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Leveraging the Exploratory and Predictive Capabilities of Design of Experiments in Development of Intraarticular Injection of Imatinib Mesylate Containing Lipospheres.

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An intraarticular, liposphere-based, formulation of Imatinib mesylate for weekly administration was developed. Lipospheres were prepared using double emulsion technique using dieryucoyl phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt), cholesterol, and tricaprylin as lipid phase in dichloromethane in a four-step process. Primary emulsion, formed using a high-pressure homogenizer, was diluted using a secondary aqueous phase in an Inline mixer to form the liposomal dispersion. Nitrogen flushing was done to remove dichloromethane, and the dispersion was finally centrifuged and adjusted for potency. The amount of cholesterol and triglyceride was taken as formulation variables, and speed of homogenization was used as a process variable in the Box-Behnken design while particle size, % drug entrapment, and drug release at the end of 4 h and 5 days were taken as response variables. Multivariate data analysis grouped the variables in two latent variable sets, one based on the speed and the other on the composition of lipospheres. Multiple linear regression analysis was used to generate mathematical model for each response. Constraints were put on the values of responses, as per the requirements of the final product, and the "freedom to operate" design space was located using an overlay plot. The center point batch sufficed all the set criteria, and Monte Carlo simulations on the factor variables indicated a defect rate of 5%. The center point batch was characterized for viscosity, osmolality, pH, drug release, and lipocrit value. The dispersion was charged in a prefilled syringe and studied for stability. The product was found to be stable at 2-8°C over a period of 6 months.

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