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Development and optimization of nanostructured lipid carriers of nilotinib for treatment of cancer through oral route

Abstract:

Background: Leukemia is a malignant tumor that arises from a clone of hematopoietic stem cells, resulting in a disruption of the normal functioning of the hematopoietic system. Traditional medications exhibit limited therapeutic efficacy as a result of their inadequate specificity and stability. The advancement of nanotechnology has introduced nonviral nanoparticles as a promising solution for the effective treatment of leukemia. Nilotinib, a tyrosine kinase inhibitor, exhibits a notably limited solubility in water and a somewhat poor and inconsistent ability to be absorbed orally. An enhanced solubility in a pharmaceutical formulation can improve the bioavailability and decrease the variability of both its own solubility and the pharmacokinetics.
Objective: The objective of the present study was to develop and enhance nanostructured lipid carriers for more effective transport of Nilotanib against acute leukemia, with the aim of examining its in vitro anti-cancer effects on the KG-1 leukemic cell line. The medicine belongs to BCS class II and is characterized by low solubility in water, a short half-life, and significant first-pass metabolism.
Method: An evaluation was conducted on various types of excipients, including solid lipid, liquid lipid, and surfactant, to determine their impact on medication solubility. Out of the excipients that were examined, stearic acid, oleic acid, and Tween 80 were chosen as independent variables, each representing a different factor. The preparation of Nilotanib loaded nanostructured lipid carriers (NLCs) involved the use of high pressure homogenization followed by ultra sonication technique. The formulations were produced using Design-Expert (DoE) and optimized for different formulation parameters such as the ratio of lipids and surfactant concentration, homogenization speed, and time. The Nilotanib loaded NLCs formulation was improved and subjected to several physicochemical characterization techniques including FTIR, DSC, PXRD, SEM. Additionally, the in-vitro drug release and anti-leukemic impact on the KG-1 cell line were examined.
Results: A total of 17 formulations were developed, with sizes ranging from 140.695 ± 2.67 to 389.64 ± 8.59 nm. The entrapment efficiency varied from 46.52 ± 0.49 to 81.047 ± 7.1%. The results of FTIR and DSC indicated that the drug was entrapped inside the NLCs and there was no chemical bonding between the drug and NLCs. The SEM examination verified that the NLCs were consistent in shape, with a uniform distribution throughout. The in vitro drug release experiments demonstrated a sustained release pattern for up to 48 hours. Pharmacokinetic studies showed a 2.31-fold rise in AUC (area under the curve) and an increase in half-life from 0.43 hours to 2.887 hours. This was accompanied by a significant decrease in clearance and elimination rate, indicating a longer duration of systemic circulation. This prolonged circulation is beneficial in the treatment of leukemia. The sustained release behaviour efficiently increased the toxicity of Nilotanib loaded NLCs to KG-1 (leukemic) cell lines in time dependent manner with lower IC50 values than that of drug solution.
Conclusion: The experimental findings indicate that Nilotanib loaded NLCs serve as an effective carrier for mitigating dose-related toxicity, while also offering a prolonged release pattern to maximize the anti-cancer effect. The system's limitations encompass its stability during extensive manufacturing and its applicability from laboratory testing to practical implementation in healthcare settings.