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Research Article

Formulation and *In-Vitro* Evaluation of Niosomal drug Delivery in Cancer Chemotherapy

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ABSTRACT

Drug delivery systems are defined as formulations aim for transportation of a drug to the desired area of action within the body. The aim of the study was to investigate the feasibility of using Niosomes as a drug delivery system for Cisplatin By entrapment of drug in Niosomes, dose also could be reduced. Niosomes were prepared by Ethanol injection method using cholesterol and Surfactant. Particle size, zeta potential, entrapment efficiency and *in vitro* drug release studies were performed. The targeted niosome delivery system is composed of drug, surfactant and cholesterol. With regard to the influence of formulation variables on the percent drug loading (PDL), different compositions with varying ratios of surfactant and cholesterol were studied. *In –Vitro* drug release mechanism was studied for 24 hours.

Introduction

Niosomes are non-ionic surfactant based Multilamellar or unilamellar vesicles in which an aqueous solution of solute(s) in entirely enclosed by membrane resulted from the organization of surfactant macro-molecules as bilayer. The potential for Niosomes in cancer drug delivery is infinite with novel applications constantly being explored [1].Niosomes is a novel drug delivery system in which drug is encapsulated in vesicles. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. They improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug. The Niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase [2].

Cisplatin is a chemotherapy drug. It is used to treat various types of cancers, including sarcomas, some carcinomas (e.g. small cell lung cancer, and ovarian cancer), lymphomas, and germ cell tumors. It was the first member of a class of platinum containing anti-cancer drugs, which now also includes carboplatin and oxaliplatin. Cisplatin is administered intravenously as short-term infusion in physiological saline for treatment of solid malignancies. In niosomes the vesicles forming amphiphilic are a nonionic surfactant such as span 60 which is usually stabilized by addition of cholesterol. Cholesterol is the membrane stabilizing agent & essential component in Niosomal formulation.

Materials and Methods

Materials

Cisplatin, Cholesterol, Span 20 were procured from S.D Fine Chem Ltd. Boisar, Chloroform from Qualigens Chem Ltd, Biosar, Dialysis bag(M.Wt: 12,000-14000) from Himedia Mumbai, Methanol(HPLC grade) Procured from Merck, India. All chemicals used were analytical grade.

Method

In this method ethanol was used as an organic solution for dissolving the cholesterol, span& Tween. It has been reported that small unilamellar vesicles can be prepared by this method. This method has been reported as one of the alternatives used for the preparation of small unilamellar vesicles (SUVs) without Sonication. In this method, an ethanol solution of surfactant is injected rapidly through a fine needle into excess of saline or other aqueous medium [3]. Vaporization of ethanol leads to the formation of vesicles. Niosomes were prepared by ethanol injection method. Cholesterol and surfactant were dissolved in 8ml diethyl ether

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mixed with 2ml methanol containing weighed quantity of Drug. The resulting solution was slowly injected using a micro syringe at a rate of 1ml/min. into 10 ml hydrating solution phosphate buffer (PH7.4) the solution was injected slowly into the aqueous phase, the differences in temperature between phase cause rapid vaporization and formation of Niosomes[4,5]. Different batches of Niosomes were prepared in order to select an optimized formula as per general method described above and proportion of surfactant and cholesterol for the preparations of Niosomes. The ratios of the formulations were of cholesterol: surfactants were given in table no.1.

Table 1: Composition of Surfactant and Cholesterol for Preparation of Niosomes

Formulation Code	Surfactant us	Surfactant: Cholesterol (micro mol	Diethyl ether	Methanol (ml)
CP1	Span20	150:100	8	2
CP2	Span20	150:150	8	2
CP3	Span20	200:150	8	2
CP4	Span20	250:150	8	2
CP5	Span20	200:200	8	2
CP6	Span20	250:200	8	2
CP7	Span20	250:250	8	2
CP8	Span20	300:250	8	2
CP9	Span20	350:250	8	2

Evaluation of anticancer Niosomes formulation

Removal of unentrapped drug from Niosomes

The unentrapped drug from niosomes was removed by dialysis technique for 24 hours. The various factors like lipid concentration, drug to lipid ratio, cholesterol content will change the entrapment efficiency.

