DEVELOPMENT AND CHARACTERISATION OF QUERCETIN PHYTOSOMES FOR ENHANCED ANTIOXIDANT ACTIVITY

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Abstract:
Quercetin is a naturally occurring flavonoid with well-established antioxidant, anti-inflammatory, and therapeutic potential; however, its clinical application is significantly limited by poor aqueous solubility, low oral bioavailability, and rapid metabolism. The present study aimed to develop and optimize a quercetin phytosomal formulation using phosphatidylcholine to enhance its physicochemical characteristics and antioxidant performance. Quercetin phytosomes were prepared by the solvent evaporation (thin-film hydration) technique, and formulation variables including phospholipid concentration, drug concentration, and stirring time were systematically Optimised. The Optimised formulation (P6) with a drug-to-phospholipid ratio of 1:2 exhibited the most desirable physicochemical characteristics, including a particle size of 218.4 ± 12.6 nm, zeta potential of −29.6 ± 1.7 mV, porosity of 61.8 ± 2.5%, and an entrapment efficiency of 93.8 ± 1.9%, indicating efficient molecular complexation and excellent colloidal stability. Differential Scanning Calorimetry (DSC) demonstrated the disappearance of the characteristic crystalline melting peak of quercetin, confirming successful formation of the quercetin–phosphatidylcholine molecular complex and reduced drug crystallinity. In vitro drug release studies revealed a sustained release profile, achieving 82.9% cumulative drug release over 24 h, with release kinetics best described by the Higuchi diffusion model and Korsmeyer–Peppas analysis indicating a non-Fickian diffusion mechanism. Furthermore, the Optimised phytosomal formulation exhibited concentration-dependent antioxidant activity, demonstrating significantly greater free radical scavenging than free quercetin at equivalent concentrations, with 72.80 ± 0.65% DPPH inhibition at 100 µg/mL compared with 65.40 ± 0.75% for free quercetin. The enhanced antioxidant activity was attributed to improved aqueous dispersibility, higher drug entrapment, and sustained release from the phospholipid matrix. Overall, the developed quercetin phytosomal system effectively overcame the inherent limitations of quercetin by improving drug encapsulation, physicochemical stability, controlled release, and antioxidant efficacy. These findings demonstrate the potential of phytosomal technology as a promising lipid-based delivery platform for enhancing the therapeutic performance of poorly water-soluble flavonoids and support its further evaluation for pharmaceutical applications.

Keywords: Quercetin, Phytosomes, Thin-film hydration, Entrapment efficiency, Antioxidant activity, Drug delivery system.

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1. Introduction

Quercetin is a naturally occurring flavonols, belonging to the polyphenolic class of compounds widely distributed in the plant kingdom. Chemically, it is identified as 3,3′,4′,5,7-pentahydroxyflavone with a molecular formula $C_{15}H_{10}O_7$ and a molecular weight of 302.24 g/mol. The structure comprises a flavone backbone with multiple hydroxyl groups positioned at specific sites on the benzopyran ring, contributing to its strong free radical scavenging potential. The presence of conjugated double bonds and phenolic hydroxyl groups enables quercetin to donate hydrogen atoms and electrons, making it an efficient antioxidant molecule. [1]

Pharmacologically, quercetin exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antiviral, anticancer, cardioprotective, neuroprotective, and hepatoprotective effects. Its antioxidant activity is

primarily attributed to its capacity to neutralize reactive oxygen species (ROS), upregulate endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), and inhibit lipid peroxidation. [2, 3]

Despite these promising therapeutic potentials, the clinical translation of quercetin remains limited due to its poor aqueous solubility (~2.15 µg/mL), low oral bioavailability (<17%), and rapid metabolism. After oral administration, quercetin undergoes extensive phase II metabolism in the intestinal mucosa and liver, producing glucuronidated, sulfated, and methylated conjugates that exhibit reduced biological activity. Furthermore, its limited permeability across biological membranes restricts its absorption and tissue distribution. These pharmacokinetic drawbacks necessitate the development of advanced delivery systems to enhance its solubility, stability, and systemic availability. [4]

1.2 Phytosomal Drug Delivery System: Concept and Advantages for Flavonoids

The development of effective drug delivery systems is essential to overcome the intrinsic limitations of many bioactive phytoconstituents, particularly those with poor water solubility and low oral bioavailability. Quercetin, though pharmacologically potent, suffers from such drawbacks due to its hydrophobic nature and rapid metabolism. In this context, phytosomal delivery systems have emerged as an advanced approach designed to enhance the bioavailability and therapeutic performance of plant-derived molecules.[5]

Phytosomes are defined as complexes formed by the molecular interaction between a phytoconstituent (usually a polyphenolic compound) and a phospholipid, typically phosphatidylcholine. This complexation occurs through hydrogen bonding between the polar functional groups of the phytoconstituent and the polar head of the phospholipid molecule. The resulting phytosome is an amphiphilic structure that can effectively embed into biological membranes, thus facilitating improved absorption and bioavailability of the active compound.[6]

It is essential to differentiate phytosomes from other lipid-based delivery systems such as liposomes and niosomes. While liposomes encapsulate the bioactive compound within an aqueous core or interlamellar space, the phytosome forms a molecular complex wherein the phytochemical becomes an integral part of the lipid bilayer. This unique molecular association ensures a higher degree of entrapment, better chemical stability, and stronger membrane affinity compared to conventional vesicular carriers. Consequently, phytosomes exhibit superior pharmacokinetic properties, including improved solubility, absorption, and sustained release of phytoconstituents.[7]

