EJPMR, 2026, 13(7), 336-341 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

FABRICATION AND *IN VITRO* EVALUATION OF LIPOSOME CONTAINING QUERCETIN

Shati Ghosh[1,2], Sudipta Das[1]*, Arnab Samanta[1]

[1]Netaji Subhas Chandra Bose Institute of Pharmacy, Chakdaha, Nadia, West Bengal, India.
[2]International Institute of Pharmaceutical Science and Research, Kalyani, West Bengal, India.

***Corresponding Author: Sudipta Das**

Netaji Subhas Chandra Bose Institute of Pharmacy, Chakdaha, Nadia, West Bengal, India.

DOI: https://doi.org/10.5281/zenodo.21068405

How to cite this Article: Shati Ghosh1,2, Sudipta Das1*, Arnab Samanta1 (2026). Fabrication And In Vitro Evaluation of Liposome Containing Quercetin. European Journal of Pharmaceutical and Medical Research, 13(7), 336–341.

Article Received on 05/06/2026 **Article Revised on 25/06/2026** **Article Published on 01/07/2026**

ABSTRACT

The present work was focused on the preparation and *in vitro* release kinetics of liposomal formulation of quercetin, which was prepared by thin film hydration method. Three batches of liposomes were prepared using varying weight ratio of L-α-phosphatidylcholine and cholesterol. Drug entrapment, *in vitro* drug release, drug release kinetics, and stability studies were used to evaluate the prepared liposomal formulation of quercetin. The *in vitro* release of drug across dialysis membrane reveals slowest rate of drug release from F3 formulation and the fastest release from F1 batch in 4 hours. F1 batch was packed in Eppendorf tube and stored at 4° C temperature for one month. In comparison to other batches, the F1 batch demonstrated the most promising results. The stability studies of the final batch (F1) for one month showed no significant changes.

KEYWORDS: Liposome, Quercetin, Cholesterol, Lecithin, Drug release.

INTRODUCTION

Liposomes are spherical microscopic vesicle in which aqueous portion is entirely enclosed by a lipid bilayer membrane. The phospholipid bilayer membrane have one hydrophobic tail group which is repelled by water and one hydrophilic head group which is attracted to water, forming amphiphilic structure. The hydrous centre of liposome entraps hydrophilic agents whereas the liposomal barrier of phospholipids entraps hydrophobic agents.

Liposomes are suitable for various routes of administration such as parenteral, ocular, pulmonary and transdermal. Liposomes are primarily composed of natural unsaturated phosphatidylcholine, as egg or soybean phosphatidylcholine or synthetic lipids or pure surfactant components like DOPE and cholesterol. Cholesterol modulates membrane permeability, changes fluidity, and improves the stability of bilayer membranes.

Liposome formulation may also contain polymer and membrane proteins to modify their pharmacokinetic properties and improve their bio-distribution profile. The size of the liposome vesicle is an important factor that control circulation half-life. The amount of the encapsulated drug depends upon both the size of the liposomes and number of the bilayer membrane.

Quercetin (QC) is a flavonoid group of drug and it has antioxidant and anti-inflammatory properties. It has ability to suppress cancer growth. Quercetin has shown to have a variety of biological effects, including anti-inflammatory, antiallergenic, antibacterial, anti-proliferative, and anti-tumoral properties. Due to its poor aqueous solubility and physiological instability, it has few applications.

There is a possibility of solubility issue as it belongs to BCS Class IV group. To improve its solubility and intensify pharmacological activity liposomal formulation of Quercetin was prepared by thin-film hydration method.[1,2]

MATERIALS AND METHODS

Quercetin hydrate 95% was procured from Loba Chemie, Mumbai; Soya lecithin and Cholesterol from Yarrowchem Products, Mumbai and Chloroform was purchased from Merck India.

Preparation of liposome by "*Thin film hydration method*"

Soya lecithin and cholesterol, in different weight ratio, were weighed and dissolved in 5 ml chloroform in a round-bottom flask. It was sonicated for few minutes to make the mixture homogeneous. The round bottom flask was placed in a thermostatic water bath and rotated until all the organic solvent was evaporated. Temperature of the water bath was constantly maintained above 42°C (i.e. T_g of the lipid phase) throughout the process. After complete drying, an aqueous solution of drug (100 mg drug in 5 ml distilled water raised to 42°C) was added into the round bottom flask and was shaken thoroughly. The suspension was sonicated for 20 minutes and the suspension was stored in refrigerator and centrifuged at 3500 rpm for 60 minutes. After centrifugation the non-entrapped portion was decanted and fresh liposome was stored and evaluated.[3, 4]

Table 1: Composition of various formulation.

