2. LITERATURE REVIEW

1. Graeme J Sills et al. (2006)\(^1\): studied on the mechanisms of action of gabapentin and pregabalin and concluded that GBP and PGB are structurally related agents with similar spectra of antiepileptic and antinociceptive activity.

2. Kenneth C. Cundy et al. (2008)\(^2\): Investigated on Clinical Pharmacokinetics of XP13512, a Novel Transported Prodrug of Gabapentin and suggested that XP13512 may provide enhanced absorption, more predictable gabapentin exposure, reduced interpatient variability, and decreased dosing frequency compared with commercial gabapentin.

3. Eduardo Abib Junior et al. (2011)\(^3\): Conducted the bioequivalence study of Gabapentin using Liquid Chromatography Coupled to Mass Spectrometry and concluded that that gabapentin 400 mg capsule was bioequivalent to Neurontin\(^\circledR\) 400 mg capsule according to both the rate and extent of absorption and the test product can be considered interchangeable in medical practice.

4. Ritu Lal et al. (2009)\(^4\): Investigated the pharmacokinetics and tolerability of gabapentin enacarbil up to supratherapeutic doses and the effects of gabapentin enacarbil on cardiac repolarization in healthy volunteers, and to provide a dose reference for a future definitive QT/corrected QT (QTc) study and concluded that Gabapentin enacarbil was associated with dose-proportional gabapentin exposure at doses up to 6000 mg and was generally well tolerated in these healthy subjects.

5. Toufigh Gordi et al. (2008)\(^5\): compared the pharmacokinetics of an oral, gastric-retentive, gabapentin extended-release (G-ER) formulation with a gabapentin immediate-release (G-IR) formulation after single and multiple daily doses in healthy subjects and found that in these healthy subjects, the daily exposure provided by less frequent G-ER dosing was not significantly different from same daily dose with G-IR, administered more frequently.

6. Ritu Lal et al. (2012)\(^6\): studied on the description of a population pharmacokinetic analysis of gabapentin enacarbil in patients with varying degrees of renal function, using data from an open-label study of gabapentin enacarbil in patients with renal impairment (XenoPort, Inc. protocol XP066), to determine whether dosage adjustments are necessary in patients with renal impairment and suggested that adjustments to gabapentin enacarbil dosage are necessary in patients with renal impairment.
7. **Pablo Kimos et al. (2006)**: studied on analgesic action of gabapentin on chronic pain in the masticatory muscles based on randomized controlled trial and suggested that gabapentin may be effective in the treatment of other chronic musculoskeletal problems based on results of clinical trial.

8. **Dan Chen et al. (2012)**: Evaluated the Gabapentin Enacarbil on Cardiac Repolarization thorough QT/QTc Study in Healthy Adults and concluded that in this population of healthy adults, gabapentin enacarbil at doses of 1200 and 6000 mg was not associated with QT prolongation and was generally well-tolerated.

9. **Torsten E. Gordh et al. (2007)**: Conducted to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain caused by traumatic or postsurgical peripheral nerve injury and found that there was no statistically significant difference between the treatments for the primary outcome efficacy variable. However, gabapentin provided significantly better pain relief (p = 0.015) compared with placebo.

10. **Dwayne A. Pierce et al. (2008)**: Investigated on probable Case of Gabapentin-Related Reversible Hearing Loss in a Patient with Acute Renal Failure and reported that a patient with acute renal failure who developed hearing loss, myoclonus, and confusion with hallucinations in the presence of elevated gabapentin concentrations.

11. **Manzumeh-Shamsi Meymandi et al. (2006)**: Investigated that gabapentin enhanced the antinociceptive effect of both analgesic and subanalgesic doses of morphine in a dose dependent manner and concluded that co-administration of gabapentin with low doses of morphine produced therapeutic analgesia which could have important clinical application.