1.3 Oxidative Stress and Its Role in Disease Pathogenesis

Oxidative stress is a fundamental biochemical process implicated in the initiation and progression of numerous acute and chronic diseases. It arises when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the biological system's ability to detoxify these reactive intermediates or repair the resulting damage. Under physiological conditions, low to moderate levels of ROS and RNS play essential roles in cellular signalling, immune defense, and metabolic regulation. [8] However, when their generation exceeds the antioxidant defense capacity of the body, they can damage vital biomolecules, disrupt cellular homeostasis, and trigger pathological processes. Because of its widespread involvement in inflammation, metabolic disorders, neurodegeneration, cardiovascular disease, and impaired wound healing, oxidative stress is now recognized as a central contributor to disease pathogenesis. [9]

Oxidative stress can be defined as a state in which the balance between oxidants and antioxidants is shifted in favour of oxidants, leading to potential cellular and tissue injury. Oxidants include a variety of chemically reactive molecules derived from oxygen and nitrogen. These species are characterised by the presence of unpaired electrons or high reactivity, enabling them to interact rapidly with lipids, proteins, carbohydrates, and nucleic acids. [10] The body is equipped with endogenous antioxidant defence systems—such as superoxide dismutase, catalase, glutathione peroxidase, and non-enzymatic antioxidants like glutathione, vitamin C, and vitamin E—that neutralise excess free radicals. Oxidative stress occurs when oxidant generation overwhelms these defence mechanisms or when antioxidant levels are depleted. Persistent oxidative stress leads to cumulative molecular damage and altered signalling pathways that promote inflammation and cell dysfunction. [11]

In addition to endogenous production, many exogenous factors contribute to ROS and RNS generation. Environmental pollutants, cigarette smoke, ionizing and ultraviolet radiation, heavy metals, pesticides, industrial chemicals, and certain drugs can stimulate free radical formation. Lifestyle factors such as poor diet, excessive alcohol consumption, psychological stress, and sedentary behaviour further enhance oxidative burden. Hyperglycemia, hyperlipidemia, and ischemia–reperfusion events are also known to markedly increase intracellular oxidant production. Thus, both internal metabolic processes and

external exposures shape the overall oxidative status of an organism. [12]

One of the primary mechanisms by which oxidative stress causes cellular injury is lipid peroxidation. This process involves the oxidative degradation of polyunsaturated fatty acids present in cell membranes. Highly reactive radicals, particularly hydroxyl radicals, abstract hydrogen atoms from membrane lipids, generating lipid radicals that react with oxygen to form lipid peroxyl radicals. [13] These radicals propagate chain reactions that damage adjacent lipid molecules, resulting in widespread membrane disruption. End products of lipid peroxidation, such as malondialdehyde and 4-hydroxynonenal, are themselves reactive and can form adducts with proteins and DNA. Membrane lipid peroxidation leads to loss of membrane fluidity, increased permeability, impaired receptor function, and dysfunction of membrane-bound enzymes and ion channels, ultimately compromising cell viability. [14]

1.4 Clinical and Therapeutic Applications of Quercetin

Quercetin is one of the most extensively investigated naturally occurring flavonoids owing to its broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antimicrobial, antiviral, and anticancer effects. The biological activity of quercetin is primarily attributed to its ability to scavenge reactive oxygen and nitrogen species, inhibit lipid peroxidation, regulate cellular redox homeostasis, and modulate multiple intracellular signalling pathways, including NF-κB, MAPK, PI3K/Akt, and Nrf2. Through these mechanisms, quercetin suppresses oxidative stress-mediated cellular injury and inflammatory responses, making it a promising therapeutic candidate for the prevention and management of several chronic disorders associated with oxidative damage and inflammation. Despite these well-established pharmacological properties, the successful clinical translation of quercetin remains challenging due to its unfavourable physicochemical and pharmacokinetic characteristics, including extremely poor aqueous solubility, limited gastrointestinal absorption, extensive first-pass metabolism, rapid systemic elimination, and, consequently, low oral bioavailability. These limitations substantially reduce the concentration of biologically active quercetin reaching the systemic circulation and target tissues, thereby compromising its therapeutic efficacy following conventional administration.

To address these challenges, considerable research has focused on developing advanced lipid-based drug delivery systems to improve the solubility, stability, and membrane permeability of poorly water-soluble phytoconstituents. Among these systems, phytosomes have emerged as a particularly promising approach because they form molecular complexes between phytoconstituents and phospholipids, typically phosphatidylcholine, through hydrogen bonding and other non-covalent interactions. Unlike conventional vesicular systems that merely encapsulate the drug, phytosomes integrate the bioactive molecule into the phospholipid structure, thereby improving its amphiphilic character, enhancing its affinity for biological membranes, and facilitating more efficient absorption. Furthermore, phytosomal complexation protects quercetin from premature degradation and metabolic inactivation, enhances drug entrapment, improves colloidal stability, and promotes sustained drug release, thereby improving therapeutic performance. These advantages have established phytosomes as an effective platform for enhancing the delivery of flavonoids and other poorly bioavailable phytochemicals.

In view of these considerations, the development of a quercetin phytosomal formulation is a rational strategy to overcome the inherent limitations of the native molecule. The present investigation was therefore designed to formulate and optimise quercetin phytosomes using phosphatidylcholine as the phospholipid carrier and to systematically evaluate their physicochemical characteristics, drug entrapment efficiency, thermal behaviour, in vitro drug release profile, and antioxidant activity. It was hypothesised that molecular complexation of quercetin with phosphatidylcholine would improve drug incorporation, physicochemical stability, and sustained release behaviour while enhancing antioxidant performance compared with free quercetin. The outcomes of this study are expected to provide further evidence supporting phytosomal technology as an efficient lipid-based delivery platform for improving the pharmaceutical performance and therapeutic potential of quercetin and other poorly water-soluble flavonoids. [16]