Formulation	Amount of Quercetin (mg)	Amount of Cholesterol (mg)	Amount of Lecithin (mg)	Amount of Chloroform (mL)
F1	100	100	100	5
F2	100	100	200	5
F3	100	100	300	5

Determination of absorption maximum (λ_{max}) of Quercetin

Quercetin, 50 mg, was weighed and taken in a 50 ml volumetric flask. Approximately 1 ml ethanol was added into the volumetric flask and Quercetin was dissolved with the help of a sonicator and the volume was made up to 50 ml with distilled water to prepare a standard stock solution of 1000µg/ml (Stock A). Then stock A solution was diluted to prepare two stock solutions of 100 µg/ml (Stock B) and 10 µg/ml (Stock C). Standard concentration of 10µg/ml was taken in a UV-Spectrophotometer and scanned within 200 to 400nm against a blank of distilled water.[5-10]

***In vitro* drug release study from liposome**

Freshly prepared liposomal suspension of Quercetin was kept for overnight in a refrigerator. The liposomal suspension, 100 mg, was taken in a dialysis membrane that separated the liposomal suspension from receptor medium. The open end of the test tube was covered with a membrane and tied with a thread. The test tube was inverted and immersed in a beaker containing distilled water (100 ml) in such a way that the membrane had just touched the water surface. The beaker was placed in a magnetic stirrer and stirred by magnetic beads. During the procedure temperature of the beaker was maintained at 37 ± 0.5^0C. The study was continued for about 4 hours. Samples were withdrawn from the receptor chamber at every 30 minutes time intervals at the same time fresh medium was also added to keep the volume of the medium constant. The absorbances of the samples were taken in a UV-spectrophotometer at 270 nm against the blank.[11-13]

Determination of drug entrapment in liposomes

Five mL liposomal suspension of Quercetin was taken in a centrifuge tube and centrifuged at 3500 rpm for 1 hour. After centrifugation the supernatant solution was separated (Solution A) and the pellet was resuspended in 3 ml ethanol and sonicated for few minutes to form a clear solution. Distilled water, 7 ml, was added into the solution and mixed thoroughly followed by centrifugation at 3500 rpm for 30 min. The clear supernatant solution (B) was taken out and absorbance was taken by UV-Spectrophotometer at 270 nm against a blank of distilled water. Similarly, the supernatant solution (A) was diluted and the absorbance was measured by UV- Spectrophotometer at 270 nm, against blank.[14-17]

Percentage of entrapment efficiency

It was determined by using the ratio of entrapped drug (mg) to the amount of total drug (mg) used in formulation.

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{The amount of drug entrapped}}{\text{Initial amount of drug taken}} \times 100$$

Optical microscopy

The prepared Quercetin liposomes were photographed under optical microscope of 100X magnification fitted with an eye-piece micrometer.

Surface morphology and particle size

FE-SEM analysis was performed using JEOL MAKE, Model: JSM7500F. The surface morphology was studied under FE-SEM. From Fig. 5 the SEM images of Vildagliptin loaded microsphere shows a spherical shape with a rough, porous surface, and visible cracks, due to mechanical stress or excessive drying. The Figure shows a magnified image with a rough and highly porous surface, indicating a rough texture suitable for enhanced drug entrapment. The por.

