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FORMULATION AND EVALUATION OF ETOPOSIDE LIPOSOMAL DRUG DELIVETY SYSTEM

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ABSTRACT

The drug release from Liposomes depends on many factors including the composition of Liposomes, the type of drug encapsulated and nature of the cell. Once it is released a drug that normally crosses the membrane of a cell will enter the cell, other drugs will not enter. Etoposide is a drug with narrow therapeutic index and short biological half-life. This study aimed at developing and optimizing liposomal formulation of Etoposide in order to improve its bioavailability. In evaluation study the effect of the varying composition of lipids on the properties such as encapsulation efficiency, particle size and drug release were studied. Phase transition study was carried out to confirm the complete interaction of Etoposide with bilayer structure of liposome. Moreover, the release of the drug was also modified and extended over a period of 8 h in all formulations. F2 emerged as the most satisfactory formulation in so far as its properties were concerned. Further, release of the drug from the most satisfactory formulation (F2) was evaluated through dialysis membrane to get the idea of drug release.

KEYWORDS: Liposomes, Etoposide, Phosphotidylcholine, cholesterol, thin film hydration technique, in vitro drug release studies.

1. INTRODUCTION

Liposomes, closed vesicular structures consisting of one or more lipid bilayers, are widely used as drug delivery vehicles. In particular, they have been investigated for their ability to improve the delivery of chemotherapeutic agents to tumors in efforts to increase therapeutic efficacy and decrease toxicity to normal cells[1]. Liposomal delivery systems are

advantageous to improve the solubilization of poorly soluble agents, and can act as a sustained release reservoir. It is also useful potentially target specifically to alveolar macrophages to ensure better uptake of drug. It is compatible with lung surfactant components.[2,3,4] Etoposide, an important antineoplastic agent and a so-called standard in therapies for small-cell lung cancer, has been widely studied on many aspects and used in other cancers for many years. Sustained release formulations of ETP in the lung provides better retention of drug as well as reduces biodistribution of drug throughout the systemic circulation and hence reduced incidence of side effects. Thus, sustained release etoposide formulations can provide prolonged drug release and hence, better anticancer activity.[5,6] The objective of the present work was to develop an effective ETP liposomal formulation for lung delivery, and thereby achieve improved therapy in lung cancer.[7]

2. MATERIALS AND METHODS

2.1 Materials

Etoposide obtained as gift sample from Aurobindo Laboratories Ltd, Lecithin, chloroform were purchased from A. R chemicals. All other ingredients used throughout the study were of analytical grade and were used as received.

2.2 METHODOLOGY[8,9,10]

2.2.1 Preparation of liposome

Liposomes were prepared by physical dispersion method using different ratio of lipids. In this method the lipids were dissolved in chloroform. This solution of lipids in chloroform was spread over flat bottom conical flask. The solution was then evaporated at room temperature without disturbing the solution. The hydration of lipid film form was carried out with aqueous medium phosphate buffer (pH 7.4). For this the flask was inclined to one side and aqueous medium containing drug to be entrapped was introduced down the side of flask and flask was slowly returned to upright orientation. The fluid was allowed to run gently over lipid layer and flask was allowed to stand for 2 h at 40^0C for complete swelling. After swelling, vesicles are harvested by swirling the contents of flask to yield milky white suspension. Then formulations were subjected to centrifugation. Different batches of liposomes were prepared in order to select an optimum formula. All batches of liposomes were prepared as per the general method described above.

Table-1: Formulation Design of Etoposide liposomes.

S. No	Formulation code	Ingredients			
		Drug (mg)	Cholesterol	Lecithin	Choroform
1	F1	10	500	500	20
2	F2	10	200	800	20
3	F3	10	100	900	20
4	F4	10	400	600	20
5	F5	10	300	700	20

3. RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

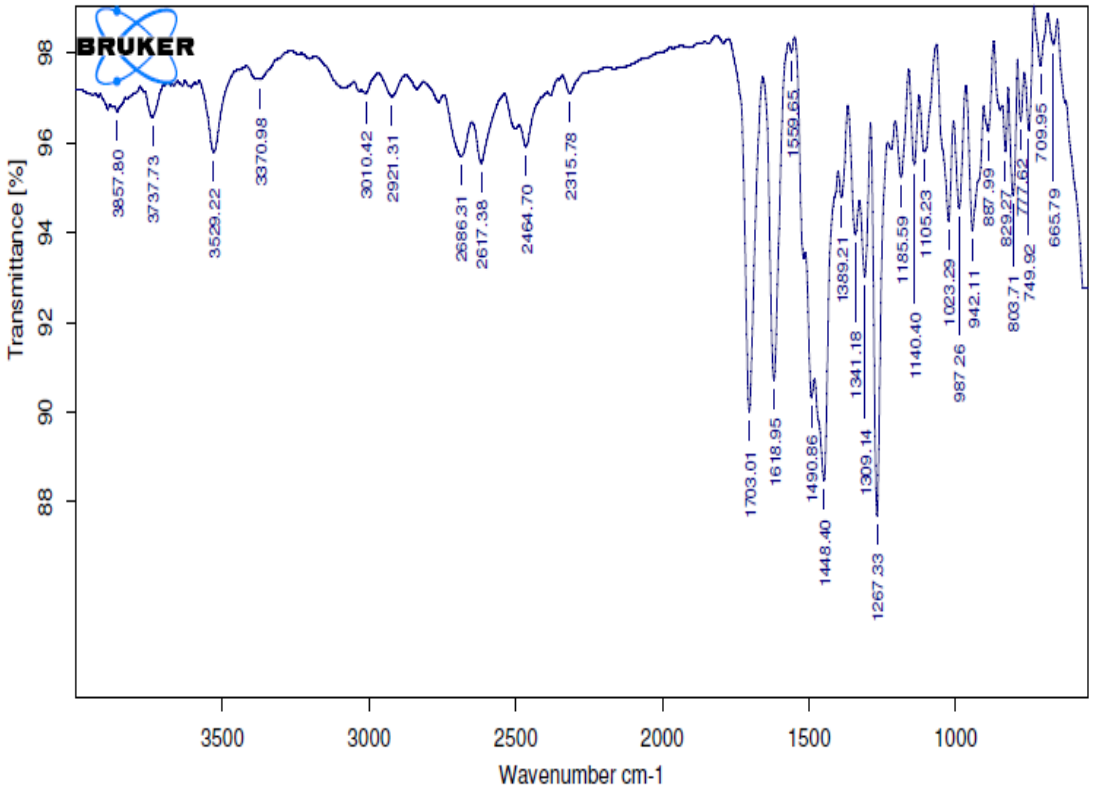

Fig-1: FT-IR Sample for Etoposide.

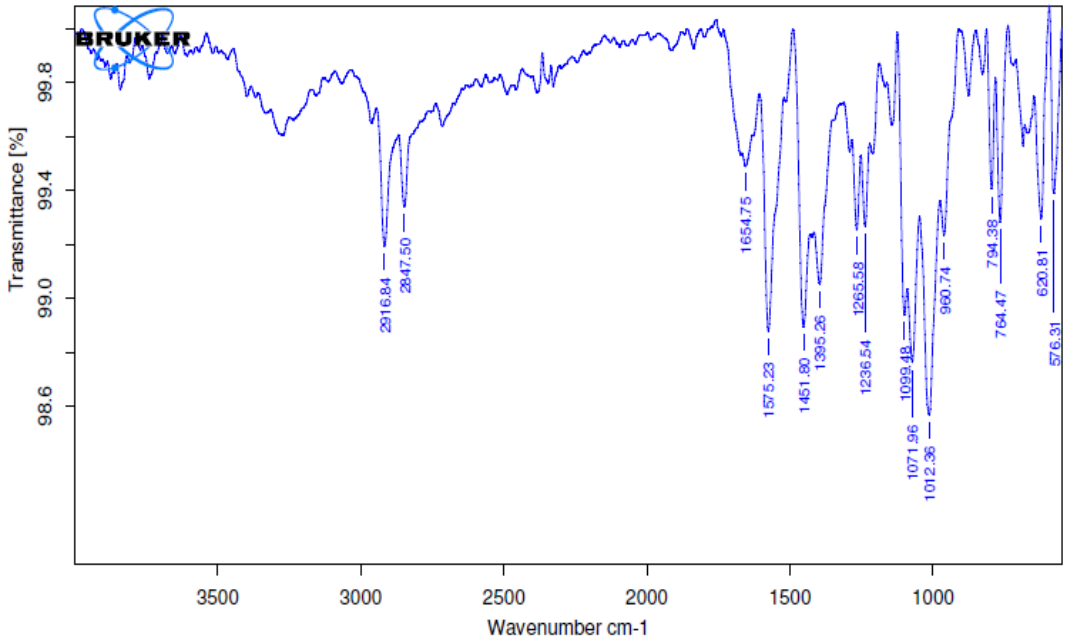

Fig-2: FT-IR Sample for Optimaized Formulation.

Entrapment efficiency

The percentage of entrapment efficiency of different liposomal batches design was found to be between ranges 69.36% to 71.56%. The maximum entrapment was observed in batch F2 i.e. 71.56 %. It can be concluded that the formulation component variables i.e. drug : lecithin: cholesterol ratio, volume of organic phase and volume of aqueous phase and formulation process variables i.e. speed of rotation, vacuum, temperature and hydration time affect the entrapment efficiency of drug.