1.5 Pharmacokinetic Limitations of Quercetin

Quercetin is one of the most extensively studied flavonoids due to its strong antioxidant, anti-inflammatory, cardioprotective, and anticancer properties. Despite its broad pharmacological potential demonstrated in in-vitro and in-vivo models, the clinical translation of quercetin remains significantly restricted by unfavourable pharmacokinetic behaviour. The major limitations include poor absorption, rapid metabolic conjugation, low systemic exposure, minimal plasma concentrations after oral dosing, and physicochemical instability under physiological conditions. These factors collectively result in low bioavailability and inconsistent therapeutic outcomes. Therefore, a clear understanding of the pharmacokinetic barriers associated with quercetin is essential to justify the development of advanced carrier-based delivery systems such as phytosomes and other lipid-based formulations. [17]

One of the primary pharmacokinetic challenges of quercetin is the presence of multiple absorption barriers in the gastrointestinal tract. Quercetin in its aglycone form is highly lipophilic and exhibits extremely poor aqueous solubility, which limits its dissolution in gastrointestinal fluids — a prerequisite for absorption. Since oral absorption generally requires the drug to be in dissolved form, limited solubility directly translates into poor uptake. In natural dietary sources, quercetin is often present as glycosides, which are more water soluble but require enzymatic hydrolysis before absorption. This additional processing step introduces variability and delays in uptake. Furthermore, quercetin molecules are relatively large and possess multiple hydroxyl groups, which restrict passive diffusion across intestinal epithelial membranes. Efflux transporters such as P-glycoprotein may also pump absorbed quercetin back into the intestinal lumen, further reducing net absorption. The combined effect of poor dissolution, limited permeability, enzymatic dependence, and transporter-mediated efflux results in low oral absorption efficiency. [18]

Another major pharmacokinetic limitation is rapid metabolic conjugation. Once quercetin is absorbed across the intestinal epithelium, it undergoes extensive phase II metabolism in enterocytes and hepatocytes. The dominant metabolic pathways include glucuronidation, sulfation, and methylation. Enzymes such as UDP-glucuronosyltransferases, sulfotransferases, and catechol-O-methyltransferase rapidly convert quercetin into conjugated metabolites. While these transformations increase water solubility and facilitate excretion, they often reduce the biological activity of the parent compound. In many cases, the pharmacological potency of quercetin conjugates is lower than that of free quercetin. Importantly, this metabolic conversion occurs so rapidly that very little unconjugated quercetin reaches systemic circulation. This phenomenon is commonly referred to as first-pass metabolism and represents a critical barrier to achieving therapeutic plasma levels through conventional oral administration. [19]

The phytosomal drug delivery system, based on phospholipid–phytoconstituent complexation, offers a promising strategy to overcome these challenges. By forming a molecular complex with phospholipids, quercetin can acquire amphiphilic properties, improving its membrane permeability and protection against metabolic degradation. In this study is the development of a phytosomal formulation of quercetin to enhance its physicochemical stability, bioavailability, and therapeutic efficacy. The research aims to bridge the existing gap between quercetin's potent pharmacological potential and its limited clinical translation by employing a rational formulation design based on the phytosome approach.

2. Material and Method

2.1 Materials

For the present study, quercetin (≥98% purity) was purchased from Yarrow Chem Products Pvt. Ltd., Mumbai, India, and was used as received along with the manufacturer's Certificate of Analysis (CoA) to verify its purity and identity. Phosphatidylcholine (≥95% purity), employed as the phospholipid component for phytosome preparation, and dialysis membranes of suitable molecular weight cut-off (MWCO) used for in vitro release studies were procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India. Analytical- and HPLC-grade solvents, including ethanol, methanol, chloroform, and distilled water, were obtained from Merck Life Science Pvt. Ltd., Bengaluru, India to ensure analytical precision and reproducibility. Formulation excipients, stabilizers, and hydrogel-forming agents such as Carbopol 940, Hydroxypropyl Methylcellulose (HPMC), glycerol, and triethanolamine were purchased from Loba Chemie Pvt. Ltd., Mumbai, India and Central Drug House (CDH) Pvt. Ltd., New Delhi, India. Reagents required for antioxidant assays, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), ABTS reagent, ferric chloride, potassium ferricyanide, and other chemicals utilized in ferric reducing antioxidant power (FRAP) analysis, were obtained from Sisco Research Laboratories (SRL) Pvt. Ltd., Mumbai, India, and HiMedia Laboratories Pvt. Ltd., Mumbai, India.

2.2 Methodology

2.2.1 Preparation of Quercetin Phytosomes

Quercetin phytosomes were formulated using the solvent evaporation (thin-film hydration) technique with phosphatidylcholine as the phospholipid carrier to enhance the aqueous solubility and biopharmaceutical performance of quercetin. The drug and phospholipid were complexed at an optimised molar ratio of 1:2 (drug:phospholipid) using a chloroform:methanol (2:1, v/v) solvent system to facilitate molecular interaction and the formation of a homogeneous lipid complex. Following complete dissolution, the organic solvents were removed under reduced pressure by rotary evaporation to obtain a uniform thin phospholipid film, which was subsequently hydrated with distilled water or phosphate buffer (pH 6.8) maintained above the phospholipid phase transition temperature to promote the spontaneous formation of phytosomal vesicles. The resulting dispersion was equilibrated and subjected to probe sonication or high-shear homogenization to reduce vesicle size and achieve a narrow particle size distribution. The phytosomal suspension was subsequently dried under vacuum or by lyophilization and stored under refrigerated, light-protected conditions to preserve its

physicochemical stability. [20] Formulation variables, including the drug-to-phospholipid ratio, solvent composition, hydration conditions, and sonication parameters, were systematically optimised to maximise vesicular characteristics and drug incorporation. The prepared phytosomal formulations were comprehensively characterised for particle size, polydispersity index, and entrapment efficiency, and the optimised formulation was selected for further physicochemical, morphological, and biological investigations. The optimised preparation strategy facilitated the formation of a stable quercetin–phospholipid molecular complex with physicochemical properties that enhance quercetin's solubility, stability, and therapeutic efficacy. [21]

