Formulation And Evaluation of Naproxen Liposomal Drug Delivery System

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ABSTRACT : ***The drug release from Liposome 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. Naproxen is a drug with narrow therapeutic index and short biological half-life. This study aimed at developing and optimizing liposomal formulation of Naproxen 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 Naproxen 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, Naproxen, bioavailability, thin film hydration technique, in vitro drug release studies.

I.INTRODUCTION

There is a high demand for advanced delivery systems that are suitable for the delivery of various active pharmaceutical ingredients (APIs), especially systems with low costs, high efficiency, low risks, and toxicity.[1] Liposomes are the most commonly investigated nanostructures used in advanced drug delivery. Liposomes are artificially spherical vesicles prepared from naturally-derived phospholipid.[2] They entail one or more lipid bilayers with discrete aqueous spaces. They are well established for a range of pharmaceutical and biomedical applications with the unique capability of entrapment of both hydrophilic (polar) and hydrophobic (nonpolar) compounds due to their amphipathic nature in aqueous media. For instance, hydrophobic compounds entrap in the bilayer membrane, while hydrophilic compounds encapsulate in the aqueous core.[3] The objectives of the present investigation include studies are to prepare selected drugs NSAIDS liposomal formulation. Incorporate the prepared liposomes.[4] Liposomal drug delivery system drug delivery system include easy encapsulation of hydrophilic drugs into their core compartment and hydrophobic drugs into their lipid bilayer, excellent biocompatibility, ability to penetrate effectively into cell membranes, delivery of drugs into the cell compartments and diversity in modifying the surface properties by altering or introducing new components into the lipid bilayer.[5] Naproxen Sodium is a non-steroidal anti-inflammatory drug, considered to be the first line drug in the symptomatic treatment of rheumatoid arthritis and ankylosing spondylitis. It is having several side effects such as abnormal heart rhythm, branchospasm etc., In order to avoid systemic side effects of Naproxen there is a need to adopt novel drug delivery approaches in the design of dosage form.[6]

II. MATERIALS AND METHODS

2.1 MATERIALS

Naproxen was collected as a gift sample from Aurobindo Laboratories Ltd, Hyderabad and various excipients like cholesterol, phosphotidyl choline and other excipients were purchased from AR chemicals, Hyderabed.

2.2 METHODOS[7,8]

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Preparation of liposomes

Table-1: Formulation development of naproxen liposomes

Formulation no	Naproxen	Cholesterol	Phosphatidylcholine
F1	10	50	100
F2	10	75	100
F3	10	100	100
F4	10	125	100

Method

Liposomes were prepared by thin film hydration 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.

Evaluations of liposomes[9,10,11]

Drug entrapment efficiency of liposomes

Entrapment efficiency of liposomes were determined by centrifugation method. Aliquots (1 ml) of liposomal dispersion were subjected to centrifugation on a laboratory centrifuge (Remi R4C) at 3500 rpm for a period of 90 min. The clear supernatants were removed carefully to separate non entrapped Naproxen and absorbance recorded at 262 nm. The sediment in the centrifugation tube was diluted to 100 ml with phosphate buffer pH 7.4 and the absorbance of this solution was recorded at 262 nm.
Amount of Naproxen in supernatant and sediment gave a total amount of Naproxen in 1 ml dispersion.
% entrapment of drug was calculated by the following formula

$$\% \text{ Drug Entrapped (PDE)} = \frac{\text{Amount of drug in sediment}}{\text{Total amount of drug}} \times 100$$

Particle size analysis

All the prepared batches of liposomes were viewed under microscope to study their size. Size of liposomal vesicles from each batch was measured at different location on slide by taking a small drop of liposomal dispersion on it and average size of liposomal vesicles were determined.

***In Vitro* Drug release study:**

The release studies were carried out by franz diffusion cell. It containing 10 ml Phosphate buffer. Phosphate buffer pH 7.4 (100 ml) was placed in a 10 ml of beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37 ± 5^0C. Dialysis membrane was taken and one end of the membrane was sealed. After separation of non entrapped Naproxen liposomal dispersion was filled in the dialysis membrane and other end was closed. The semi permeable membrane containing the sample was suspended in the medium. 1ml of aliquots were withdrawn at specific intervals, filtered after withdrawal and the apparatus was immediately replenished with same quantity of fresh buffer medium.