12. **M. Segerdahl et al. (2006)**: Investigated the effect of gabapentin on muscle and cutaneous pain in healthy volunteers and concluded that single or repeated dosing of gabapentin reduced cutaneous but not muscle pain in healthy volunteers.

13. **Kok-Yuen Ho et al. (2006)**: Reviewed the evaluation the efficacy and tolerability of perioperative gabapentin administration for the control of acute postoperative pain and concluded that gabapentin has an analgesic and opioid-sparing effect in acute postoperative pain management when used in conjunction with opioids.

14. **M. Baulac et al. (1998)**: evaluated the gabapentin add-on therapy in a large population under conditions close to real practice and to determine the therapeutic doses as reached with adaptable dosages and found that in 190 patients led to similar efficacy levels, with a tendency for more frequent somnolence and asthenia.
15. Robert H. Dworkin et al. (2008): conducted a randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster and found that the results of this clinical trial provide a foundation for evidence-based treatment for acute pain in herpes zoster.

16. Adam Bisaga et al. (2006): Conducted that a randomized placebo-controlled trial of gabapentin for cocaine dependence and concluded that when combined with weekly individual relapse-prevention therapy, gabapentin 1600 mg bid was no more effective than placebo in the treatment of cocaine dependence.

17. David J. Berry et al. (2003): Studied on the absorption of gabapentin following high dose escalation and concluded that larger than recommended doses of GBP can be efficiently absorbed by some patients and also that GBP plasma levels do not fluctuate greatly between dosage intervals, therefore, twice daily dosage is a possibility.

18. Bernd Huber et al. (2003): Assessed the antiepileptic efficacy and tolerability of GBP in routine therapy and concluded that the efficacy of GBP in learning disabled patients with highly therapy-resistant partial seizures is limited.

19. Grigoris Zoidis et al. (2005): Investigated on the novel GABA adamantane derivative (AdGABA) w.r.t. design, synthesis, and activity relationship with gabapentin and concluded that AdGABA was found to antagonize the pentylenetetrazole (PTZ) and semicarbazide (SCZ) induced tonic convulsions and exhibits analgesic activity in the hot plate test on mice.


21. Carmen E. Burgos-Lepley et al. (2006): Studied on Carboxylate bioisosteres of gabapentin and observed that when the carboxylate was replaced by a tetrazole, this group was recognized by the a2-d protein.

22. Olcay Sagirli et al. (2006): Developed the Determination of gabapentin in human plasma and urine by high-performance liquid chromatography with UV–vis detection and finally validated for the determination of gabapentin (GBP) in human plasma and urine and found that The method is precise (relative standard deviation, R.S.D.)
<4.05%) and accurate (relative mean error, RME <0.15%); mean absolute recoveries were 72.21% for plasma and 72.73% for urine.

23. **Anthony B. Ciavarella et al. (2007)**: Developed and applied of a validated HPLC method for the determination of gabapentin and its major degradation impurity in drug products and found that method was used successfully for the quality assessment of four gabapentin drug products.

24. **Laura Mercolini et al. (2010)**: Analysed using original high-performance liquid chromatographic method with fluorescence detection for the simultaneous determination of the three antiepileptic drugs gabapentin, vigabatrin and topiramate in human plasma and found that the method seems to be suitable for the therapeutic drug monitoring (TDM) of patients treated with gabapentin, vigabatrin and topiramate.

25. **Farhan Ahmed Siddiqui et al. (2010)**: Developed the Spectrophotometric determination of gabapentin in pharmaceutical formulations and using ninhydrin and p-acceptors and found that the proposed methods are simple, rapid, accurate, precise and economical for the routine analysis of gabapentin in pharmaceutical quality control laboratories.

26. **Abhay Gupta et al. (2008)**: Developed and applied of a validated HPLC method for the analysis of dissolution samples of gabapentin drug products and a simple isocratic reversed-phase HPLC method was developed and validated for the analysis of dissolution samples of gabapentin tablets and capsules and this method was used successfully for the quality assessment of five gabapentin drug products.

