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Lutein Ester-Loaded Liposomes: Pharmaceutical Potential, Formulations trategies, Characterization and current research perspectives

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Abstract
Lutein is a dietary xanthophyll carotenoid with established relevance to macular pigment biology and growing interest in nutraceutical and pharmaceutical research. Lutein ester, an esterified form of lutein found prominently in marigold (Tagetes erecta), offers useful stability during handling and storage but remainshighly lipophilic and practically insoluble in water. These characteristics can restrict dispersion,gastrointestinal availability and formulation performance. Liposomes provide a versatile lipid-based carrier capable of incorporating hydrophobic molecules within phospholipid bilayers while simultaneously improving aqueous dispersibility and protecting sensitive bioactives from environmental degradation. This review discussesthephysicochemicalandbiologicalcharacteristicsofluteinester,itsmajorsourcesandhealth-related applications, the biopharmaceutical limitations that motivate advanced delivery, and the principles governing liposomal formulation. Particular attention is given to thin-filmhydration, phospholipid–cholesterol composition, vesicle-size reduction, particle-size distribution, zeta potential, entrapment efficiency, morphology, in vitro release and stability evaluation. The dissertation-based formulation work used soylecithin and cholesterol and employed thin-film hydration followed by probe sonication. The optimized formulation reported a particle size of approximately 152.4 nm, polydispersity index of 0.22, zeta potential of approximately −34.7 mV and entrapment efficiency of approximately 81.4%. In vitro release reached approximately 78% at 24 h and was best described by the Higuchi model, while refrigerated stability testing showed only gradual changes in physicochemical characteristics over 90 days. Collectively, the reviewed evidence and dissertation findings support further investigation of lutein ester-loaded liposomes as a platform for improving the formulation performance of this poorly water-soluble carotenoid. However, additional work involving validated analytical methods, comprehensive bioavailability studies, long-term stability, scale-upand appropriate biological models is required before clinical or commercial claims can be made.

Keywords:
luteinester;lutein;liposomes;phospholipid;cholesterol;thin-filmhydration;nanocarrier; entrapment efficiency; controlled release; ocular health

I. Introduction

Carotenoids are naturally occurring pigments with important biological and nutritional functions. They are broadly divided into carotenes and xanthophylls, the latter containing oxygen in their molecular structures. Lutein is a xanthophyll carotenoid that is particularly associated with the retina and macular pigment and has been investigated extensively in relation to visual function, oxidative stress and cognitive health.[1–4] The human body does not synthesize lutein de novo, making dietary intake and supplementation important sources of exposure.[5,6]

Lutein is present in foods such as leafy vegetables, corn and egg yolk, whereas marigold (Tagetes erecta) is a major commercial source for lutein-rich preparations. In plant-derived material, lutein can occur in esterified forms in which hydroxyl groups are linked to fatty acids. Esterification can improve handling and storage characteristics, but the resulting material remains strongly lipophilic and poorly dispersible in aqueous media. The dissertation identifies poor aqueous solubility, high lipophilicity, sensitivity to light, oxygen and heat, and low oral bioavailability as important formulation limitations of lutein ester. Because the performance of a bioactive compound is strongly influenced by solubility, stability andabsorption,lipid-baseddeliverysystemshavereceivedconsiderableattentionforcarotenoids.Liposomesare

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vesicular systems composed principally of phospholipid bilayers and can incorporate hydrophobic molecules within the lipid phase.[7–10] Their structural versatility, biocompatibility and ability to protect encapsulated compounds have supported applications in pharmaceutical and nutraceutical delivery.[11,12]

The present reviewintegrates the literature framework and experimental findings contained in the dissertation, with emphasis on the scientific rationale for lutein ester-loaded liposomes and the formulation, characterization, release and stability parameters relevant to their development.

1. LuteinEster:Chemistry,SourcesandBiopharmaceuticalCharacteristics

Chemicalnatureandsources

Lutein belongs tothe xanthophyllclassofcarotenoids.Freeluteinhasthemolecularformula$C_{40}H_{56}O_2$anda molecular weight of approximately 568.87 g/mol. Its conjugated polyene structure is responsible for its characteristic yellow-orange appearance and its interaction with visible light. Esterification of lutein hydroxyl groups with fatty acids produces lutein esters, including mono- and diesters. The dissertation describes lutein ester as a highly lipophilic material that is practically insoluble in water but soluble in oils and organicsolvents.

Marigold flowers are described in the dissertation as the principal commercial source of lutein ester. Other dietary sources include spinach, kale, broccoli, corn, egg yolk and selected fruits and vegetables, although these sourcesgenerallyprovide free luteinrather thantheconcentratedesterifiedmaterial usedfor commercial extraction. The biological availability of carotenoids is affected by food matrix, lipid environment, digestion and absorption processes.[13,14]

Physicochemicalpropertiesrelevanttoformulation

The formulation behavior of lutein ester is dominated by its hydrophobicity and chemical sensitivity. The dissertation reports practical insolubility in water, high lipophilicity, strong absorption in the approximately 445–450 nm region and susceptibility to light, oxygen and heat. These characteristics create several formulation challenges: poor aqueous dispersion, potential degradation during processing and storage, and dependence of intestinal uptake on lipid-mediated dispersion and digestion. Carotenoid bioavailability is known to be influenced by physicochemical properties, food matrix, lipid composition and gastrointestinal processes.[13,14]

For a formulation scientist, these limitations create a clear delivery objective: maintain lutein ester in a protected lipid environment while generating a sufficiently fine aqueous dispersion for administration and subsequent interaction with gastrointestinal fluids. Liposomal encapsulation is therefore mechanistically attractive because the hydrophobic carotenoid can partition into the phospholipid bilayer rather than requiring molecular dissolution in water.