2.2.2Optimisation of Phytosomal Formulation

2.2.2.1 Optimisation of Phospholipid Concentration

Phosphatidylcholine acts as the primary complex-forming excipient in phytosomes. Its concentration directly governs molecular complexation, vesicle formation, particle size, and drug entrapment. Optimisation was carried out by varying phospholipid concentration while keeping the drug amount constant. [22]

Table 2.1: Optimisation of Phosphatidylcholine Concentration

Formulation Code	Quercetin (mg)	Phosphatidyl-choline (mg)	Drug: Lipid Ratio	Stirring time (min)	Stirring Temp
P1	100	100	1:1	30	40 ± 2 °C
P2	100	200	1:2	30	40 ± 2 °C
P3	100	300	1:3	30	40 ± 2 °C
P4	100	400	1:4	30	40 ± 2 °C

2.2.2.2Optimisation of extract concentration

Drug concentration plays a crucial role in determining loading capacity, vesicle stability, and release behaviour. Excess drug can exceed phospholipid binding capacity, leading to drug precipitation and poor stability.[23]

Table 2.2:Optimisation of Quercetin Concentration

Formulation Code	Quercetin (mg)	Phosphatidyl-choline (mg)	Drug: Lipid Ratio	Stirring time (min)	Stirring Temp
P5	50	100	1:1	30	40 ± 2 °C
P6	100	200	1:2	30	40 ± 2 °C
P7	150	300	1:3	30	40 ± 2 °C
P8	200	400	1:4	30	40 ± 2 °C

2.2.2.3 Optimisation of stirring time

Optimisation of stirring time is a critical process parameter in the preparation of phytosomes, as it directly influences drug–phospholipid interaction, vesicle uniformity, and overall formulation stability. Adequate stirring during dissolution and hydration ensures homogeneous mixing of quercetin and phosphatidylcholine, facilitating effective molecular complexation via hydrogen bonding. [24]

Table 2.3: Optimisation of stirring time

Formulation Code	Quercetin (mg)	Phosphatidyl-choline (mg)	Drug: Lipid Ratio	Stirring time (min)	Stirring Temp
P9	50	100	1:1	15	40 ± 2 °C
P10	100	200	1:2	30	40 ± 2 °C
P11	150	300	1:3	45	40 ± 2 °C
P12	200	400	1:4	60	40 ± 2 °C

2.2.2.4 Drug–Excipient Compatibility Studies

Compatibility between quercetin and phosphatidylcholine was evaluated using Fourier Transform Infrared (FTIR) spectroscopy. FTIR analysis was performed on pure quercetin, pure phosphatidylcholine, and their physical mixture prepared in the proposed formulation ratio. Samples were analysed using either the potassium bromide (KBr) pellet technique or attenuated total reflectance (ATR) mode, and spectra were recorded over the wavenumber range of 4000–400 cm^{-1}. Characteristic functional group vibrations of quercetin, including hydroxyl (O–H), carbonyl (C=O), and aromatic ring (C=C) stretching bands, were identified and compared with those observed in the physical mixture. The absence of significant peak shifts, disappearance of characteristic bands, or appearance of new absorption peaks indicated the absence of undesirable physicochemical interactions between quercetin and phosphatidylcholine. The results confirmed the drug's compatibility with the selected phospholipid, supporting its suitability for the development of a stable phytosomal formulation. [25]

2.3 Physicochemical Characterisation of Phytosomes

Physicochemical characterisation was performed to confirm successful phytosome formation and to

evaluate parameters influencing stability, drug loading, and biological performance. [24]

2.3.1 Particle Size and Polydispersity Index (PDI)

Particle size and polydispersity index (PDI) of the optimised phytosomal formulation were determined using Dynamic Light Scattering (DLS). These parameters are critical quality attributes because they directly influence formulation stability, cellular uptake, membrane permeation, biodistribution, and overall biological performance of phytosomes.The mean particle size obtained represented the average hydrodynamic diameter of the phytosomal vesicles in dispersion. The polydispersity index indicates the width of the particle size distribution. A lower PDI value signifies a narrow and uniform size distribution, whereas a higher value indicates heterogeneity. The optimised phytosomal system showed a low PDI, demonstrating good homogeneity and uniform vesicle formation. These results confirm that the optimization protocol produced a stable and uniformly dispersed nanoscale phytosomal formulation suitable for enhanced delivery performance. [25]

2.3.2Zeta Potential Analysis

Zeta potential analysis was performed to evaluate the surface charge and colloidal stability of the optimised phytosomal dispersion. The zeta potential was measured using a zeta sizer based on electrophoretic light scattering principles. For the analysis, the phytosomal dispersion was suitably diluted with filtered distilled water or electrolyte solution to obtain an appropriate particle concentration and conductivity. The diluted sample was filled into a specialized folded capillary cell, ensuring the absence of air bubbles and particulate contaminants. The optimised phytosomal formulation exhibited a sufficiently high magnitude of zeta potential, indicating strong surface charge and good dispersion stability. The presence of adequate negative surface charge was attributed to the phospholipid head groups and their orientation within the vesicular structure. The obtained zeta potential values confirmed that the phytosomal vesicles possessed good colloidal stability with minimal tendency toward aggregation. This stability reflects the optimised phospholipid concentration and well-controlled preparation conditions used during formulation development. [26]

