Development and Characterization of Vincristine Liposomal Drug Delivery System

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Abstract
The present research work was aimed at the development and characterization of a liposomal drug delivery system for Vincristine, a potent chemotherapeutic agent widely used in the treatment of haematological malignancies and solid tumors. Conventional Vincristine formulations are associated with dose-limiting neurotoxicity, rapid systemic clearance, and poor selectivity toward tumor tissues. To overcome these drawbacks, liposomes were formulated as nanocarriers to enhance therapeutic efficacy and reduce adverse effects. Liposomes were prepared using the thin-film hydration method followed by sonication to obtain uniform vesicles. Drug and lipids compatibility determined by using FTIR. The prepared formulations were evaluated for vesicle size, encapsulation efficiency, and *in vitro* drug release profile. Morphological characterization was carried out using Scanning electron microscopy (SEM) to confirm the spherical shape and Nano-range distribution of vesicles. Optimized formulations showed high encapsulation efficiency, *in vitro* drug release, and favorable stability under storage conditions. The findings suggest that the developed Vincristine liposomal system could serve as a promising nanocarrier for targeted and sustained cancer therapy with minimized systemic toxicity.

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Keywords: Vincristine, thin-film hydration, phosphatidylcholine, FTIR Studies, *in vitro* drug release studies

Introduction

Liposomes are spherical vesicular structures composed of phospholipid bilayers that mimic the biological membrane, allowing biocompatibility, improved cellular uptake, and targeted delivery. Their unique structure enables sustained and controlled drug release, protection of unstable molecules from degradation, and enhanced biodistribution, making them suitable for chemotherapy agents, vaccines, and biologicals [1]. Cancer chemotherapy, while effective, is often associated with significant limitations such as poor bioavailability, nonspecific tissue distribution, rapid systemic clearance, and dose-limiting toxicities. Conventional administration of chemotherapeutic drugs results in severe adverse effects due to exposure of healthy tissues, highlighting the need for more efficient and safer delivery strategies [2]. Liposomal encapsulation of anticancer drugs has shown the ability to reduce toxicity, enhance pharmacokinetic performance, prolong circulation time, and selectively accumulate in tumor tissues through the enhanced permeability and retention (EPR) effect. Vincristine, a vinca alkaloid derived from Catharanthus roseus, is widely used in the treatment of various malignancies including leukemia, Hodgkin's lymphoma, neuroblastoma, and breast cancer. Despite its clinical significance, vincristine presents challenges such as neurotoxicity, low therapeutic window, rapid clearance, and poor selectivity toward tumor cells [3].

These limitations restrict dose escalation and reduce therapeutic potential, necessitating the development of advanced drug delivery systems that improve efficacy while minimizing toxicity [4]. The present study focuses on the development and characterization of a vincristine-loaded liposomal delivery system intended to enhance therapeutic efficacy while reducing toxicity associated with conventional vincristine therapy. This research aims to demonstrate the potential of liposomal encapsulation as a viable strategy for improving vincristine's clinical performance in cancer management [5].

Materials

Vincristine was procured from Hetero Labs, HYD. Phosphatidylcholine, Cholesterol were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

Methodology

IR Spectroscopic Analysis

For IR spectroscopy KBr powder was dried out at 60°C for one hour. The dried KBr powder was uniformly mixed with drugand IR spectra was taken for this mixture using ATR-FTIR 4000 (Jasco, Japan) IR Spectrophotometer [6]

Preparation of liposomes

Phosphatidylcholine and cholesterol were dissolved in 10.0 mL chloroform in 250mL round bottom (RB) flask. The diethyl ether was evaporated under vacuum using rotary flash evaporator, which allows phosphatidyl choline to form a thin dry film on the walls of the flask. This system was maintained at vacuum and 37°C for an additional 10min, after complete removal of organic solvent as indicated by visual observations. Vesicles were prepared by hydrating the lipid film in the presence of 10mL phosphate buffer pH 7.4 Liposomes formed were sonicated for 5 min. to reduce the size of the vesicles [7].

