Profiling VANE: A Novel Therapeutic Approach for Epilepsy Treatment

Muhammad Aqid Raza*, Raheela Rahmat Zohra, Mahnaz Ahmad
Department of Biotechnology, University of Karachi, Karachi, Pakistan.
*E-mail: aqidmirza8484@gmail.com

ABSTRACT

Introduction: Valproic acid (VPA) is known for the treatment of epilepsy and several relevant neurological disorders. Although it is one of the most efficient antiepileptic drugs, it is still challenged with its delivery that often limits its therapeutic potential. The drug has variation of bioavailability among patients because of the difference in mechanism of absorption and metabolism. Moreover, a large amount of the dosage undergoes hepatic metabolism, ultimately excreted by kidneys. Even after bypassing the liver, it is restricted to cross the blood brain barrier (BBB). Ultimately, only a small fragment of drug reaches the target site. These factors result in unpredictable increase in plasma concentrations of drug leading to risk of side effects. Recently, lipid based nanosystems such as nanoemulsions have gained attention of researchers as drug carriers, in this case, the valproic acid. They have the potential to improve solubility, protect drugs from metabolic degradation and ensure efficient delivery across biological barriers. With this background, this research is mainly focused on developing and profiling two valproic acid nanoemulsion formulations named as VANE 500 and VANE 1000. These formulations were selected because of the compatibility with the CSF condition during epilepsy.

Objectives: This research was primarily aimed to prepare two stable nanoemulsion systems of VPA using medium chain triglycerides (MCT) and safflower oil as the oil phase, lecithin as surfactant component and Tween 80 dissolved in double distilled water was optimized as water phase. The second objective was to characterize both VANE formulations by analyzing their pH, drug content (DC%) and surface morphology under scanning electron microscopy (SEM). Secondarily, this study was focused to observe that variations in the surfactant to oil ratio could affect the incorporation and the stability of the drug. Ultimately, it was aimed to compare and contrast the results of the VANE formulations with VPA solution to identify nanoemulsification as improvement in the physicochemical behavior and bioavailability of the compound.

Methodology: Valproic acid was dissolved in the oil phase composed of medium chain triglycerides (MCT Oil) and safflower oil. Lecithin and Tween 80 were added as surfactant and co surfactant for the oil and water phase respectively. α-tocopherol was also added as an antioxidant to enhance stability. The two prepared formulations were emulsified through ultrasonication process to ensure fine dispersion of the oil droplets. The prepared nanoemulsions were stored at 4°C until analysis. The pH was determined in triplicate at 25 ± 2°C using a calibrated pH meter. Drug content was analyzed by UV - Vis spectrophotometry after extraction of VANE with methanol. For analysis through UV Vis spectrophotometry, 310 nm of wavelength was optimized for VANE and 370 nm for plain VPA. Morphological studies of droplets were performed through SEM after the lypholization of VANE samples. Statistical analysis were performed including one way ANOVA and Tukey's post-hoc test. Significance level was kept on $\alpha = 0.05$.

Key Findings: VANE 500 and VANE 1000 showed pH values close to the physiological range of blood and CSF. VANE 500 had an average pH of about 6.1, while VANE 1000 showed 5.9. These ranges are biocompatible with the tissue environment. In comparison, the plain VPA solution showed slightly higher values, i.e. 7.1 - 7.4. Drug content results confirmed that most of the valproic acid was successfully incorporated into the nanoemulsion structure. VANE 500 incorporated around 92% VPA and VANE 1000

about 94%. The slightly higher value for VANE 1000 could be because of increased surfactant concentration that stabilized the drug within the oil phase.

SEM analysis showed spherical particles with smooth surfaces. No visible aggregations were observed. VANE 500 consisted of relatively smaller and more uniform droplets. VANE 500 ranged about 270 nm in size while VANE 1000 had a broader size distribution between 200 nm to 500 nm. Despite this variation, the structure morphology was found to be stable, suggesting good colloidal stability. The smooth surface texture and absence of aggregates favors that preparation method successfully synthesized a stable nanoemulsion system.

Conclusion: This study shows the potential of nanoemulsion system to efficiently encapsulate valproic acid ensuring improved physicochemical characteristics. Both VANE 500 and VANE 1000 possess near to physiological pH values, high drug loading tendancy along with stable nanosized droplets. All of these properties support their capability as enhanced delivery systems for VPA. In comparison, VANE 1000 showed slightly better results, suggesting that a higher surfactant ratio has better capability to provide additional stability and better drug retention. These results suggest that VANE is efficient enough to be applied as therapeutic agent in replacement of VPA for brain targeted delivery in epilepsy. It is suggested that future research should focus on detailed in vitro release assay and in vivo pharmacokinetic studies to determine its efficiency for clinical applications.

Keywords: Bioavailability, Blood-Brain Barrier, Nanoemulsion, Spectrophotometry, Valproic Acid.

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