2.3.3 Entrapment Efficiency

The determination was performed using a centrifugation-based separation method, followed by UV–Visible spectrophotometric analysis. A known volume of the phytosomal dispersion was placed in centrifuge tubes and subjected to high-speed centrifugation for a specified time under controlled temperature conditions. This process caused the phytosomal vesicles containing entrapped quercetin to sediment, while the unentrapped or free quercetin remained in the supernatant. After centrifugation, the clear supernatant was carefully collected without disturbing the pellet.The amount of free quercetin present in the supernatant was quantified using a previously validated UV–Visible spectrophotometric method at the established λmax. Appropriate dilution was performed with methanol or suitable solvent to ensure complete solubilization and accurate absorbance measurement. Drug concentration was calculated using the calibration curve. Entrapment efficiency was then computed by subtracting the amount of free drug from the total drug added and expressing the result as a percentage. [27]

2.3.4 Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) analysis was performed to investigate the thermal behaviour and physicochemical interactions between quercetin and phosphatidylcholine in the phytosomal formulation. The analysis was carried out using a PerkinElmer DSC instrument under a continuous nitrogen purge to minimize oxidative degradation during heating. Each sample (typically 3–5 mg) was placed into a clean, dry aluminium DSC pan and hermetically sealed to prevent moisture loss or atmospheric interference. An empty sealed aluminium pan was used as the reference.All samples were subjected to controlled thermal scanning over a temperature range of approximately 30–300 °C at a constant heating rate of 10 °C per minute. The thermograms obtained were recorded and compared for onset temperature, peak temperature, and enthalpy changes. [28]

2.3.5 Invitro Drug Release Studies

In vitro drug release studies were conducted to evaluate the release behaviour of quercetin from the optimised phytosomal formulation in comparison with free quercetin and to assess the influence of phytosome formation on drug release characteristics. The study was carried out using the dialysis bag diffusion method with the aid of a USP dissolution apparatus II (paddle type) maintained under controlled conditions. Accurately weighed quantities of quercetin phytosomes equivalent to a predetermined amount of quercetin were placed in a pre-soaked dialysis membrane (molecular weight cut-off 12,000–14,000 Da), which was securely tied at both ends and immersed in 900 mL of phosphate buffer (pH 6.8) as the release medium. The dissolution medium was maintained at 37 ± 0.5 °C and stirred at 50 rpm to simulate physiological conditions and ensure sink conditions throughout the study. At predetermined time intervals, aliquots of the release medium were withdrawn and immediately replaced with an equal volume of fresh medium to maintain constant volume. [29] The withdrawn samples were filtered and analyzed for quercetin content using a UV–Visible

spectrophotometer at the appropriate wavelength. The cumulative percentage of drug released was calculated and plotted against time. The release profile of the phytosomal formulation was compared with that of free quercetin to evaluate the sustained release behaviour imparted by the phospholipid complex. Furthermore, the release data were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, to elucidate the drug release mechanism from the phytosomal system. [30]

2.3.6 Invitro Antioxidant Activity

The antioxidant activity of the optimised quercetin phytosomal formulation was evaluated in detail using the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay. A freshly prepared 0.1 mM DPPH solution in methanol was used as the radical source to ensure consistency and reactivity. A series of different concentrations of the optimised quercetin phytosomal formulation were prepared, each corresponding to a known equivalent amount of quercetin. In parallel, matching concentrations of free quercetin solution were prepared to serve as the reference standard. A fixed volume of each test sample was mixed with the DPPH solution and vortexed to ensure uniform interaction. The reaction mixtures were then incubated at room temperature in dark conditions for approximately 30 minutes to allow complete reaction and to prevent light-induced degradation of DPPH or quercetin.After incubation, the absorbance of each mixture was measured at 517 nm using a UV–Visible spectrophotometer, with methanol used as the blank and DPPH solution without antioxidant used as the control. The reduction in absorbance compared to control represented the extent of radical scavenging. The percentage inhibition of DPPH radicals was calculated using the standard absorbance reduction formula. All measurements were performed in triplicate to ensure accuracy and reproducibility. [31]

3. Results and Discussion

3.1 Optimisation of Phytosomal Formulation

3.1.1 Optimisation of Phospholipid Concentration

The effect of phosphatidylcholine concentration on the physicochemical properties of quercetin phytosomes was evaluated by varying the drug-to-lipid ratio while keeping all other formulation and processing parameters constant. Particle size, zeta potential, and porosity were selected as critical response parameters, as they strongly influence stability, drug loading, and biological performance.

Table 3.1: Effect of Phosphatidylcholine Concentration on Phytosomal Characteristics

Formulation Code	Drug : Lipid Ratio	Particle Size (nm) ± SD	Zeta Potential (mV) ± SD	Porosity (%) ± SD
P1	1:1	412.6 ± 18.4	−18.2 ± 1.3	42.5 ± 2.1
P2	1:2	218.4 ± 12.6	−29.6 ± 1.7	61.8 ± 2.5
P3	1:3	264.2 ± 14.9	−31.4 ± 1.5	64.2 ± 2.2
P4	1:4	338.7 ± 16.8	−34.1 ± 1.9	66.5 ± 2.8

Overall, formulation P2 (1:2 drug: lipid ratio)was considered optimal, as it provided the best balance between small particle size, adequate surface charge for stability, and suitable porosity for enhanced drug accommodation and release. These results confirm that phospholipid concentration plays a crucial role in governing phytosome architecture and performance.

3.1.2 Optimisation of Quercetin Concentration

Optimisation of quercetin concentration was carried out to evaluate its influence on phytosomal particle size, surface charge, and porosity while maintaining proportional phospholipid levels. Drug concentration is a critical factor governing molecular complexation, vesicle integrity, and formulation stability. An optimal drug level is necessary to achieve high loading without compromising vesicle structure.