Stability test

Prepared liposome formulation was packed in Eppendorf's tube and refrigerated at 4^0 C temperature for one month. At the end of one month the samples were reconstituted and studied for drug release studies and color inspection.[18-22]

RESULTS AND DISCUSSIONS

Absorption maximum (λ_{max}) of Quercetin

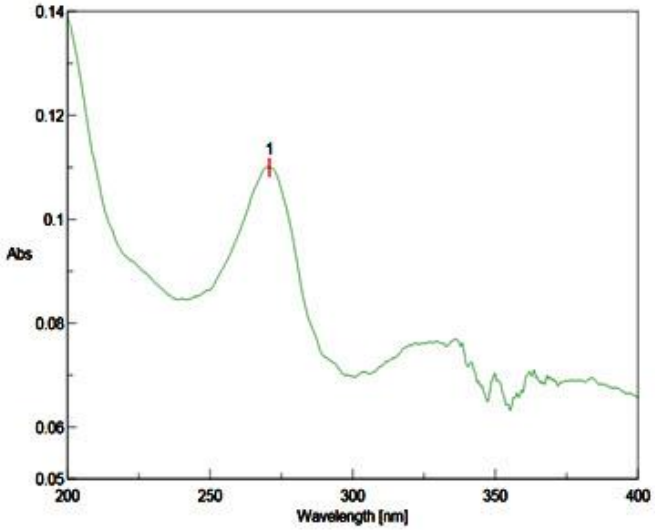

Figure 1: UV-spectrum of Quercetin.

The absorption maximum (λ_{max}) of Quercetin was found at 270nm. All further determination of absorbance of Quercetin solutions were carried out at 270 nm.

Drug Entrapment Study

Table 2: Drug entrapment efficiency (%) of Quercetin liposomes.

Batch No.	Drug Entrapment Efficiency (%)
F1	80.5 ±7.9
F2	81.0 ± 8.3
F3	83.8 ±6.5

Table 2 shows that entrapment efficiency increases with decrease in cholesterol concentration in the lipid phase. F3 formulation contains 25% cholesterol in the lipid phase and it showed highest entrapment efficiency.

In vitro drug release study from liposome

The liposomal suspension was taken in the donor chamber. The drug permeated across the dialysis membrane into the receptor chamber was sampled. The concentration of the drug was estimated by UV-Spectrophotometry. The release profiles of F1, F2 and F3 formulations are plotted in Fig. 2 for comparison.

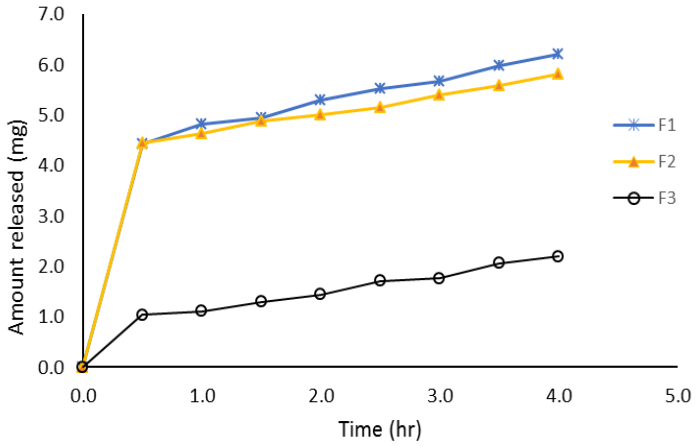

Figure 2: Drug release study of F1, F2 and F3.

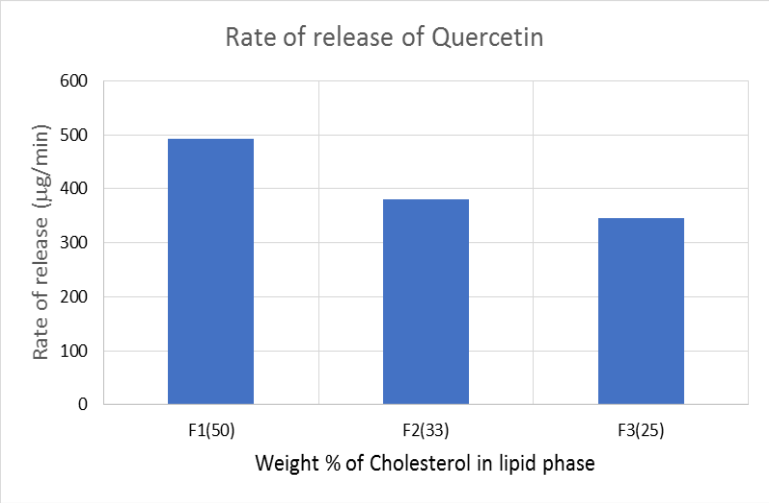

Figure 3: Rate of release (µg/min) of Quercetin from liposomes having different percentages of cholesterol in the lipid mix.