Table-2: Results of entrapment efficiency of etoposide liposome.

S. no	Drug entrapment efficiency
F1	69.36
F2	63.28
F3	71.56
F4	68.19
F5	70.58

Particle size

Vesicle shape: Vesicle shape of the prepared formulation was found to be spherical from the SEM(scanning electron microscope) analysis at 15.00kV.

Table-3: Results of particle size of Etoposide liposomes.

S. no	Particle size(nm)
F1	88
F2	71
F3	75
F4	73
F5	86

Scanning electron microscopy

Scanning electron microscopy micrograph of optimized drug loaded liposomes showed that the colloidal particles have uniform loose aggregates in spherical shape with a smooth surface and they are uniformly distributed.

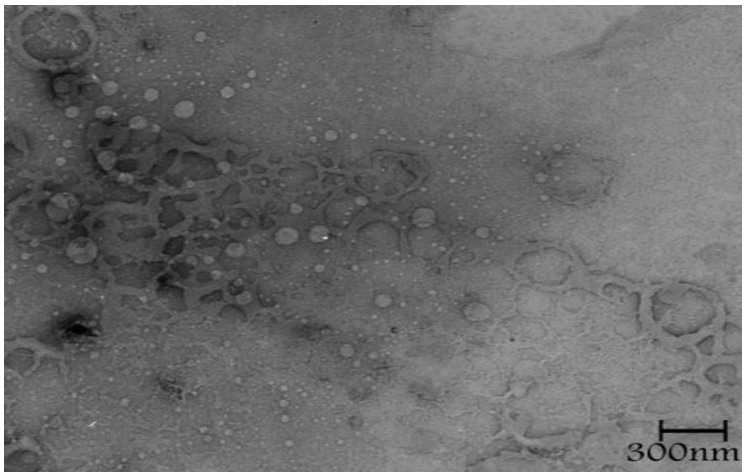

Fig-3: SEM analysis of Etoposide liposome.

Drug release studies

Table-4: Cumulative percentage drug release from various formulation of liposome.

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	17.38	16.80	19.99	18.26	16.19
2	24.07	24.15	27.54	21.85	23.49
3	26.14	29.31	28.50	28.11	27.45
4	30.32	32.72	33.50	30.19	31.29
5	31.85	30.16	32.80	36.45	35.65
6	34.41	41.48	44.50	42.17	40.28
7	46.14	47.20	51.55	49.29	45.84
8	56.52	54.20	62.54	59.14	58.99

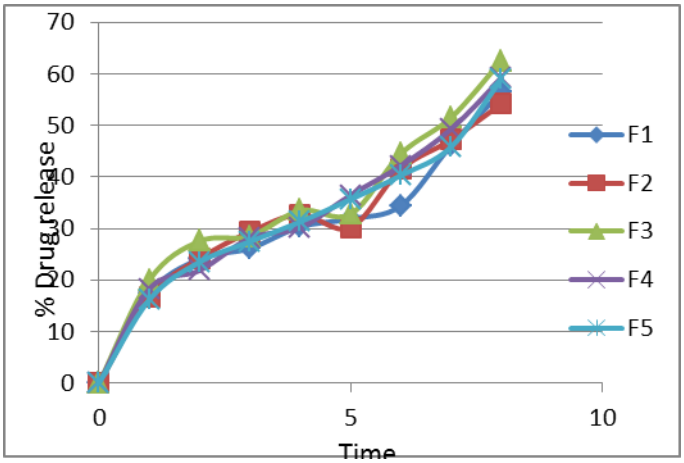

Fig-4: *In vitro* drug release of various formulations.

All the three batches of formulation F3 were found to release the drug in 8 h. The cumulative percentage release was found to be 62.54%.

Stability studies

Stability studies were carried out for a period of two month at 4±2^{0}C, 25±2^{0}C and 37±2^{0}C. The entrapment efficiency was estimated at an interval of 15 days.

Table-5: Stability studies for the formulation F3.

Sampling Intervals (Days)	% Drug entrapped at		
	4 ± 2^{0}C	25 ± 2^{0}C	37 ± 2^{0}C
0	62.54	62.54	62.54
15	62.42	62.40	62.38
30	62.38	62.36	61.32

4. CONCLUSION

From the performed work it was concluded that Etoposide possesses all requisite qualities required for liposomal drug delivery. Among the various formulation, the combination F2 was found to be most suitable because of high encapsulation efficiency with smaller particle size. The formulation F3 comprising phosphatidylcholine, cholesterol 8:2 ratio, fulfills the requirement of good liposomal formulation. *In vitro* drug release upto 8 h and more than 96.54% drug released. Follows peppas model in release studies. It shows encapsulation efficiency of 71.56 % and particle size of 81 nm.

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