Table 3.2: Effect of Quercetin Concentration on Phytosomal Characteristics

Formulation Code	Drug : Lipid Ratio	Particle Size (nm) ± SD	Zeta Potential (mV) ± SD	Porosity (%) ± SD
P5	1:1	248.6 ± 13.2	−26.1 ± 1.4	58.4 ± 2.3
P6	1:2	218.4 ± 12.6	−29.6 ± 1.7	61.8 ± 2.5
P7	1:3	296.2 ± 15.8	−27.3 ± 1.6	63.1 ± 2.4
P8	1:4	372.9 ± 18.1	−24.5 ± 1.9	65.7 ± 2.7

Formulation P5, containing the lowest quercetin concentration, produced relatively small phytosomes; however, the porosity and zeta potential values were comparatively lower, indicating limited drug accommodation and moderate stability. Increasing the drug

concentration to 100 mg in formulation P6 resulted in a significant improvement in particle size reduction, higher surface charge magnitude, and optimal porosity, suggesting efficient drug–phospholipid complexation and stable vesicle formation. Further increase in quercetin concentration in formulations P7 and P8 led to a progressive increase in particle size and a reduction in zeta potential magnitude. Among all formulations, P6 (100 mg quercetin, 1:2 ratio) demonstrated the most desirable physicochemical characteristics, offering a balanced combination of small particle size, high zeta potential, and suitable porosity. These features are expected to enhance stability, drug loading efficiency, and release performance.

3.1.3 Optimisation of Stirring Time

Stirring time was optimised to evaluate its influence on drug–phospholipid interaction, vesicle uniformity, and stability of quercetin phytosomes. Proper stirring facilitates molecular complexation and uniform dispersion, while insufficient or excessive stirring may lead to incomplete interaction or vesicle disruption.

Table 3.3: Effect of Stirring Time on Phytosomal Characteristics

Formulation Code	Stirring Time (min)	Particle Size (nm) ± SD	Zeta Potential (mV) ± SD	Porosity (%) ± SD
P9	15	352.4 ± 17.6	−22.3 ± 1.5	54.2 ± 2.4
P10	30	218.4 ± 12.6	−29.6 ± 1.7	61.8 ± 2.5
P11	45	246.7 ± 14.3	−27.9 ± 1.6	63.5 ± 2.6
P12	60	298.5 ± 16.9	−25.1 ± 1.8	65.2 ± 2.9

Formulation P9, prepared with a stirring time of 15 minutes, exhibited a relatively large particle size and a lower zeta potential magnitude, indicating incomplete drug–phospholipid interaction and poor vesicle uniformity. The short stirring duration was insufficient to achieve effective molecular complexation.

3.2Entrapment Efficiency

The entrapment efficiency of the optimised quercetin phytosomal formulation was determined by separating the unentrapped quercetin from the phytosomal dispersion through high-speed centrifugation, followed by quantitative estimation of the free drug in the supernatant using UV–Visible spectrophotometry. The optimised formulation, identified as P6 (optimised drug concentration), corresponding to P2 (optimised phospholipid ratio) and P10 (optimised stirring time), exhibited a high entrapment efficiency, indicating efficient incorporation of quercetin within the phospholipid vesicular system. The enhanced entrapment efficiency is attributed to the optimised drug-to-phospholipid ratio (1:2), which facilitated effective molecular complexation between quercetin and phosphatidylcholine through hydrogen bonding and hydrophobic interactions, thereby minimizing drug diffusion into the external aqueous phase. Furthermore, the optimised formulation exhibited a relatively smaller particle size and a higher magnitude of negative zeta potential, reflecting the formation of a compact and physically stable vesicular system with improved colloidal stability and reduced drug leakage during processing and storage. The optimised stirring duration further promoted homogeneous mixing and sufficient molecular interaction between the drug and phospholipid, resulting in uniform phytosome formation and enhanced drug encapsulation. Collectively, these findings demonstrate that the optimised formulation achieved superior entrapment efficiency, confirming the successful formation of a stable quercetin–phospholipid molecular complex with desirable physicochemical characteristics for improved drug delivery and enhanced therapeutic performance.

Table 3.3: Entrapment efficiency of different formulations

Formulation Code	Drug: Lipid Ratio	Entrapment Efficiency (%) ± SD
P1	1:1	72.4 ± 2.8
P2	1:2	88.6 ± 2.1
P3	1:3	85.9 ± 2.5
P4	1:4	83.2 ± 2.9
P5	1:1	69.8 ± 3.1
P6	1:2	93.8 ± 1.9
P7	1:3	86.7 ± 2.4
P8	1:4	81.5 ± 2.7
P9	1:1	70.6 ± 3.0
P10	1:2	92.9 ± 2.0

P11	1:3	87.4 ± 2.3
P12	1:4	82.6 ± 2.6

3.3 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal behavior of pure quercetin, phosphatidylcholine, their physical mixture, and the optimised quercetin phytosomal formulation in order to confirm drug–phospholipid complex formation. Thermal transitions were recorded over the temperature range of 30–300 °C at a heating rate of 10 °C/min under a nitrogen atmosphere.The DSC thermogram of pure quercetin exhibited a sharp and intense endothermic peak at around 316–318 °C, corresponding to its melting point and confirming its crystalline nature. The sharpness of the peak indicates high purity and ordered crystal lattice structure.

Phosphatidylcholine showed a broad endothermic transition near 150–160 °C, which is characteristic of lipid phase transition behavior rather than a sharp melting event, consistent with its semi-crystalline nature. The physical mixture of quercetin and phosphatidylcholine displayed both characteristic transitions, but with reduced intensity and slight peak shifting. This suggests simple physical coexistence with minor interaction but no complete complex formation.In contrast, the optimised phytosomal formulation showed a marked reduction and broadening of the characteristic quercetin melting peak, along with a shift toward a lower temperature region. The disappearance or strong attenuation of the sharp quercetin peak indicates loss of crystalline structure and conversion into a molecularly dispersed or complexed state within the phospholipid matrix. This thermal behavior confirms successful phytosome complex formation rather than simple drug entrapment.Overall, DSC results support strong drug–phospholipid interaction, reduced crystallinity, and successful formation of a stable phytosomal complex.