Percentage drug Entrapment efficiency

Cisplatin was incorporated into niosomes by ethanol injection method by using phosphate buffer saline pH7.4 as hydrating medium that ensured better drug stability. Niosomes consisting of different ratio of surfactant and cholesterol indicated those variables on the degree of entrapment.

After the removal of unentrapped drug by dialysis method, the entrapment of all the formulation was studied. The various factors like lipid concentration, drug to lipid ratio, cholesterol content will change the entrapment efficiency. The decrease amount of cholesterol will decrease the entrapment efficiency of Cisplatin citrate. The lipophilicity also influences the entrapment of drug. The results are shown in the following Table no. 2.

Vesicles diameter vesicles diameter measured by using optical microscope with a calibrated eyepiece micrometer. The vesicles size of niosome is measured individually for all batches and its mean value is calculated [6-,8].

Zeta potential

Zeta potential of a niosome is commonly used to characterize the surface charge property of niosomes. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. The zeta potential of the optimized formulation was found to be -30.3mv. The obtained result of the zeta potential of prepared formulation remains suspended and so were found to be stable and particles being suspended. The formulation was found to be effective for parenteral administration in the treatment of cancer [9-,12]. The result of zeta potential shows that niosomes can be suspended in water well and this is important for their storage and administration. Polydispersity index an estimate of the width of distribution, indicates the size heterogeneity [13-15].

***In Vitro* Drug release study of Cisplatin Niosomes**

In Vitro release was found to be biphasic as the release was controlled by dialysis membrane and lipid bilayer. Incorporation of cholesterol affected the release rate of encapsulated drug. Based on the entrapment efficiency of the formulation were subjected to *in vitro* drug release studies. The media used for this study is phosphate buffer (pH7.4). The temperature of the receptor medium is maintained at 37±10oC. Aliquots of 5ml sample were withdrawn same volume of the medium was replaced. The collected samples were analyzed at UV spectrophotometer.

Table 2: Percentage drug Entrapment Efficiency Cisplatin Niosomes

Sr. No.	Batch Code	Surfactant used	Surfactant:Cholestrol (micromolar ratio)	% of drug dialyzed	Entrapment efficiency (%)
1.	CP1	Span20	150:100	17.92	82.18±0.42
2.	CP2	Span20	150:150	19.71	80.29±0.79
3.	CP3	Span20	200:150	15.35	84.65±0.31

4.	CP4	Span20	250:150	24.54	75.46±0.59
5.	CP5	Span20	200:200	7.16	92.21±0.78
6.	CP6	Span20	250:200	27.46	72.54±0.72
7.	CP7	Span20	250:250	32.85	67.15±0.24
8.	CP8	Span20	300:250	29.59	70.41±0.67
9.	CP9	Span20	350:250	35.4	64.60±0.42

