Development of liposomal drug delivery system as a strategy for improving bioavailability and therapeutic efficacy, by Design of Experiments. A case study

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There is mounting evidence for the anticancer effects of all-trans retinoic acid (ATRA) in different types of malignancies. However, ATRA treatment is usually associated with side effects, and most importantly with retinoid acute chemoresistance. Furthermore, ATRA shows reduced physicochemical stability, aqueous solubility and plasma half-life. Nanocarriers have emerged as promising strategies for delivering drugs to tumors. Therefore, this study aimed at developing an ATRA-based liposomal formulation with enhanced stability and therapeutic efficacy.

ATRA-loaded liposomes (L-ATRA) were prepared by ethanol injection from egg phosphatidylcholine and cholesterol. Design of Experiments (DOE) was employed to study the influence of several formulation factors on the quality attributes of L-ATRA. 11 formulations were prepared according to a 2³ full factorial design, and characterized in terms of size, polydispersity, ATRA content and entrapment efficiency. An optimum liposomal formulation with desirable characteristics was evaluated in vitro regarding ATRA release.

L-ATRA exhibited a mean size of 200-400 nm, and a narrow size distribution (polydispersity index < 0.25). ATRA was successfully loaded into the liposomes with an efficiency of 70-80%. According to the DOE statistical analysis, L-ATRA attributes were mainly influenced by the concentrations of phospholipid and ATRA. The in vitro release study showed a maximum percentage of 72.5% ATRA released after 48h in a mixture of PBS pH 6.5 and ethanol 1:1 (v/v) at 37°C.

Overall, this study reports the successful formulation and preparation of an ATRA-loaded liposomal formulation by DOE. L-ATRA could be a promising candidate for effective and safe delivery of ATRA in cancer patients.

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