Table-1: Composition of lipids for preparation of liposomes

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Phosphatidylcholine (mg)	100	100	100	100	100	100	100	100
Cholesterol(mg)	100	200	300	400	500	600	700	800
Chloroform (ml)	10	10	10	10	10	10	10	10
Vincristine (mg)	20	20	20	20	20	20	20	20
Phosphate buffer pH 7.4(ml)	10	10	10	10	10	10	10	10

Evaluations of liposomes

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 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 UV spectrophotometer for free drug determination.The entrapment efficiency of the liposomes was estimated using the following equation. (Eq 1) [8].

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 [9].

SEM analysis

The morphology of liposomes was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminium 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.

Kinetics of drug release studies

The quantitative elucidation of the values obtained in the diffusion study is facilitated by the usage of a generic equation that mathematically translates the diffusion curve in function of some parameters related to the liposomes. For understanding the mechanism of drug release and release rate kinetics of the drug 45 from dosage form, the *in vitro* drug release data of optimized formulations obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix and Korsmeyer-Peppas models.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$Q0 - Qt = K0t$$

Arrangement of equation yields: $Qt = Q0 + K0t$

Where Qt is the amount of drug dissolved in time t,
Q0 is the initial amount of drug in the solution (most times, Q0 = 0)
and K0 is the zero-order release constant expressed in units of concentration/time.
To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

First order Kinetics

The equation for first order release is given below

$$Log\ Qt = log\ Q0 + K1t/2.303$$

Where Qt is the amount of drug released in time t,
Q0 is the initial amount of drug in the solution
and K1 is the first order release constant.
A graph of the decimal logarithm of the released amount of drug versus time will be linear. Liposomes following this dissolution profile release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

Higuchi described drug release as a diffusion process based on the Fick's law, square root time dependent. The simplified Higuchi equation is represented as

$$Qt = Kt^{1/2}$$

Where Qt = amount of drug released in time t,
K = Higuchi's constant
A linear relationship between amount of drug released (Q0 versus square root of time (t½) is observed if the drug release from the microspheres is diffusion controlled.

Korsmeyer-Peppas model

This mathematical model, also known as the Power Law, has been used, very frequently; to describe the drug release from several different pharmaceutical modified release dosage forms. The Korsmeyer-Peppas model relates drug release exponentially to time. It is described by the following equation

$$Mt/M\infty = atn$$

Where 'a' is a constant incorporating structural and geometric characteristics of microspheres, 'n' is the release exponent, indicative of the drug release mechanism, and the function of 't' is Mt/ M∞ (fractional release of drug).

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, 2 and 3months. These were tested for drug release, in the manner described.

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.