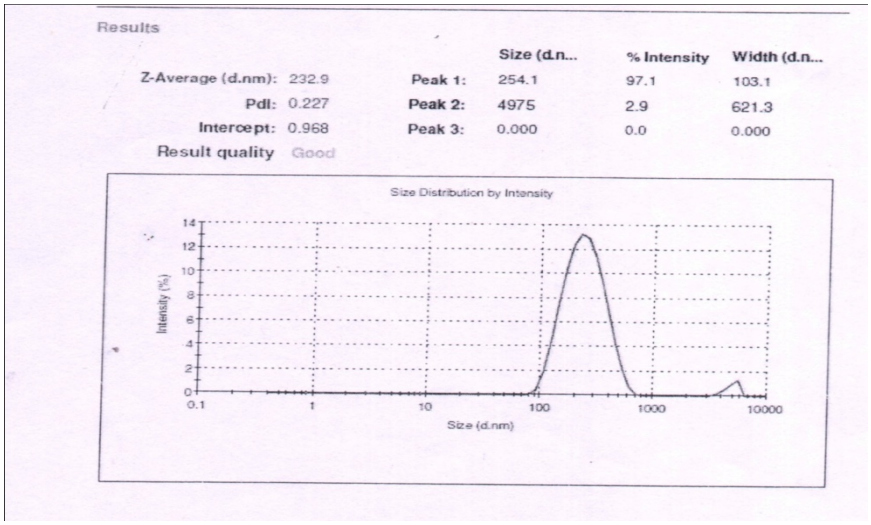

Figure No. 1: Zeta Size of Cisplatin Niosomes vesicles

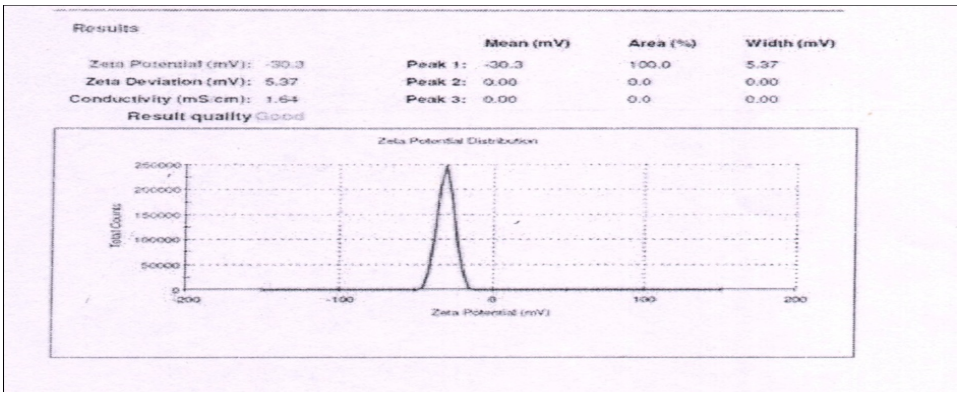

Figure No. 2 Zeta Potential of Cisplatin Niosomes vesicles

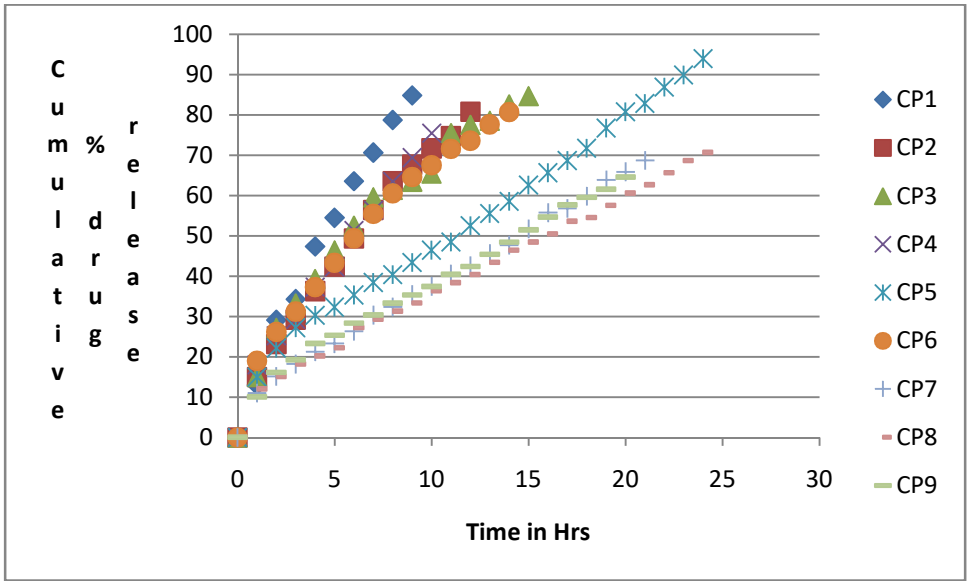

Figure No. 3. Comparative *In Vitro* Release study of Cisplatin Niosomal Formulation (CP1-CP9)

Conclusion

Niosomes of Cisplatin was prepared successfully by ethanol injection method. Relationship between surfactant type and characterization parameters of niosomes was established. In present study, the finding revealed that the process parameters critically affect the formulation of niosomes with regards to drug entrapment and need to be carefully controlled. The results of this study showed that cholesterol content and the type of surfactant altered the entrapment efficiency and drug release.

Entrapment efficiency and *in vitro* studies showed that formulation CP5 might be more beneficial for drug delivery among other formulations. The optimized formulation was showing small vesicles size, high percentage of entrapment with the desired sustained release of Cisplatin. *In Vitro* release from Niosomal formulations showed extended release of drug for 24hours. The formulation Cisplatin having entrapment efficiency of 92.21% and *In vitro* release after 24 hours for the best formulation was 93.9%.

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