Journal or Innovative Development in Pharmaceutical and Technical Science (JIDPTS)
Volume:9, Issue:11, Nov:2026

(J I D P T S)
ISSN(O):2581-6934

FORMULATION AND CHARACTERIZATION OF LIPOSOMAL DRUG DELIVERY SYSTEM FOR QUERCETIN IN CANCER THERAPY

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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 Quercetin in form of lyophilized liposomes. Liposomes have been loaded by Quercetin as a model drug using thin film hydration technique for targeted delivery of this drug. Quercetin containing liposomes with an encapsulation efficiency of 90.05% were prepared, and the in vitro release of Quercetin from the liposomes complied with a first-order kinetic equation. In conclusion, the formulation was optimized, the prepared liposomes had a high Quercetin encapsulation rate and good reproducibility, and their in vitro release had a certain delayed-release effect.

Keywords: Quercetin, Cholesterol, Phosphotidyl choline, FTIR studies, thin film hydration technique, In vitro drug release studies.

INTRODUCTION

LIPOSOMES

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 carrier of preference for the delivery of various potential drug candidates that are lipophilic as well as hydrophilic. Generally, the the liposomes used in clinical practice have the size with diameter in the range of 50 to 300 nm.

Fundamental Structure and Composition

The membranes of liposomal vesicle are linked with the plasma membrane, and are consisting 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 exist in the typical amphiphilic molecular structure. 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. The drugs hydrophilic in nature are enclosed inside 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 bio membranes 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.

History and Advantages

Bangham et al, in 1961 in England, first elucidated the liposomes formation. They initially displayed that when phospholipids are hydrated in an aqueous solution, they impulsively form closed structures. There may be more than one phospholipid bilayer membranes present in these vesicles and depending on the drug's nature, these vesicles are capable of trapping lipid or aqueous drugs. These nanocarriers can offer significant advantages as drug delivery systems which are as fallows.

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- Entirely biodegradable, biocompatible, flexible, nonimmunogenic, non-toxic, drug delivery system for non-systemic and systemic administrations
- Solubility enhancement of amphiphilic and lipophilic drugs
- Increased effectiveness and potency
- To attain active targeting flexibility to pair with site-specific ligands
- For labile drugs superior stability
- Decreased toxicity due to drug targeting properties
- Site avoidance effect resulting in reduced toxicity
- Improved pharmacokinetic effects.

Limitations of Liposomal Delivery

Liposomal mode of drug delivery has some inherent limitations due to the presence of complex multiphasic structure. Some of the key limitations are highlighted below:

- Because of liposomes uptake, there is fast clearance by the reticuloendothelial system
- During storage leakage of an encapsulated drug cause destabilization
- Large scale production and sterilization is not easy
- Batch to batch variation due to multiple-step processing
- High cost of production/manufacturing
- Once administered by SC/IM route, liposomes cannot be removed
- Possibility of dumping, due to faulty administration/ formulation failure
- Low stability as phospholipids has a tendency for hydrolysis and oxidation and thermal degradation

MATERIALS

Quercetin was procured from Aurobindo ltd, Hyd, Cholesterol, Lecithin, Chloroform and DMSO 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 drug and IR spectra was taken for this mixture using ATR-FTIR 4000 (Jasco, Japan) IR Spectrophotometer.

Preparation of liposomes

Method

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 370C 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: composition of lipids for preparation of liposomes

Ingredients	F1	F2	F3	F4
Phosphatidylcholine (mg)	100	100	100	100
Cholesterol(mg)	100	200	300	400
Chloroform (ml)	10	10	10	10
Drug(mg)	10	10	10	10
Phosphate buffer pH 7.4(ml)	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 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 check the uv device for free drug determination. 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 aluminum 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.

RESULTS& DISSUSSION

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.

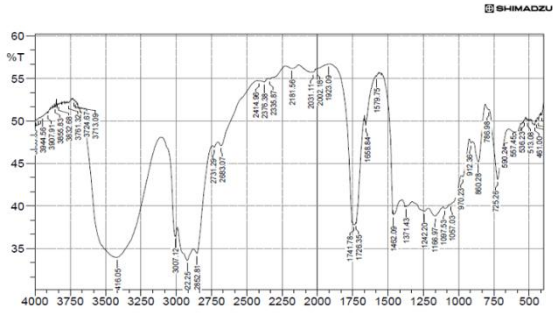


Fig-1: FTIR Studies of Quercetin

Table-2: Characteristic Peaks for Quercetin

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH Bending	1000-1500	1242.20
2	C-H stretching	3000-2500	2852.81
3	C=O stretching	2000-1500	1726.35