27. **Ahmed N. Allam et al. (2011)**: Reviewed the bioavailability of Pharmaceutical drugs and found that the bioavailability of drugs was based on biopharmaceutical classification system and stated that this approaches to improves drug solubility as well as drug permeability are the two main strategies in order to enhance the bioavailability of drugs.

28. **Raimar LoÈbenberg et al. (2000)**: Reviewed the Modern bioavailability, bioequivalence and biopharmaceutics classification system and new scientific approaches to international regulatory standards and reported a brief overview of the BCS and its implications.

29. **Laszlo Endrenyi et al. (1998)**: Studied on individual bioequivalence for forthcoming draft Guidance of the Food and Drug Administration and suggested that their resolution should be carefully and widely discussed, and that more research and experience is needed before the possible implementation of the new approach.
30. **Mei-Ling Chen et al. (2011)**: provided a summary of the workshop entitled “Harmonization of Regulatory Approaches for Evaluating Therapeutic Equivalence and Interchangeability of Multisource and Complex Drug Products” and stated that this workshop provided an opportunity for pharmaceutical scientists from academia, industry and regulatory agencies to have open discussions on current regulatory issues and industry practices, facilitating harmonization of regulatory approaches for establishing therapeutic equivalence and interchangeability of multisource drug products.

31. **Thomas Mathew et al. (2008)**: Assessed on Pilot–pivotal trials for average bioequivalence and provided that how to deals with the design of a pivotal trial, based on the evidence from the pilot trial.

32. **L.Z. Benet et al. (1999)**: Studied on understanding the bioequivalence study and stated that how bioequivalence studies are carried out at present, the limits of differences allowed for acceptable products, and some history concerning actual differences between generic and innovator products as provided by the FDA.

33. **Herman P. Wijnand et al. (1994)**: Updated of bioequivalence programs (including statistical power approximated by Student's t) and demonstrated that good approximations of power can be obtained by Student's t-statistic.

34. **Vangelis Karalis et al. (2009)**: Compare the performance of the reference scaled average bioequivalence (scABER) method proposed with other approaches focusing on the human exposure expressed as the product sample size x periods of drug administration and stated that the classic 0.80–1.25 limits were favoured at low intrasubject variability and high exposure, whereas the levelling-off limits demonstrated a preferred overall performance when variability was high and exposure was limited.

35. **Peter Meredith et al. (2003)**: commented on Bioequivalence and Other Unresolved Issues in Generic Drug Substitution and stated that measures of individual and population bioequivalence are proposed to be more accurate than measures of average bioequivalence.

36. **Marc Lindenberg et al. (2004)**: Reviewed on classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system and reported that orally administered drugs on the Model list of Essential Medicines of the World Health Organization
(WHO) are assigned BCS classifications on the basis of data available in the public domain.

37. **Gudrun Freitag et al. (2007)**: studied on a nonparametric test for similarity of marginals with applications to the assessment of population bioequivalence and suggested a completely nonparametric test for the assessment of similar marginals of a multivariate distribution function.

38. **Vangelis Karalis et al. (2003)**: Studied on Pharmacodynamic considerations in bioequivalence assessment: comparison of novel and existing metrics and stated that all BE indices of either purely PK or PD nature were classified in a semiquantitative manner according to their strictness in declaring BE.

39. **Venkata Ramana S. Uppoor et al. (2001)**: Studied on Regulatory perspectives on in vitro (dissolution) / in vivo (bioavailability) correlations and concluded that IVIVC can impart in vivo meaning to the in vitro dissolution test and can be useful as surrogate for bioequivalence.

40. **K.K. Midha et al. (1994)**: Studied on the application of partial areas in assessment of rate and extent of absorption in bioequivalence studies of conventional release products and stated that the partial area method is applicable to the evaluation of both relative rate and extent of absorption from conventional release products.