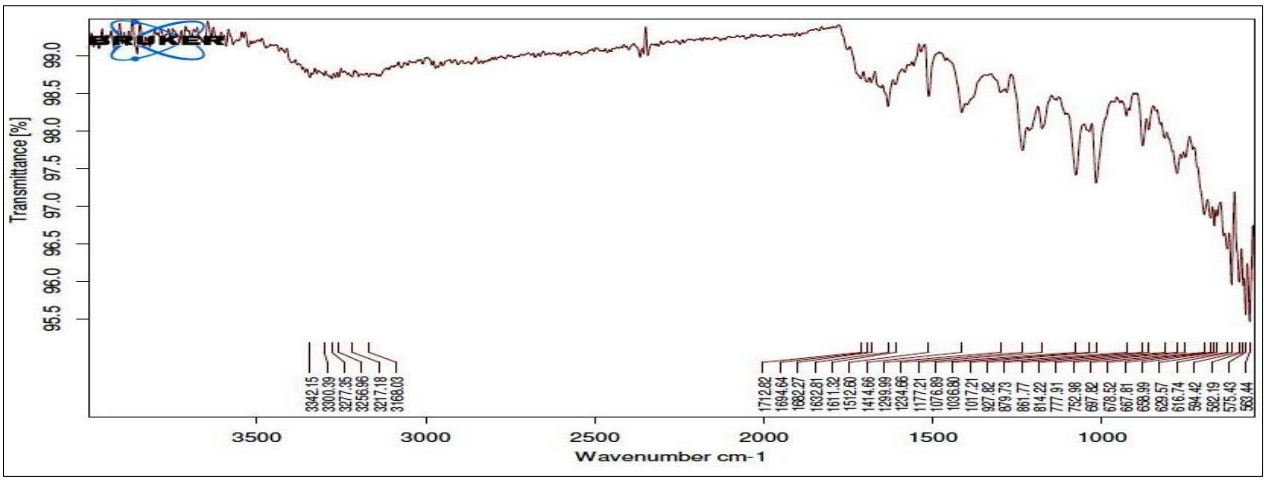

Fig 1: FTIR Studies of Vincristine

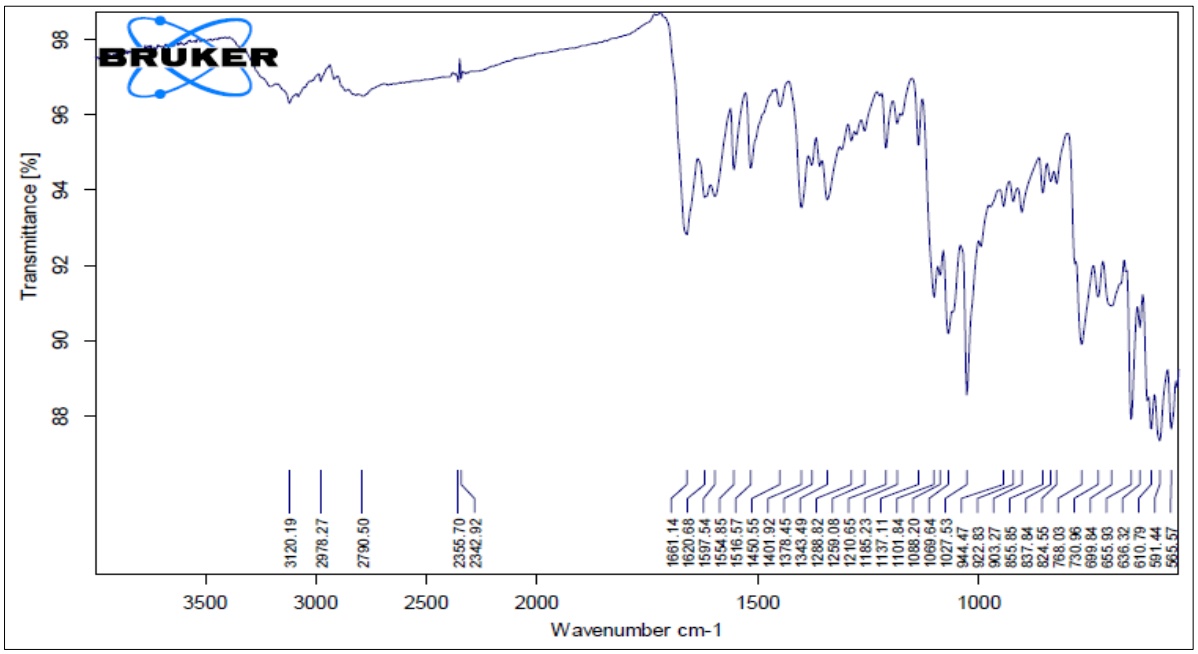

Fig 2: FTIR Studies of optimized formulation

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

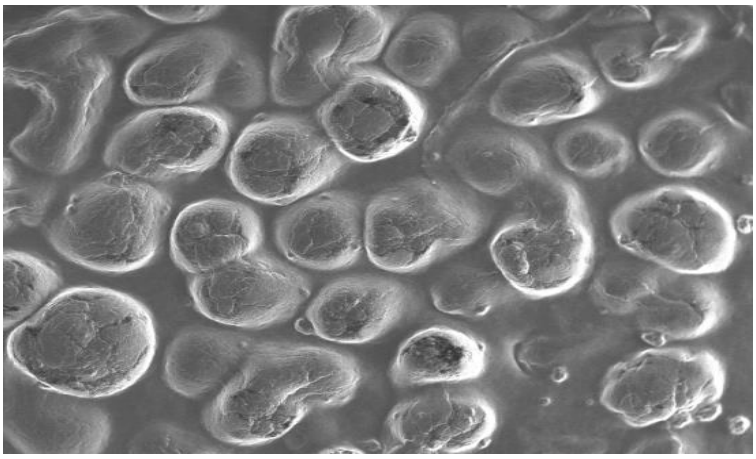

Fig 3: SEM Analysis of Vincristine liposomes

Vesicle Size:

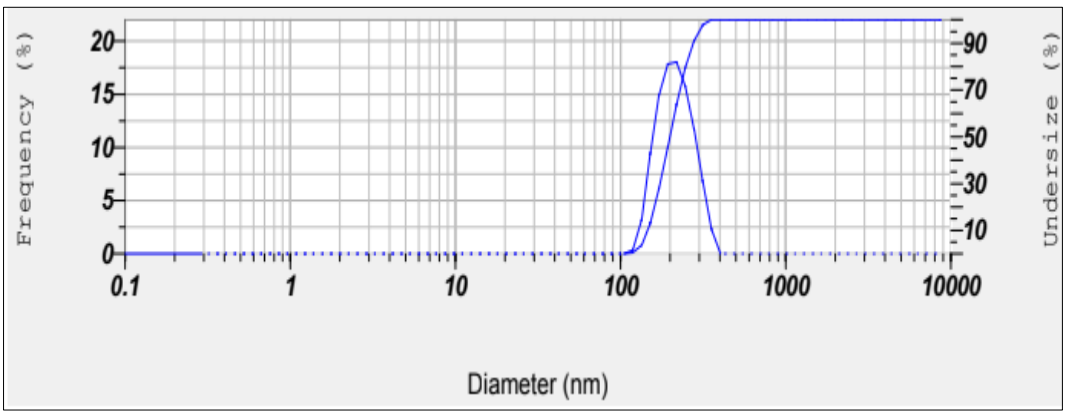

Fig 4: Particle size of Vincristine liposomes

Table 2: Mean particle size of different formulation of liposomes

Formulation No.	Particle size
F1	189
F2	190
F3	186
F4	176
F5	199
F6	201
F7	193
F8	186

Drug Entrapment Efficiency

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

Formulation no.	DEE
F1	89.69
F2	85.21
F3	92.36
F4	93.50
F5	95.36
F6	92.45
F7	94.36
F8	90.15