Stability studies:[12]

Optimized medicated films were subjected to short term stability testing. The Naproxen liposomes were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 30 days as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

III. 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.

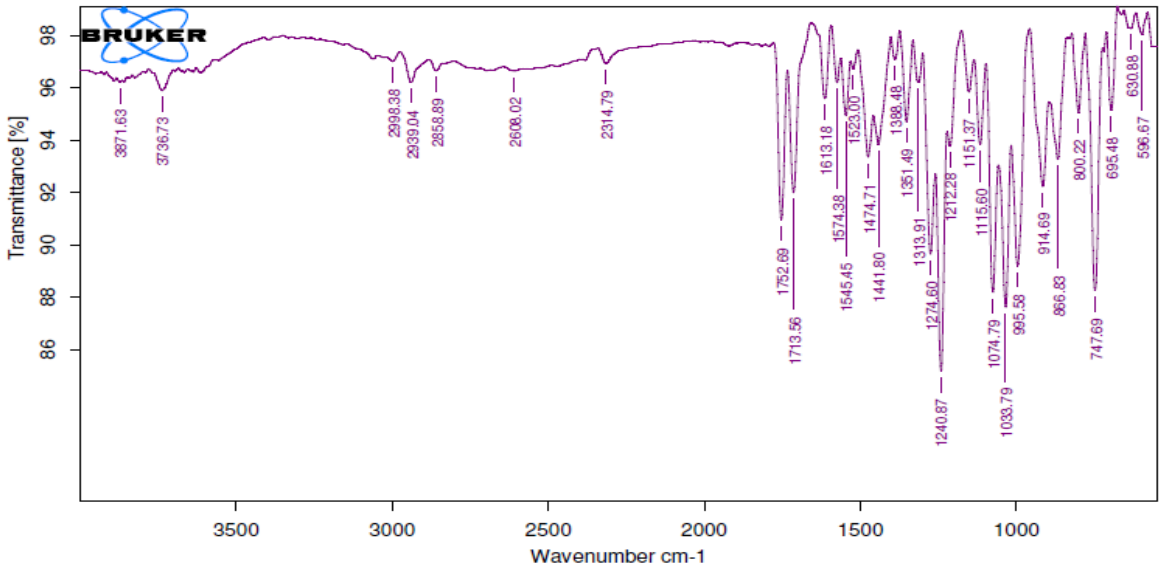


Fig-1: FT-IR graph for Naproxen Pure drug

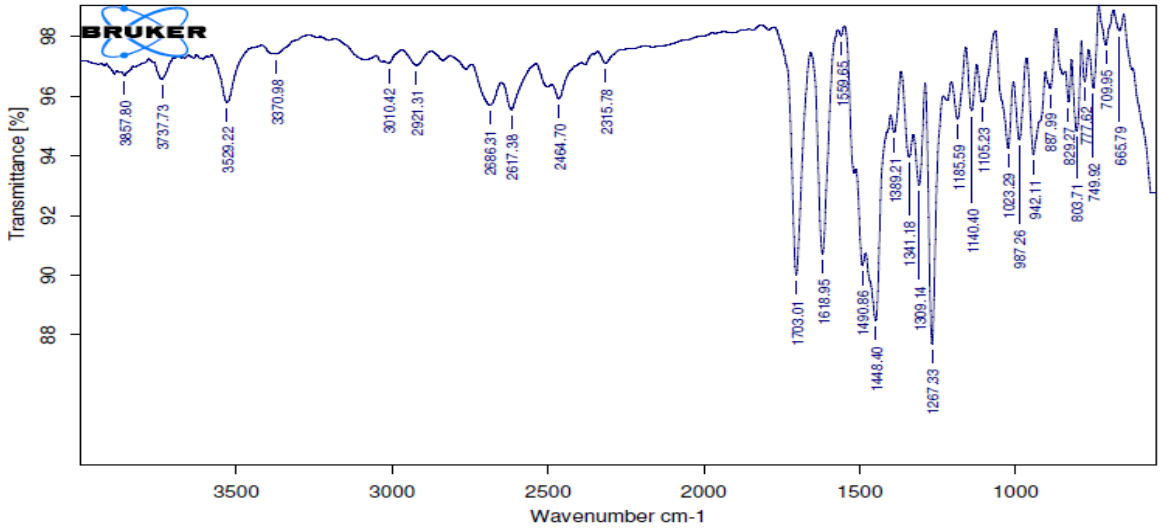


Fig- 2: FT-IR graph for physical mixture of drug and excipients

In the present study, it has been observed that there is no chemical interaction between Naproxen and the excipients used. From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation

between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Entrapment efficiency