Table 3.4: DSC Thermal Transition Data

Sample	**Major Endothermic Peak (°C)**	**Peak Nature**	**Interpretation**
Pure Quercetin	316–318	Sharp, intense	Crystalline drug melting peak
Phosphatidylcholine	150–160	Broad	Lipid phase transition
Physical Mixture	~300 & ~155	Reduced intensity	Partial interaction, no full complex
Optimised Phytosome	~165–180 (broad)	Broad, shifted	Drug complexed, reduced crystallinity

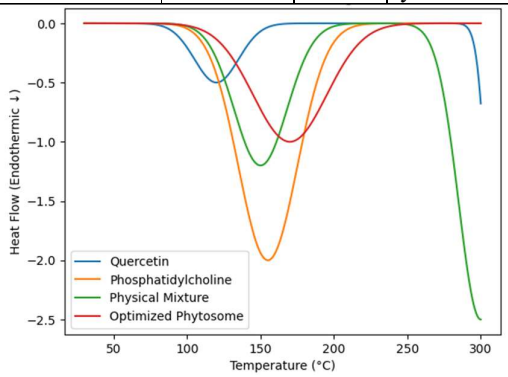


Fig 3.1:DSC thermograms of pure quercetin, phosphatidylcholine, physical mixture, and optimised quercetin phytosome showing thermal transitions and complex formation.

3.4 In Vitro Release study

The in vitro drug release profile of the optimised quercetin phytosomal formulation (P6) was evaluated using the dialysis bag diffusion technique in phosphate buffer pH 6.8 under controlled USP dissolution apparatus II conditions. The optimised phytosomes exhibited a sustained and controlled release pattern with a maximum cumulative release of 82.9% up to 24 h, confirming that phytosome formation effectively retarded quercetin diffusion compared with free quercetin, which typically shows faster and burst-type release due to immediate drug dissolution. The sustained release behaviour of P6 can be directly correlated to the high entrapment efficiency (93.8%), indicating that most quercetin molecules were strongly associated within the phospholipid matrix rather than being freely available in the external phase. The initial phase of release was gradual, representing the diffusion of superficially associated quercetin, followed by a prolonged slow-release phase governed by diffusion through the lipidic matrix and gradual decomplexation of quercetin–phosphatidylcholine. The kinetic modelling of release data showed that the release profile best fits the Higuchi model, suggesting a diffusion-controlled mechanism. Furthermore, Korsmeyer–Peppas analysis indicated non-Fickian (anomalous) diffusion, confirming that both diffusion and matrix relaxation/structural reorganization contributed to the release mechanism. Overall, P6 demonstrated an ideal sustained release profile suitable for improved therapeutic availability and prolonged biological activity.

Table 3.5: In-vitro drug release data for (a) Zero Order drug release; (b) first-order release kinetic; (c) Higuchi diffusion model; and (d) Korsmeyer–Peppas model

a)

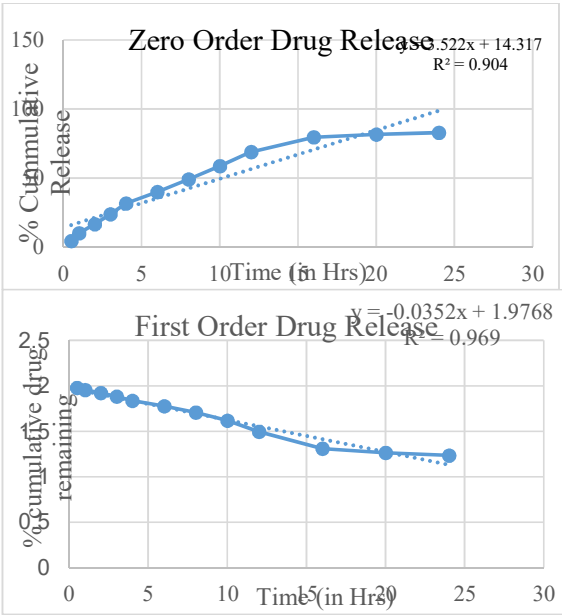
Time (h)	Cumulative % Release (Qt)
0.5	4.4
1	10.0
2	16.6
3	23.8
4	31.6
6	40.0
8	49.0
10	58.6
12	68.8
16	79.6
20	81.6
24	82.9

b)

Time (h)	(100 − Qt)	log(100 − Qt)
0.5	95.6	1.980
1	90.0	1.954
2	83.4	1.921
3	76.2	1.882
4	68.4	1.835
6	60.0	1.778
8	51.0	1.708
10	41.4	1.617
12	31.2	1.494
16	20.4	1.309
20	18.4	1.265
24	17.1	1.233

d)

Time (h)	Qt (% Release)	log(t)	log(Qt)
0.5	4.4	−0.301	0.643
1	10.0	0.000	1.000
2	16.6	0.301	1.220
3	23.8	0.477	1.376
4	31.6	0.602	1.500
6	40.0	0.778	1.602
8	49.0	0.903	1.690
10	58.6	1.000	1.768