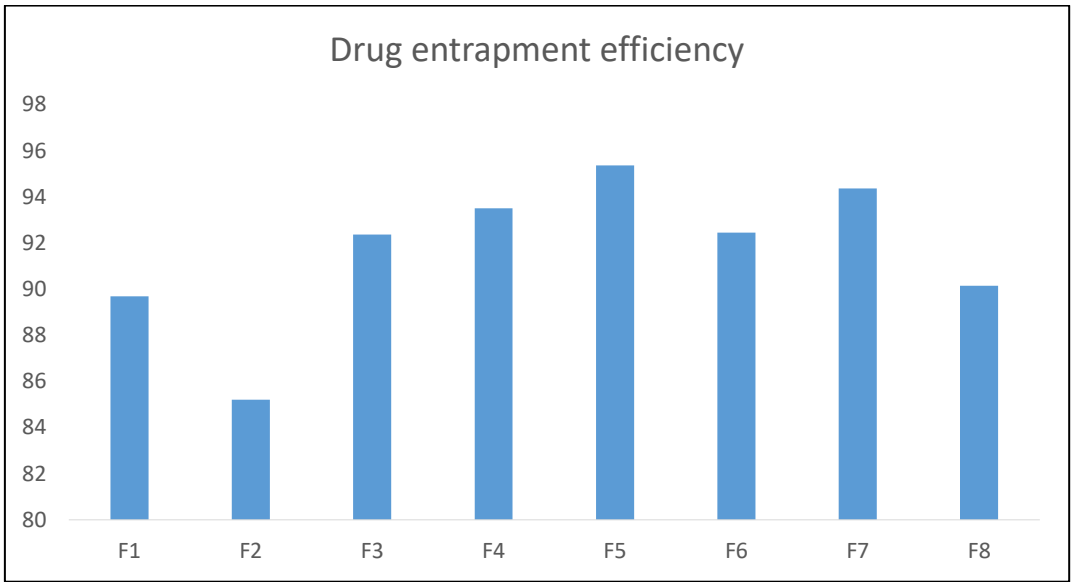

Fig-5: Drug entrapment efficiency of all formulations

Drug Release Studies

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

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	15.98	16.22	14.50	17.46	18.56	15.10	16.42	14.20
2	27.58	27.49	28.19	27.82	29.63	25.31	22.30	20.39
3	39.56	32.25	36.82	37.17	38.12	37.40	36.59	35.12
4	45.31	45.91	48.19	47.35	43.26	44.02	42.15	43.08
5	58.93	58.60	57.58	58.10	60.24	62.19	63.25	65.12
6	63.20	69.35	68.55	69.85	71.23	72.22	73.10	75.58
7	82.59	82.30	81.29	82.35	83.69	80.05	81.23	80.25
8	92.36	95.18	94.19	93.20	96.86	93.22	95.36	94.56

