



PREPARATION AND EVALUATION OF NIOSOMES CONTAINING TAMOXIFEN

Naresh Kalra^{*1}, Dr. G. Jeyabalan² and Suresh Choudhary²

¹Department of Pharmaceutical Sciences, Sunrise Pharmacy College, Alwar.

²Department of Pharmaceutical Sciences, Alwar Pharmacy College, Alwar, Rajasthan.

***Corresponding Author: Naresh Kalra**

Department of Pharmaceutical Sciences, Sunrise Pharmacy College, Alwar.

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ABSTRACT

This study was aimed at developing and optimizing Niosomal formulation of Tamoxifen Citrate in order to improve its bioavailability. In evaluation study the effect of the varying composition of non ionic surfactant and cholesterol on the properties such as encapsulation efficiency, particle size and drug release were studied. In this drug delivery systems are defined as formulations aim for transportation of a drug to the desired area of action within the body. 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. Different batches of Niosomes were prepared in order to select an optimized formula and proportion of surfactant and cholesterol for the preparations of Niosomes.

KEYWORD: Niosomes, Ethanol injection method, *In-vitro* release. Span 20.

INTRODUCTION

Niosomes are non-ionic surfactant based Multilamellar or unilamellar vesicles in which an aqueous solution of solute(s) is 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]

Tamoxifen (TAM), an estrogen receptor antagonist is known to be a drug of choice for hormone sensitive breast cancer.^[3] Tamoxifen citrate is extensively metabolized after oral administration. N-desmethyl Tamoxifen appears to be similar to that of Tamoxifen citrate. 4-hydroxy Tamoxifen and a side chain primary alcohol derivative of Tamoxifen citrate have been identified as minor metabolites in plasma. Tamoxifen is a

substrate of cytochrome P- 450 3A, 2C9 and 2D6, and an inhibitor of P- glycoprotein.

MATERIALS AND METHODS

Materials

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

Method

Niosomes were prepared by ethanol injection method. Cholesterol and surfactant were dissolved in 8ml diethyl ether 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. 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 no1.

Table No. 1: Composition of Tamoxifen Niosomes.

Sr. No.	Batch Code	Surfactant used	Surfactant:Cholesterol (micro molar ratio)	Diethyl ether (ml)	Methanol (ml)	Entrapment efficiency (%)
1.	T1	Tween20	100:100	8	2	41.07±1.28
2	T2	Twen40	100:100	8	2	38.63±0.47
3	T3	Tween60	100:100	8	2	35.24±0.73
4	T4	Tween80	100:100	8	2	34.80±1.18
5	T5	Span20	100:100	8	2	69.18±0.42
6	T6	Span40	100:100	8	2	60.29±0.79
7	T7	Span60	100:100	8	2	71.65±0.31
8	T8	Span80	100:100	8	2	58.46±0.59
9	T9	Span60	200:100	8	2	62.21±0.67
10	T10	Span60	100:200	8	2	85.54±0.72
11	T11	Span60	200:200	8	2	90.66±0.24
12	T12	Span60	300:200	8	2	81.41±0.67
13	T13	Span20	200:100	8	2	66.83±0.42
14	T14	Span20	100:200	8	2	82.26±0.35
15	T15	Span20	200:200	8	2	87.40±0.13
16	T16	Span20	300:200	8	2	93.80±0.36
17	T17	Span20	400:200	8	2	84.35±0.67

*Drug taken 10gm in each formulation

*Hydration media:- phosphate buffer saline 7.4

*Cholesterol acts as a membrane stabilizing agent.

Evaluation of anticancer Niosomes formulation

Removal of untrapped drug from Niosomes

The untrapped 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

Tamoxifen 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 untrapped 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 Tamoxifen. The lipophilicity also influences the entrapment of drug.

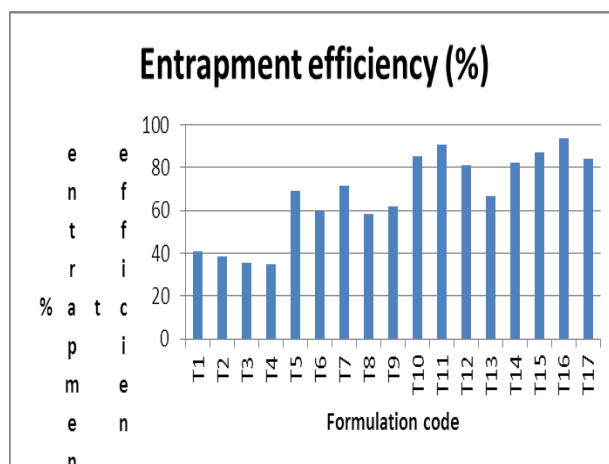


Figure: 1. Percentage Drug Entrapment efficiency Tamoxifen Niosomes.

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.^[4,6]

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 -29.2mv. 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. 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.^[7,8]