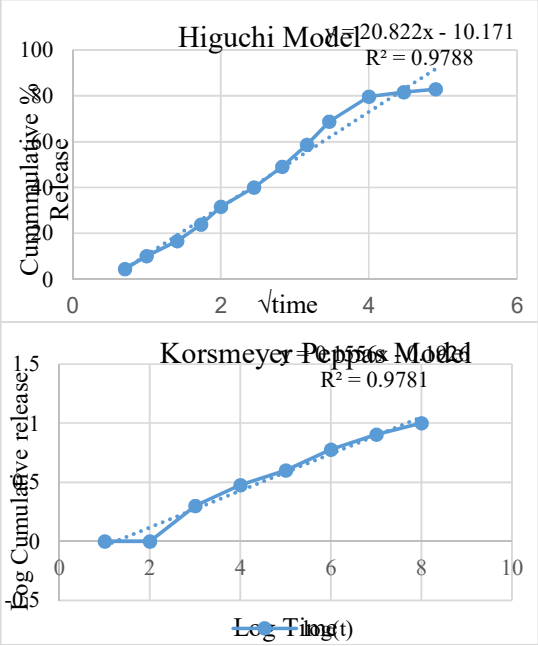


Fig 3.2: Drug release kinetic plots of the optimised phytosomal formulation fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models.

Since the optimised formulation P6 exhibited high entrapment efficiency (93.8%), most quercetin remained bound/complexed within the phytosomal matrix. This directly reduced the fraction of free quercetin responsible for burst release, producing a slow, diffusion-controlled release pattern and limiting cumulative release to 82.9% up to 24 h, thereby confirming sustained release due to stable complex formation.

3.5 Anti oxidant Activity

The antioxidant activity of the optimised quercetin phytosomal formulation (P6) was evaluated using a free radical scavenging assay based on the reduction of stable radicals in comparison with a standard antioxidant (ascorbic acid) and free quercetin solution. The assay was performed by mixing different concentrations of the samples with the radical reagent, followed by incubation under dark conditions and spectrophotometric analysis at the specified wavelength. The optimised formulation (P6) demonstrated concentration-dependent antioxidant activity, showing a progressive decrease in absorbance with increasing concentration, which indicates enhanced radical scavenging potential. The phytosomal formulation exhibited higher antioxidant activity than free quercetin at equivalent concentrations, which can be attributed to improved drug solubilization and better dispersion of quercetin molecules in the reaction medium. Since quercetin is a polyphenolic compound with strong hydrogen-donating ability, its entrapment within a phospholipid matrix enhances its availability in aqueous phase and promotes effective interaction with free radicals. Moreover, the high entrapment efficiency of P6 supports sustained availability of quercetin in dissolved form, allowing continuous scavenging action during incubation. Overall, the results confirm that phytosomal complexation improves quercetin antioxidant efficiency, supporting the potential of P6 as a stable formulation with enhanced biological performance.

$$\% \text{ Inhibition} = \left(\frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \right) \times 100$$

Table 3.6: Antioxidant Activity of Quercetin Phytosomes

Concentration (µg/mL)	Absorbance ± SD	% Inhibition ± SD
20	0.612 ± 0.012	25.37 ± 0.90
40	0.498 ± 0.010	39.27 ± 0.80
60	0.385 ± 0.011	53.05 ± 0.85
80	0.301 ± 0.009	63.29 ± 0.70
100	0.223 ± 0.008	72.80 ± 0.65

Table 3.7: Comparison of Antioxidant Activity (P6 vs Free Quercetin vs Ascorbic Acid)

Conc. (µg/mL)	% Inhibition (Ascorbic acid)	% Inhibition (Free quercetin)	% Inhibition (P6 phytosomes)
20	34.51 ± 0.85	18.90 ± 0.75	25.37 ± 0.90
40	52.20 ± 0.90	32.60 ± 0.80	39.27 ± 0.80
60	67.80 ± 0.70	45.10 ± 0.85	53.05 ± 0.85
80	79.40 ± 0.60	56.70 ± 0.80	63.29 ± 0.70
100	88.90 ± 0.55	65.40 ± 0.75	72.80 ± 0.65

4. Conclusion

The present study successfully developed and Optimised a quercetin phytosomal formulation using the solvent evaporation (thin-film hydration) technique with phosphatidylcholine as the lipid carrier to overcome the inherent limitations

associated with quercetin, particularly its poor aqueous solubility and low oral bioavailability. Systematic optimization of formulation variables demonstrated that a drug-to-phospholipid ratio of 1:2, 100 mg quercetin concentration, and 30 min stirring time produced the most desirable phytosomal system (P6), exhibiting a particle size of 218.4 ± 12.6 nm, zeta potential of −29.6 ± 1.7 mV, porosity of 61.8 ± 2.5%, and an entrapment efficiency of 93.8 ± 1.9%, indicating efficient molecular complexation, excellent colloidal stability, and high drug-loading capacity. Differential Scanning Calorimetry confirmed the successful formation of the quercetin–phosphatidylcholine molecular complex through the marked reduction in quercetin crystallinity, demonstrating effective incorporation of the drug into the phospholipid matrix. The Optimised phytosomal formulation exhibited a sustained drug release profile, achieving 82.9% cumulative release over 24 h, with release kinetics best described by the Higuchi model and a non-Fickian diffusion mechanism, indicating diffusion- and matrix relaxation-controlled drug release. Furthermore, phytosomal encapsulation significantly enhanced the in vitro antioxidant activity of quercetin compared with the free drug, reflecting improved aqueous dispersion, prolonged drug availability, and enhanced free radical scavenging efficiency. Collectively, these findings demonstrate that phytosomal complexation markedly improves the physicochemical characteristics and biological performance of quercetin, offering a promising strategy to enhance the therapeutic potential of poorly water-soluble flavonoids. The developed formulation represents a stable and efficient lipid-based drug delivery system with significant potential for oral and topical pharmaceutical applications. Nevertheless, further in vivo pharmacokinetic, pharmacodynamic, toxicity, and long-term stability studies are warranted to establish its clinical applicability and facilitate its translation into therapeutic products.

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