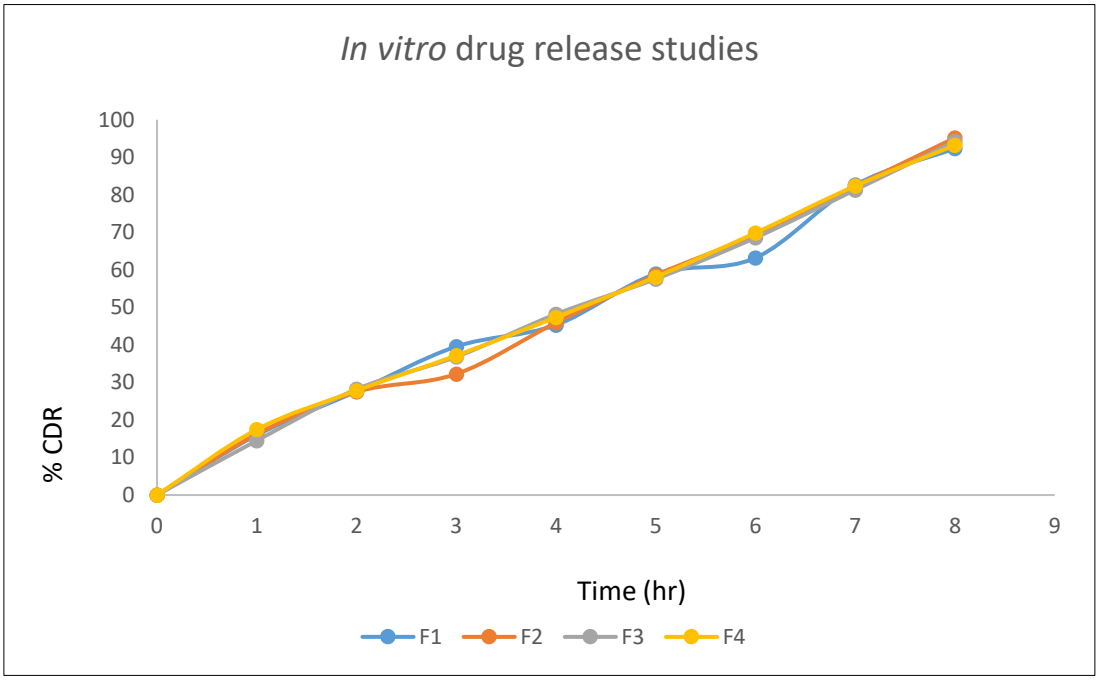

Fig 6: *In Vitro* drug release of (F1-F4) formulations

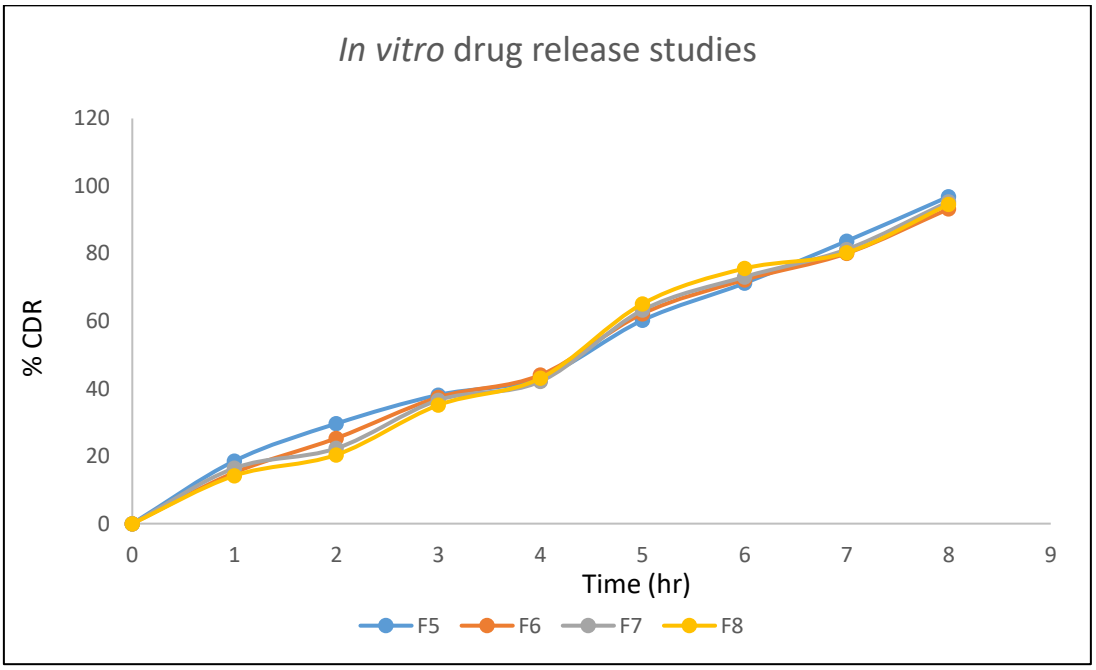

Fig 7: *In Vitro* drug release of (F5-F8) formulations

Formulation F5 were found to release the drug in 8 h. The cumulative percentage release was found to be 96.86 %.

Drug Release Kinetics

The results obtaining *in vitro* release studies were plotted in different model of data treatment as follows:

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's
- Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero Order Kinetics

