical skills, Jaya has built and successfully lead cross-functional teams. She has mentored teams on technical as well as behavioral aspects of goal orientation and driving business value creation.

Jaya started her career with Cadila Group in 1994 and spent eleven years with Torrent Pharmaceuticals leading the Formulation and Drug delivery functions.

Currently, she heads the three R&D sites of Alvogen group in Taiwan, Romania, Korea.