From Fig. 2 it is evident that all the formulations showed an initial burst of drug release within first 30 minutes; after that, the drug was released slowly up to four hours. The release rates were calculated form the slope of Fig.2. The fastest drug release was found with F1 formulation and lowest with F3 formulation. Fig.3 shows that as the cholesterol percentage decreases the rate of release decreases.

Drug release kinetics

Various models of drug release kinetics were tried to fit the release profiles of different formulations – Zero Order, First Order, Higuchi, Hixon-Crowell, Korsmeyers-Peppas in order to determine the probable release models. MS Excel was used to calculate the correlation coefficient (R). R^2 values obtained from various drug release models were compared and found that all the formulations (F1 to F3) were significantly fitting to Zero-order release model [vide Table 3]**.**

Table 3: The Correlation co-efficient (R^2) of various release kinetics models of F1,F2 & F3.

Release Kinetic Model	F1	F2	F3
	R^2	R^2	R^2
Zero Order	0.9781*	0.9665*	0.9873*
First Order	-0.7841	-0.7468	-0.9402
Higuchi	0.9170	0.893	0.9571
Hixon-Crowel	-0.7806	-0.7438	-0.9394
Korsymeyer Peppas	0.7738	0.7379	0.9378

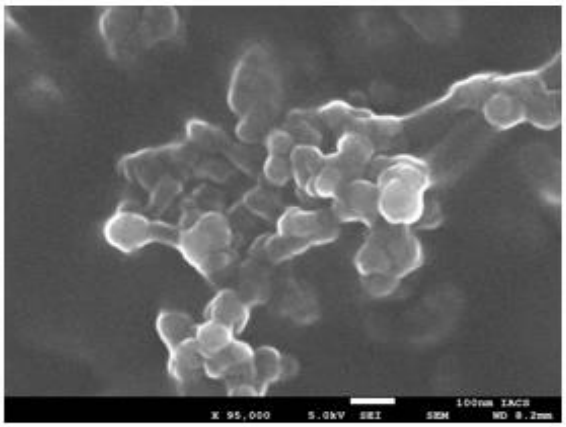

Figure 4: FE-SEM images of formulation (F1).

The FE-SEM analysis was performed using JEOL MAKE, Model: JSM7500F and shown in figure 5.

Stability Study

Formulation F1 was placed in Eppendorf tubes, reconstituted and checked visually for color change and *in vitro* release study was performed up to 6 hours. The overall release percentage was determined to be 83%.

Table 4: Result obtained after undergoing stability study for one month at refrigerated condition (4^0 C).

Time	Batch	Color	Percentage release after 4 hours (n = 3)	Physical properties
0 month	F1	Yellowish green	81.6 ± 8.1	–
1 month	F1	Yellowish green	83.2 ± 6.6	No change

The novelty of this work lies in the modification of phospholipid composition and its direct impact on drug entrapment efficiency, release kinetics, and stability behaviour that govern the therapeutic potential of quercetin-loaded liposomes. Additionally, the study establishes a clear correlation between formulation composition and drug-release mechanism (Zero-model), thereby offering a rational basis and design flexibility for developing both immediate- and sustained-release liposomal systems of Quercetin.

CONCLUSION

In this experiment, all the formulations exhibited acceptable physical characteristics; however, differences in cholesterol concentration in the lipid phase significantly influenced drug entrapment efficiency and release behaviour. The *in vitro* release of drug across dialysis membrane reveals slowest rate of drug release from F3 formulation and the fastest release from F1 batch in 4 hours Among the three batches, Formulation F3 exhibited optimal balance between high entrapment efficiency, prolonged release, and good short-term stability, making it a potential candidate for sustained-release liposomal delivery of quercetin and followed the Zero-order release model. Short-term stability studies over one month demonstrated good formulation stability, suggesting the system's potential feasibility for extended use. Overall, the findings highlight that phospholipid-based liposomes can significantly enhance quercetin entrapment and provide controlled and predictable release characteristics. These formulations require a long-term stability study and more comprehensive research for future development.

ACKNOWLEDGEMENT

The authors express gratitude to the authority of Netaji Subhas Chandra Bose Institute of Pharmacy, Chakdah-741222, Nadia, West Bengal, India for providing the necessary facilities to conduct the study.

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