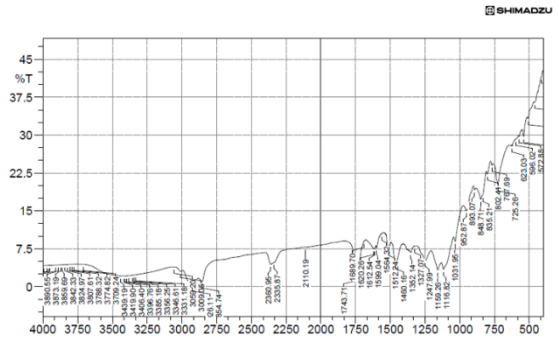


Fig-2: FTIR Studies of optimized formulation

Table-3: Characteristic Peaks for optimized formulation

S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3859.69
2	OH Bending	2500-2000	2360.95
3	C=O stretching	2000-1500	1743.71

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

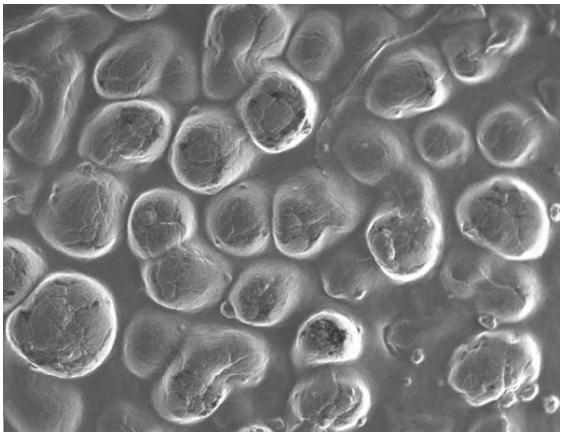


Fig-3: SEM Analysis of Quercetin liposomes

Vesicle size:

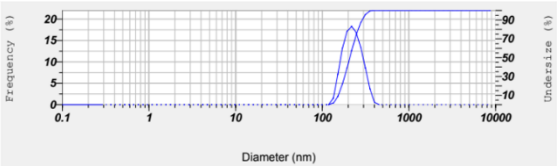


Fig-4: particle size of Quercetin liposomes

Table-4: Mean particle size of different formulation of liposomes

Sr. No	Formulation No.	Particle size
1	F1	198
2	F2	186
3	F3	153
4	F4	190

Drug entrapment efficiency

Table-5: Different batches of liposome made by using different ratio of lipids

Formulation no.	DEE
F1	89.63
F2	85.12
F3	90.05
F4	88.89

The characterization studies demonstrated successful preparation of Quercetin-loaded liposomes with desirable physicochemical properties. SEM analysis confirmed the formation of spherical and uniformly distributed vesicles. Particle size analysis revealed nanosized liposomes ranging from 153–198 nm, with formulation F3 exhibiting the smallest particle size (153 nm). Drug entrapment efficiency studies showed high encapsulation of Quercetin in all formulations, with F3 achieving the highest entrapment efficiency (90.05%). Based on the particle size and entrapment efficiency results, F3 was identified as the optimized formulation. The smaller vesicle size and higher drug entrapment suggest improved stability, enhanced bioavailability, and superior drug delivery performance. Therefore, the developed Quercetin-loaded liposomal formulation holds significant potential as an effective carrier system for improving the therapeutic efficacy of Quercetin.

Drug release studies

Table-6: Cumulative percentage drug release from various formulation of liposomes

Time (hr)	F1	F2	F3	F4
0	0	0	0	0
1	16.39	17.43	18.10	17.82
2	22.10	23.29	28.93	26.91
3	34.10	35.49	38.43	35.60
4	45.96	47.10	48.12	47.43
5	51.26	57.89	59.35	55.18
6	65.39	69.25	68.43	67.83
7	82.20	85.31	86.10	83.50
8	93.69	92.10	97.37	95.58

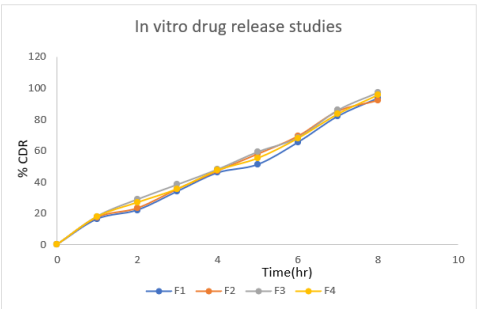


Fig-5: In vitro drug release of (F1-F4) formulations

Formulation F3 were found to release the drug in 8 h. The cumulative percentage release was found to be 97.37 %.

Stability studies

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

Table- 7: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	250C/60%RH % Release	97.37	96.71	95.76	94.78	Not less than 85 %
F-3	300C/75% RH % Release	97.37	96.20	95.20	94.13	Not less than 85 %
F-3	400C/75% RH % Release	97.37	96.13	95.63	94.23	Not less than 85 %

SAMMARY AND 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. Quercetin 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 up to 8 h and more than 97.37% drug released. It shows encapsulation efficiency of 90.05 % and particle size of 153 nm.

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