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FORMULATION AND EVALUATION OF IRINOTECAN LIPOSOMAL FOR TARGETED DRUG DELIVERY

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Abstract:

In the present work an attempt is being made to provide for stable drug delivery system with or having improved therapeutic index for Irinotecan in form of lyophilized liposomes. Liposomes were prepared using the thin-film hydration method and optimized for various formulation parameters. The developed liposomal formulations were evaluated for particle size, zeta potential, drug entrapment efficiency, in vitro drug release and stability. Irinotecan containing liposomes with an encapsulation efficiency of 92.67 % were prepared, and the in vitro *release of Irinotecan from the liposomes. In conclusion, the formulation was optimized, the prepared liposomes had a high Irinotecan encapsulation rate and good reproducibility, and there* in vitro *release had a certain delayed-release effect. The optimized formulation exhibited nanoscale particle size (236 nm), high entrapment efficiency (>80%), and a sustained drug release profile over 8 hours. The liposomal encapsulation of Irinotecan showed potential for improved pharmacokinetics and site-specific targeting, thereby minimizing systemic toxicity. In conclusion, the liposomal delivery system developed in this study demonstrates a promising approach to enhance the therapeutic efficacy and safety of Irinotecan.*

Keywords: *Irinotecan, Cholesterol, phosphatidyl choline, FTIR studies, thin film hydration technique, In vitro drug release studies.*

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INTRODUCTION:

Liposomes are biocompatible as well as biodegradable bilayer vesicles comprising of a hydrophilic aqueous core and are made of phospholipids. From the last several years the liposomal vesicles have been extensively considered as a carrier of preference for the delivery of various potential drug candidates that are lipophilic as well as hydrophilic. [1] Generally, the liposomes used in clinical practice have the size with diameter in the range of 50 to 300 nm. [2] The membranes of liposomal vesicle are linked with the plasma membrane, and consist of bilayers made up of phospholipids. Instinctively, vesicles formation occurs upon hydration by means of aqueous media from phospholipids as a consequence of tails of hydrophobic fatty acid, and a head group of hydrophilic phosphatidyl that exists in the typical amphiphilic molecular structure. [3] In the liposomal membrane, cholesterol (CH) can be simply incorporated just as plasma membrane in the matching style which stabilizes the membrane and adjust the release of the drug.[4]The drugs hydrophilic in nature are enclosed inside the internal aqueous phase, whereas, in the bilayer area of the lipid tail the hydrophobic drugs are located. Liposomal membranes are fluidic in nature like the biomembranes and therefore, the enclosed drugs may be leaked out or released by the liposomes. The release rate is reliant on the components present in the membrane of liposome, like types of phospholipid's fatty acid acyl chain, degree of unsaturation, charge on lipid and inclusion of CH. [5] These nanocarriers can offer significant advantages as drug delivery systems, which are as fallows. Entirely biodegradable, biocompatible, flexible, nonimmunogenic, non-toxic, drug delivery system for non-systemic and systemic administrations. [6] Irinotecan an anticancer agent is indicated for treatment of patients with cancer. The present study involves preparation and evaluation of liposome containing Irinotecan.

MATERIALS:

Irinotecan was collected as a gift sample from Aurobindo Laboratories Ltd Hyderabad, polymers, excipients were purchased from Synpharma Research Labs, Hyd.

METHODODOLOGY:

Formulation development

Table-1: Formulation table

Ingredients	F1	F2	F3	F4
Drug (mg)	10	10	10	10
Phosphatidylcholine (mg)	200	200	200	200
Cholesterol(mg)	100	200	300	400
Chloroform (ml)	10	10	10	10
Phosphate buffer pH 7.4(ml)	10	10	10	10

Preparation of liposomes:

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 37^0C 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. [7,8]

Drug excipient compatibility studies [9]

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.

Evaluations of liposomes [10,11,12]

Encapsulation efficiency determination

The entrapment efficiency (EE) of liposomal preparations was evaluated by ultra-centrifugation technique. Briefly, ultra-centrifugation devices from Amicon (Amocon ultra, 0.5ML 10K, Merck, USA)

were used to process 500uL sample of tacrolimus liposomes. After centrifugation for 20 min at 10,000 rpm in a TarsonMC-1, Spin win micro centrifuge, the ultra-filtrate was collected and injected into HPLC device for free drug determination.[53] The entrapment efficiency of the liposomes was estimated using the following equation. (Eq 1).

Entrapment efficiency (%) = [(TD – FD)/TD] × 100 (1)
Where
FD is the quantity of drug estimated in the filtrate and TD is the theoretical amount of tacrolimus that is present in liposomal preparation.

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.

SEM analysis:
The morphology of liposomes was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminum stubs and the surface was coated with a layer of gold particles using a sputter coater. The shape of the liposomes was determined by scanning electron microscopy (SEM) (XL30, Philips, the Netherlands) at 15 kV and 750 mA.