Table-2: Results of entrapment efficiency of Naproxen liposomes

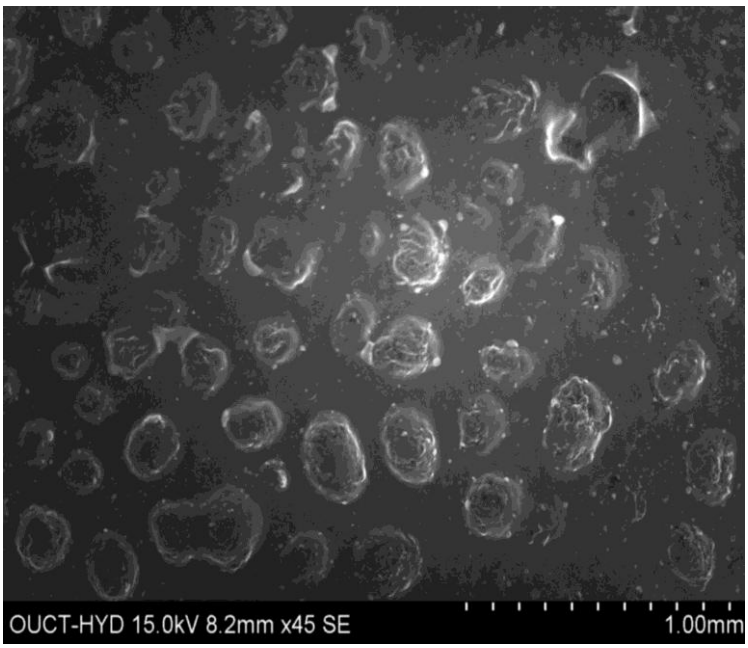
S. no	Drug entrapment efficiency
F1	78.60
F2	89.52
F3	70.50
F4	85.59

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 Naproxen liposomes

S. no	Particle size(µm)
F1	238
F2	243
F3	229
F4	224



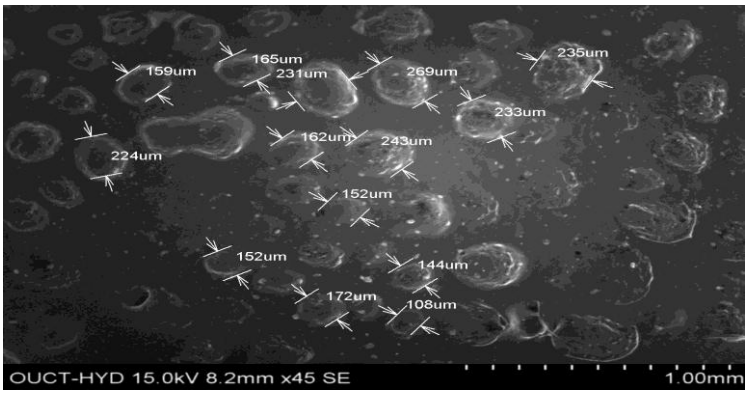


Fig-3: Particle size of Naproxen liposome

Drug release studies

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

Time	F1	F2	F3	F4
0	0	0	0	0
1	18.56	17.15	15.96	12.12
2	25.95	26.98	23.85	22.78
3	34.15	37.90	35.48	32.17
4	49.86	50.91	48.22	47.82
5	55.87	58.85	57.36	55.15
6	69.89	70.15	68.18	67.12
7	78.18	81.26	75.86	74.83
8	89.15	90.39	85.13	88.92

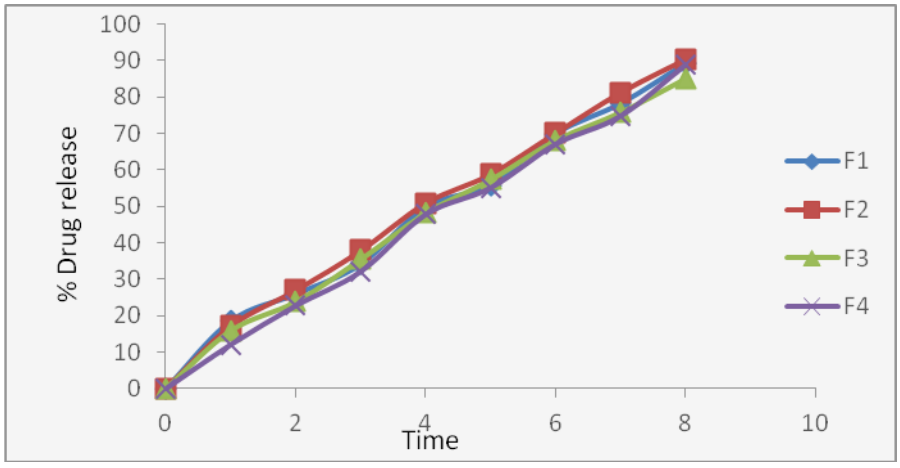


Fig-4: *In vitro* drug release of various formulations

All the four batches of formulation F2 were found to release the drug in 8 h. The cumulative percentage release was found to be 90.39%.

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 30 days.

Table-5: Stability studies for the formulation F2

Sampling Intervals (Days)	% Drug entrapped at		
	4 ± 2^{0}C	**25 ± 2^{0}C**	**37 ± 2^{0}C**
0	90.39	90.39	90.39
15	89.99	89.90	89.78
30	88.95	88.95	87.56

IV. CONCLUSION

From the performed work it was concluded that Naproxen 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 F2 comprising phosphatidylcholine, cholesterol, fulfills the requirement of good liposomal formulation. *In vitro* drug release upto 8 hr and more than 90.39% drug released. It shows encapsulation efficiency of 89.52 % and particle size of 243 µm.

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