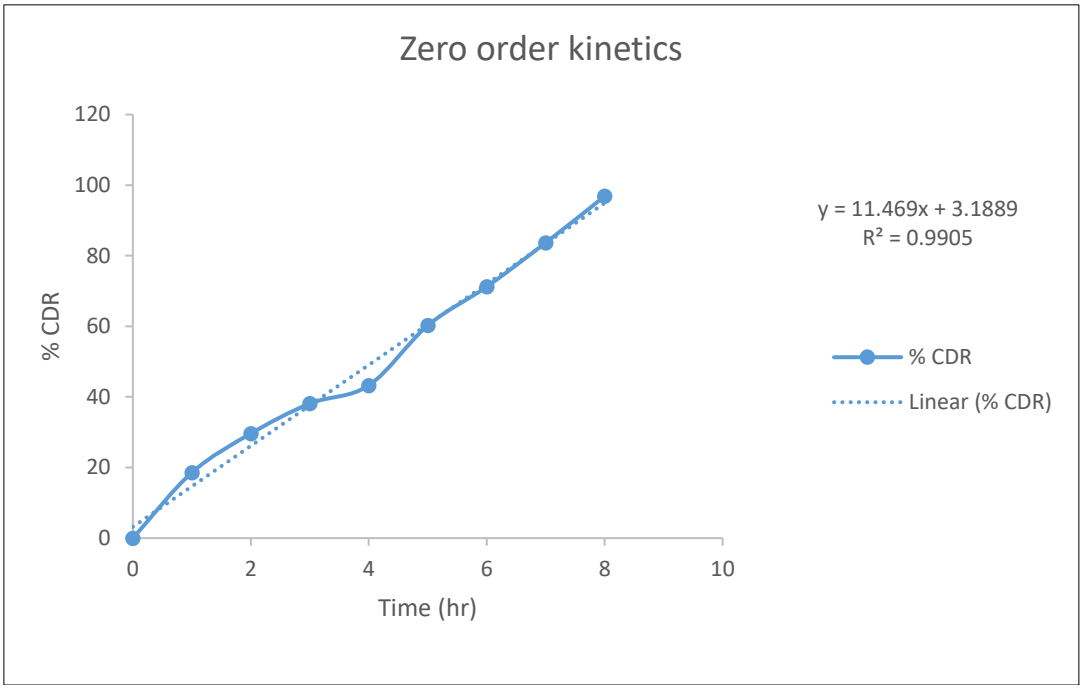

Fig 8: Zero order kinetics of optimized formulation

First Order Kinetics

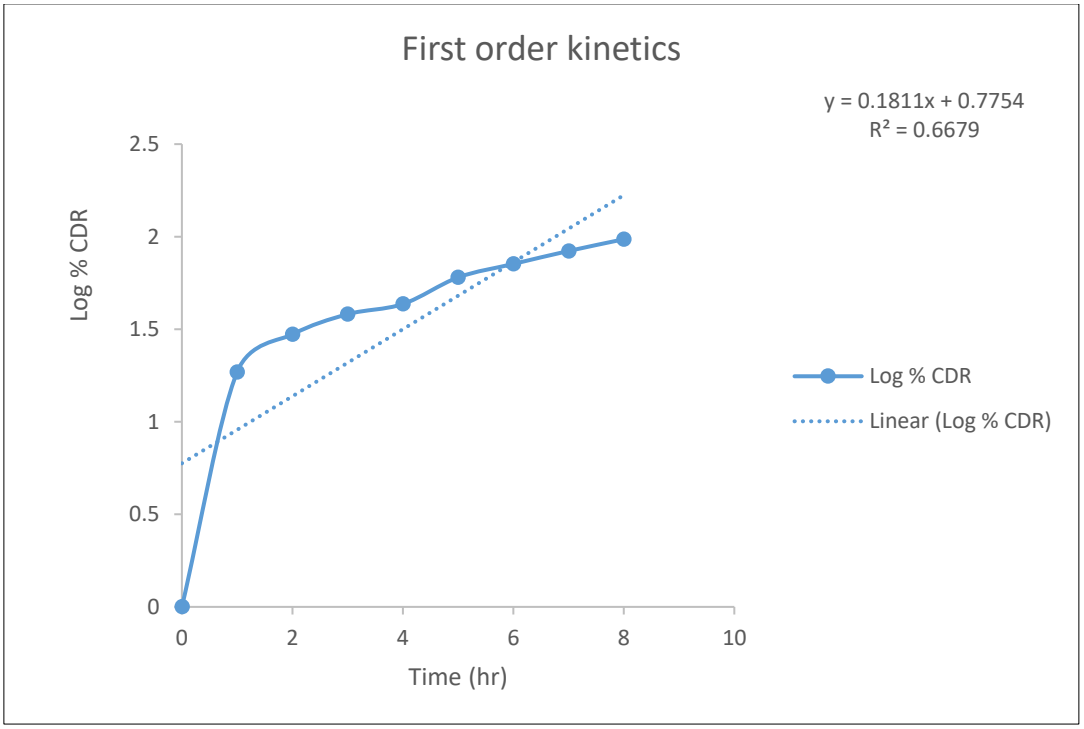

Fig 9: First order kinetics optimized formulation

Higuchi Model

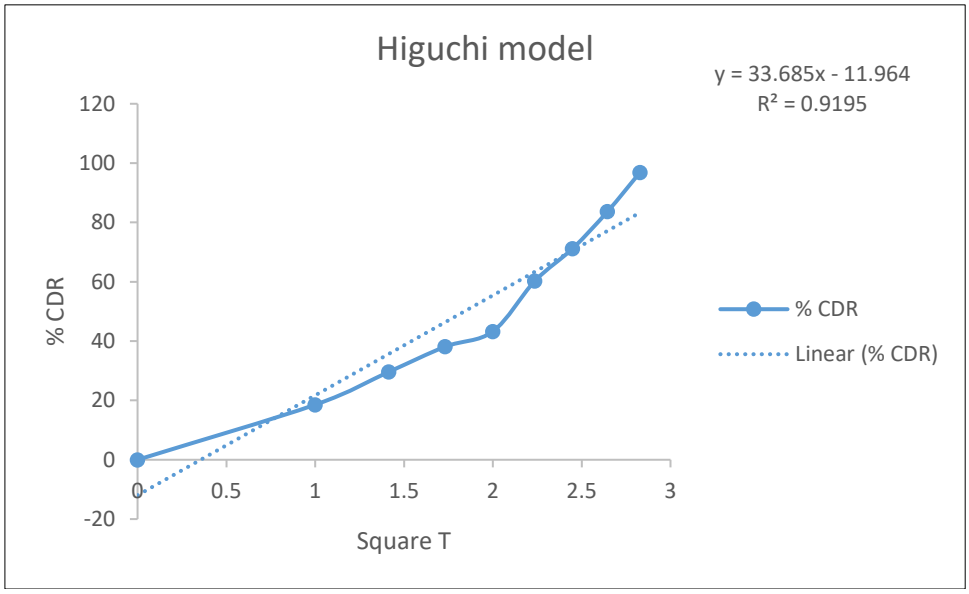

Fig 10: Higuchi model optimized formulation

Korsmeyer Peppas

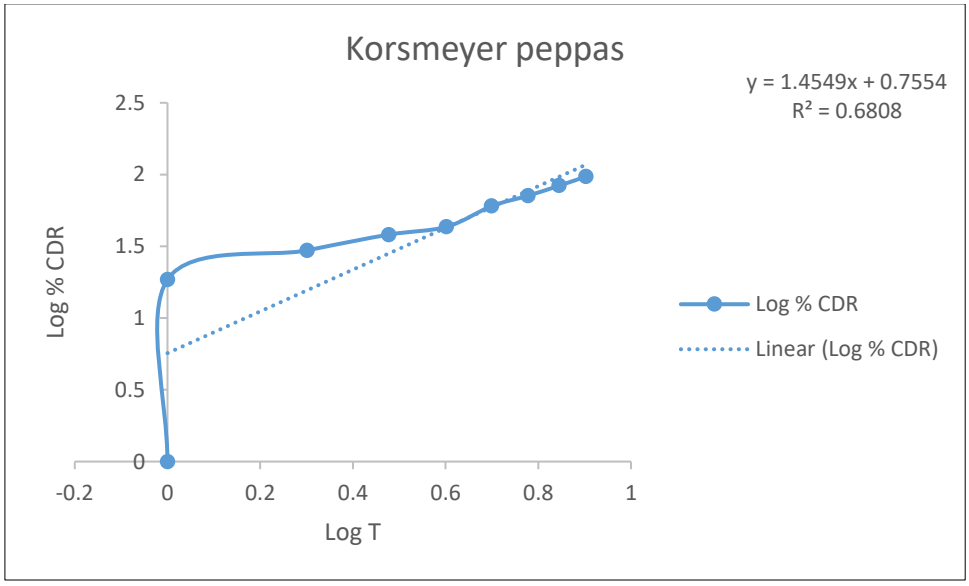

Fig 11: Korsmeyer peppas optimized formulation

The values of *in vitro* release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas were respectively. Regression values are higher with Zero order release kinetics. Therefore, all the Torsemide microspheres Zero order release kinetics. The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation.

Stability studies

There was no significant change in physical and chemical properties of the liposomes of formulation F-5 after 3 months. Parameters quantified at various time intervals were shown;

Table 14: Results of stability studies of optimized formulation F-5

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	25^0C/60%RH % Release	96.86	95.67	94.33	93.35	Not less than 85 %
F-5	30^0C/75% RH % Release	96.86	95.26	94.28	93.15	Not less than 85 %
F-5	40^0C/75% RH % Release	96.86	95.28	94.12	93.02	Not less than 85 %

Conclusion

The study demonstrated that liposomal encapsulation of Vincristine is a promising strategy to overcome limitations of the conventional formulation. Liposomes provided:

- Improved drug entrapment and stability
- Sustained release profile, reducing the frequency of administration
- Potential for enhanced tumor targeting through passive accumulation (EPR effect)
- Reduced systemic side effects by controlling drug distribution

Thus, Vincristine liposomal drug delivery system may offer superior therapeutic efficacy with reduced toxicity, making it a valuable approach for future clinical applications in cancer therapy. Further *in vivo* studies and clinical evaluation are needed to confirm the translational potential of the developed system.

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