***In Vitro* Drug release study:**
In Vitro drug release studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 8 ml. The cellulose acetate membrane was used for the determination of drug from the prepared Liposomes. The cellulose acetate membrane having a pore size 0.45 µ was mounted between the donor and receptor compartment of the diffusion cell. The prepared Liposomes was placed on the cellulose acetate membrane and covered with aluminium foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads, and the temperature was maintained at 32 ± 0.5°C, because the normal skin temperature of human is 32°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Stability studies:
The stability of optimized liposomes formulation was assessed for a period of 3 Months by storing the liposomes at 3 specified temperature conditions, i.e. 25±20 /60% RH (Room temperature; RT), 40±2°C/75% RH (Accelerated conditions) and 2-80 C (Refrigerator; control). The liposomal formulation was kept in sealed laminated aluminum tubes (10 ml capacity) which were previously flushed with nitrogen. Samples were periodically taken at specified time period of 0, 1, 2and 3months. These were tested for drug release, in the manner described.[13,14]

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.

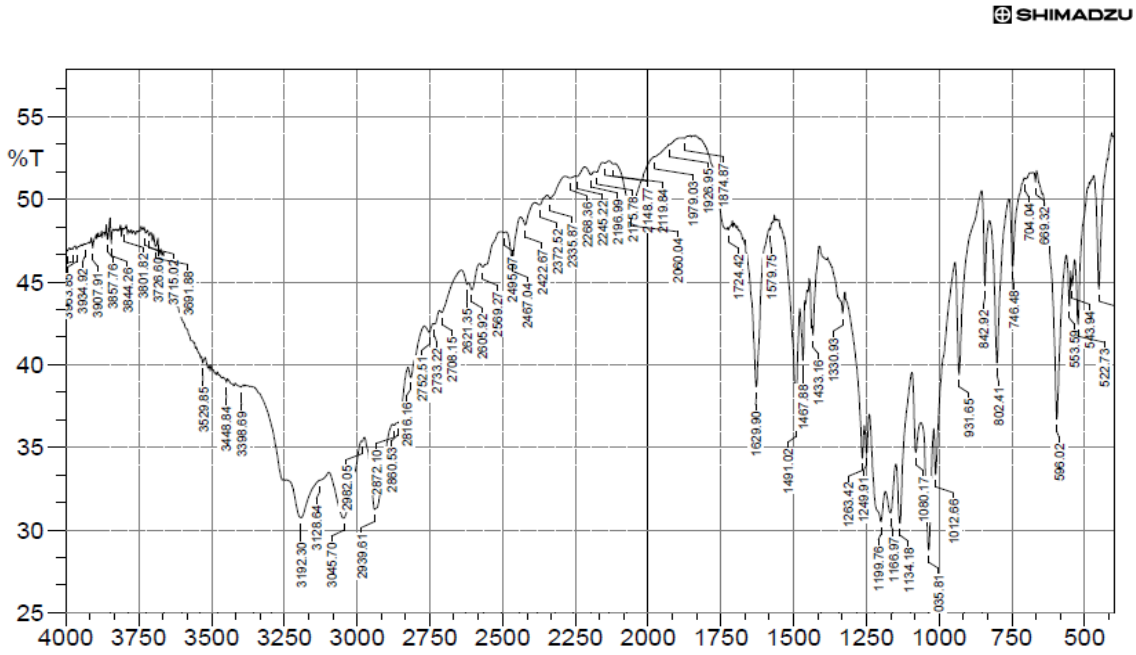

Fig-1: FTIR Studies of Irinotecan

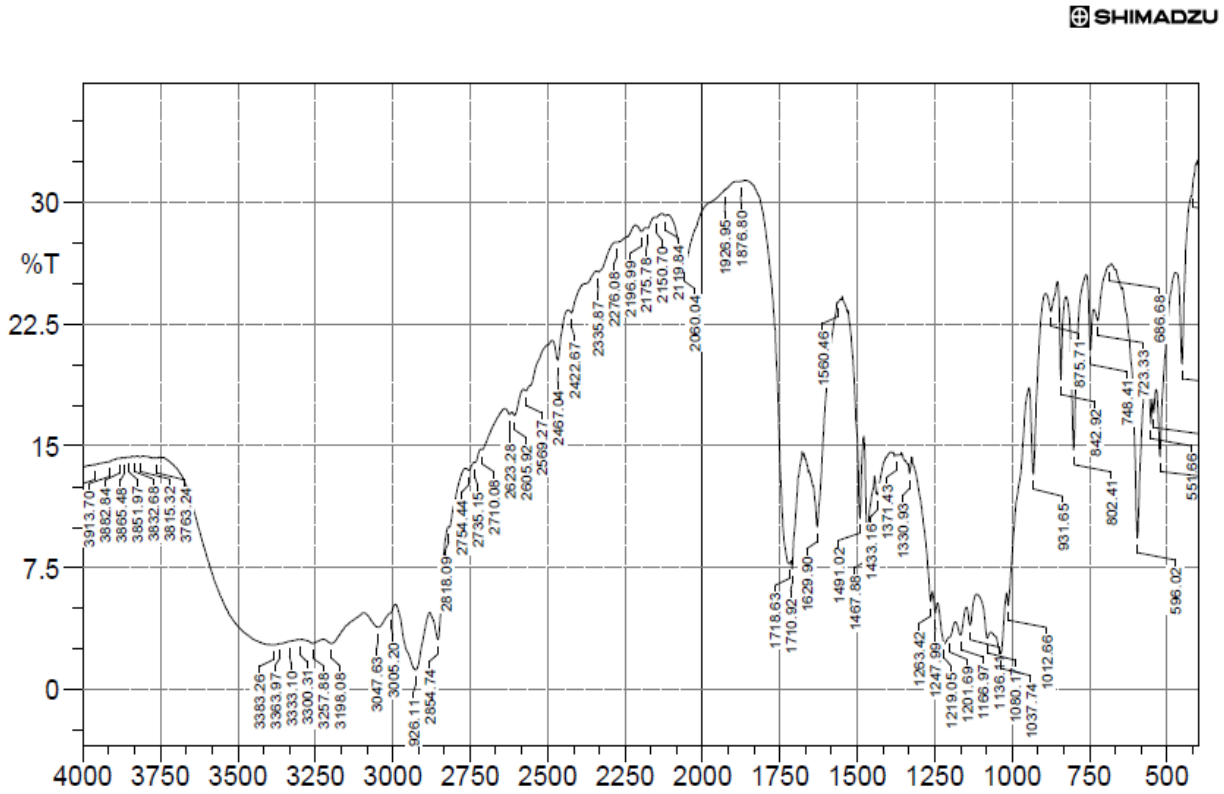

Fig-2: FT-IR graph for optimized formulation

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.

SEM Analysis:

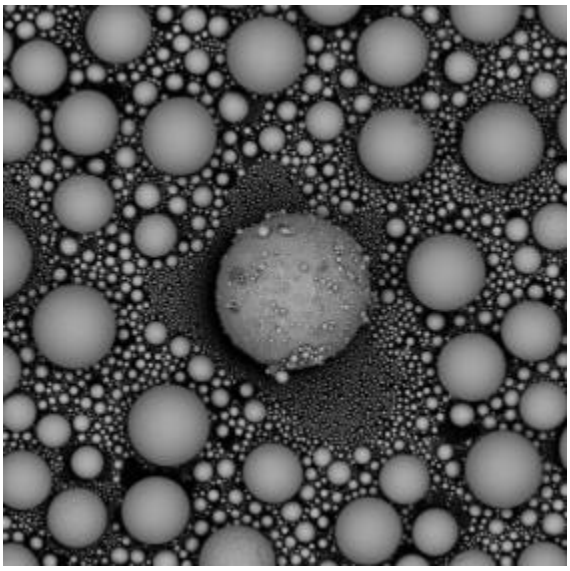

Fig-3: SEM Analysis of Irinotecan liposome

Vesicle size:

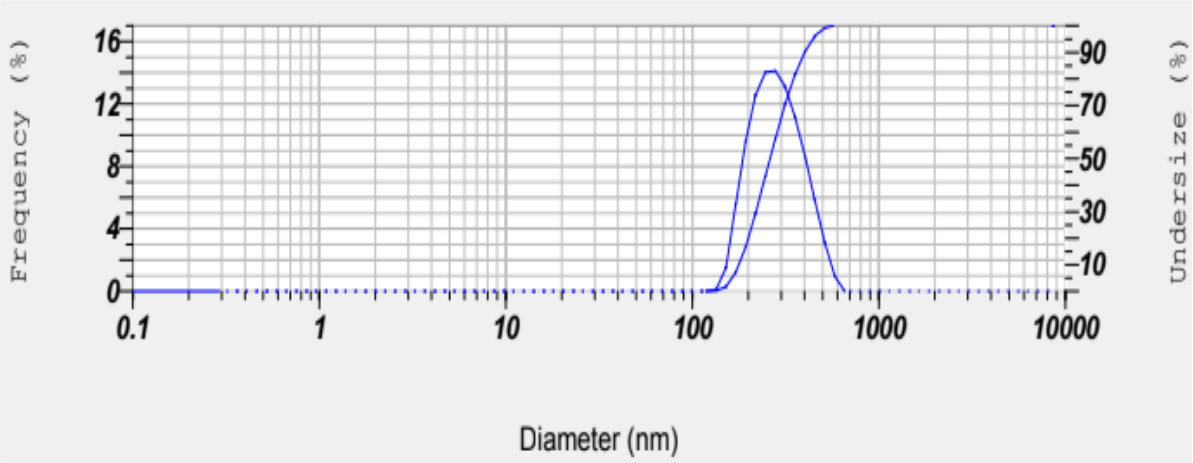

Fig-4: particle size of Irinotecan liposomes

Table-2: Mean particle size of different formulation of liposomes

Sr. No	Formulation No.	Particle size
1	F1	241
2	F2	247
3	F3	236
4	F4	248

Drug entrapment efficiency

Table-3: Different batches of liposome made by using different ratio of lipids

Formulation no.	% DEE
F1	89.63
F2	90.13
F3	92.67
F4	91.28

Drug release studies

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

Time	F1	F2	F3	F4
0	0	0	0	0
1	15.96	16.93	18.15	17.20
2	28.47	27.58	29.64	27.53
3	36.50	37.95	38.46	36.12
4	46.98	47.90	49.51	48.46
5	57.45	58.12	58.11	55.02
6	68.10	69.35	70.15	67.43
7	81.23	82.26	86.43	85.12
8	93.67	95.16	98.42	96.15

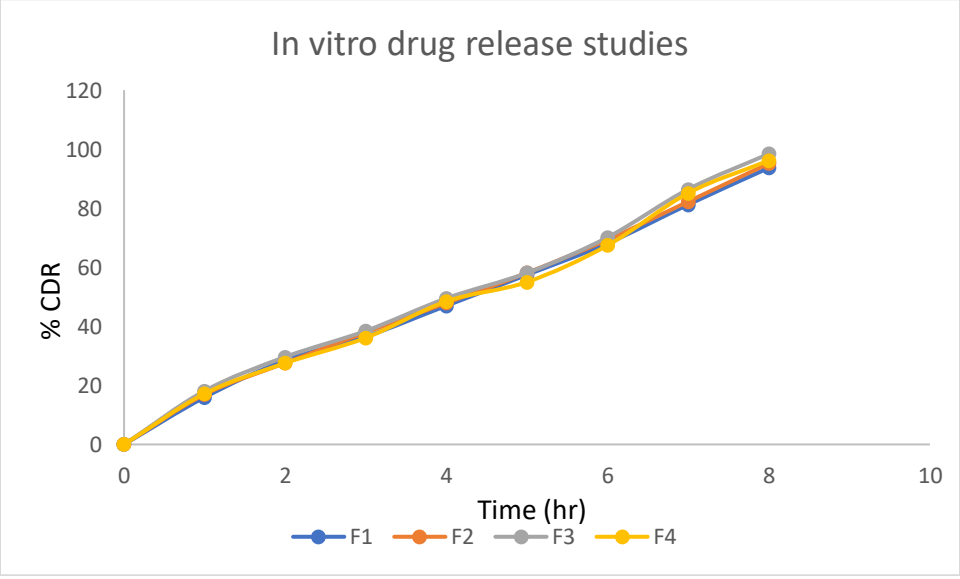

Fig-5: *In vitro* drug release of (F1-F4) formulations

Formulation F3 were found to release the drug in 8 h. The cumulative percentage release was found to be 98.42 %.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 months. Parameters quantified at various time intervals were shown;

Table-5: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	**25^0C/60%RH % Release**	98.42	97.56	96.38	95.52	**Not less than 85 %**
F-4	**30^0C/75% RH % Release**	98.42	97.28	96.23	95.36	**Not less than 85 %**
F-4	**40^0C/75% RH % Release**	98.42	97.25	96.12	95.30	**Not less than 85 %**

CONCLUSION:

Liposomes are novel form of drug delivery. They offer a great way of delivering drugs at a higher efficacy and lower toxicity. They do, however, have their limitations and as for as drug delivery goes there seems to be an emphasis on the use of sterically stabilized liposome. Irinotecan possesses all requisite qualities required for liposomal drug delivery. Among the various formulation, the combination F3 was found to be most suitable because of high encapsulation efficiency with smaller particle size. The formulation F3 comprising phosphatidylcholine, cholesterol fulfills the requirement of good liposomal formulation. *In vitro* drug release upto 8 h and more than 98.42 % drug released. It shows encapsulation efficiency of 91.28 % and particle size of 236 nm. In vitro release studies indicated a sustained release profile compared to conventional drug solution, which may potentially lead to reduced dosing frequency and better patient compliance. Hence, the developed liposomal formulation of Irinotecan provides a promising platform for targeted and controlled drug delivery in cancer therapy. Further in vivo studies are recommended to confirm its therapeutic efficacy and biodistribution.

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