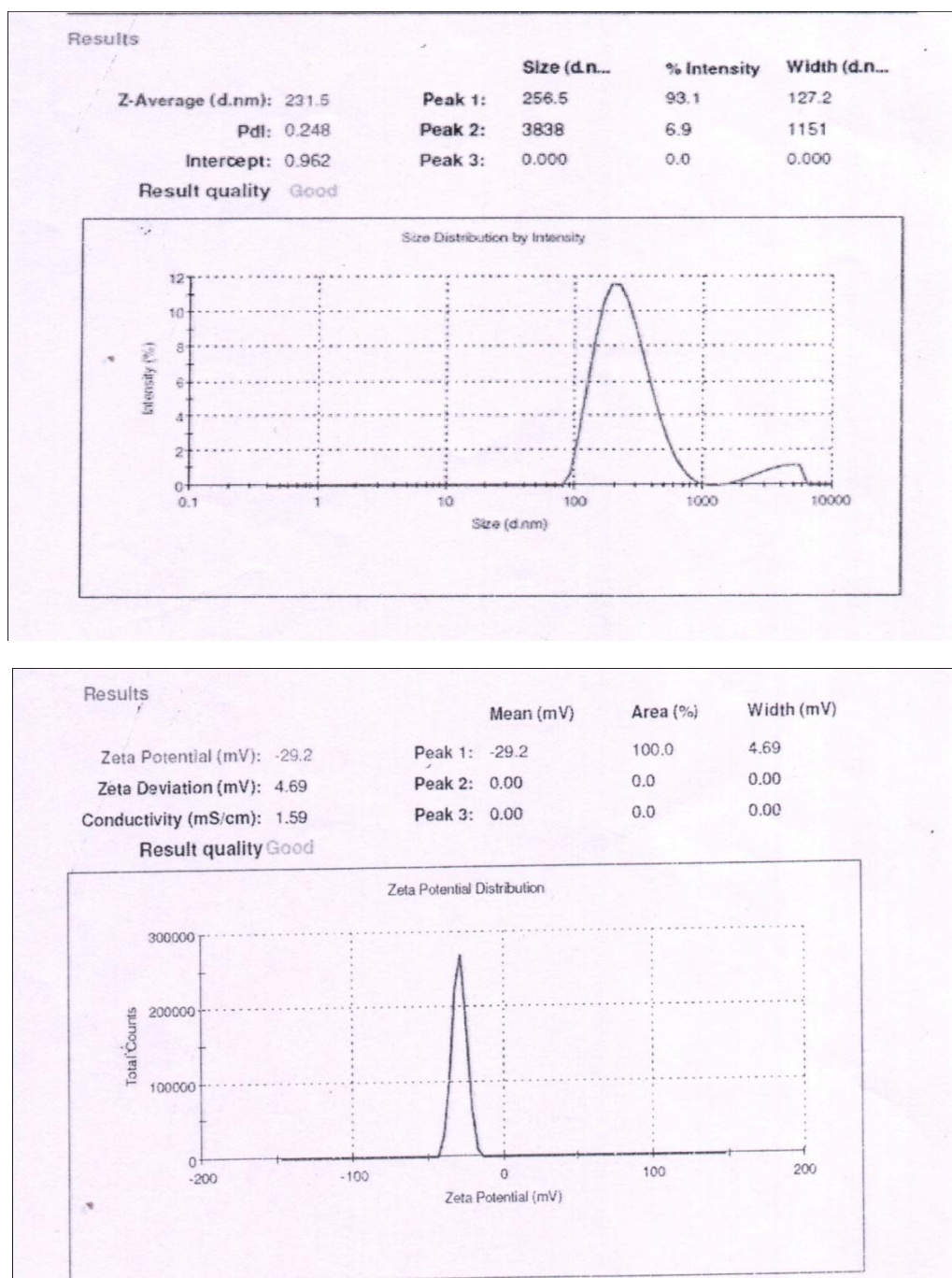


Figure 2. Zeta Potential of Tamoxifen Niosomes vesicles.

***In Vitro* Drug release study of Tamoxifen 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 formulation T9 to T17 containing Tween 20 and Tween 80 surfactant & cholesterol by various micro molar concentrations were subjected to *in vitro* studies.

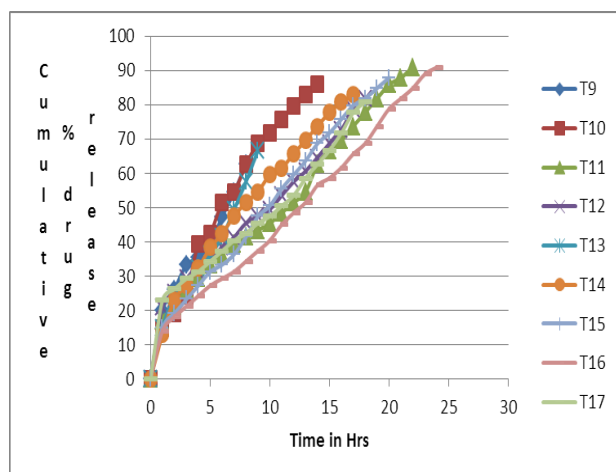


Figure 3. Comparative *In Vitro* Release study of Tamoxifen Niosomal Formulation (T9-T17).

The formulation T9 containing Span 20 & Cholesterol the percentage amount of drug release found to be 62.54% at 8th hours. The release of the drug from the bilayer was fast because of less attractive forces between the drug, cholesterol and span20. Formulations T10, T11 and T12 were tried with span20 surfactant & Cholesterol as shown in formulation table the percentage amount of drug release were 85.83%, 90.88% and 81.79% in corresponding time at 14th, 22th and 18th hrs respectively. The release profile for the Formulations T13, T14, T15, T16 and T17 were 66.57%, 82.81%, 87.85% 90.89% and 84.81% in corresponding time at 9th, 17th, 20th, 24th and 19th hrs respectively. The burst release in the first hours can be attributed to the drug loaded on the surface of niosomes and also due to the untrapped drug in Niosomal formulations. Formulation T16 was selected as best formulation because it yielded sustained and controlled release of drug. Hence the formulation T16 contains span 60 and Cholesterol in the ratio 300:200 as optimized.

CONCLUSION

The present study demonstrated the successful preparation of Tamoxifen niosomes and their evaluation. Niosomes of Tamoxifen 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 T16 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 Tamoxifen.

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