2. BiologicalandTherapeuticRelevanceof Lutein

Ocularrelevance

Lutein and zeaxanthin are major components of the macular pigment and contribute to optical filtering and protection of retinal tissues.[3,4,15] The macular pigment absorbs short-wavelength visible light and is associated with protection against photo-oxidative stress. Observational and clinical research has examined relationships between carotenoid intake, macular pigment characteristics and visual outcomes.[16–18] The AREDS2 trial also evaluated lutein plus zeaxanthin as part of a large clinical investigation of nutritional supplementation in age-related macular degeneration.[19]

The evidence supports an important distinction between biological plausibility and therapeutic proof. Lutein has a well-established nutritional and physiological role, while the magnitude of benefit fromsupplementation varies with population, formulation, baseline status and clinical endpoint. Therefore, a formulation that improves dispersion or bioavailability should be evaluated with appropriate pharmacokinetic and clinical endpoints rather than assuming that improved physicochemical performance automatically produces clinical benefit.

Antioxidantandbroaderbiologicalactivities

Carotenoids can participate in antioxidant processes and interact with reactive oxygen species and lipid oxidation pathways.[1,2] The dissertation describes antioxidant, anti-inflammatory, neuroprotective, cardioprotective, hepatoprotective, photoprotective and immunomodulatory activities associated with lutein. Experimental findings in these areas provide a rationale for continued investigation, but the strength of evidence differs substantially

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among indications. The most mature biological context for lutein remains ocular and nutritional research, whereas many systemic applications remain investigational.

Lutein has also attracted interest in cognitive health because it is detected in neural tissues and has been investigated in relation to cognitive performance.[6,20] These observations support continued research into delivery systems capable of improving exposure, but they should not be interpreted as proof that lutein ester liposomes treat neurodegenerative or systemic disease.

3. BiopharmaceuticalLimitationsofLuteinEster

The major formulation limitations identified in the dissertation can be summarized as: (i) very low aqueous solubility; (ii) high lipophilicity; (iii) susceptibility to light-, oxygen- and heat-associated degradation; (iv) limited aqueous dispersion; and (v) potentially low and variable oral bioavailability. Carotenoid absorption is complex and depends on release from the food or dosage-form matrix, incorporation into mixed micelles during digestion, uptake by intestinal cells and subsequent transport.[13,14]

Conventional tablets or capsules can therefore face difficulties in delivering a reproducible dispersed dose of lutein ester. Lipid-based delivery systems, including liposomes, nanoemulsions and lipid nanoparticles,provide different approaches to overcoming these barriers.[21,22] Among these systems, liposomes are particularly relevant when the objective is to retain a lipophilic bioactive within a phospholipid membrane while creating an aqueous dispersion.

4. LiposomesasDeliverySystems

Structureandmechanism

Liposomes are closed vesicles formed by one or more phospholipid bilayers surrounding an aqueous compartment. Their amphiphilic structure enables hydrophilic compounds to be associated with the aqueous core and lipophilic compounds to partition into the bilayer.[7,8]This dual-loadingcapability, together with the ability to modify size, composition, surface charge and lamellarity, makes liposomes adaptable carriers for pharmaceutical and nutraceutical compounds.[9–12]

The use of liposomes in drug delivery originated from observations of phospholipid self-assembly and subsequently developed into a broad pharmaceutical technology.[7,23] Improvements in preparation methods, lipid composition and surface modification have enabled control over vesicle size, stability, drug retention and release. Cholesterol is commonly incorporated into liposomal membranes to influence lipid packing,membrane rigidity and permeability, thereby affecting drug retention and physical stability.[7,9]

Advantagesforluteinester delivery

Lutein ester is well suited to a hydrophobic lipid domain. When incorporated into the phospholipid bilayer, it can be maintained in a lipid-compatible environment while the overall formulation is dispersed in an aqueous phase. The lipid membrane can also provide a degree of protection from external environmental conditions. Previous studies summarized in the dissertation describe improved stability, retention, antioxidant activity or bioaccessibility for lutein-containing liposomal systems.[24–26]

The expected advantages are therefore formulation-specific rather than automatically therapeutic: improved aqueous dispersibility, protection from environmental degradation, efficient incorporation into the lipid phase, potential controlled release and improved conditions for gastrointestinal processing. These properties shouldbe confirmed experimentally for each formulation because lipid composition, carotenoid loading, processing conditions and storage environment can materially change liposome performance.

5. LiposomalFormulationApproachesforLutein

Thin-filmhydration

Thin-film hydration, historically associated with the Bangham approach, is one of the most widely used laboratory methods for preparing liposomes.[7,27] In the dissertation, lutein ester, soy lecithin and cholesterol are dissolved in an organic solvent system. Solvent removal under reduced pressure produces a thin lipid film, which is subsequently hydrated with phosphate-buffered saline. Hydration generates multilamellar vesicles, followed by probe sonication to reduce vesicle size and improve dispersion.

The method is attractive because lipid composition can be varied systematically and the incorporation of a highly lipophilic compound into the bilayer is conceptually straightforward. However, scale-up, residual-solvent control, reproducibility of film hydration and control of vesicle size require

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careful process development. Alternative methods such as reverse-phase evaporation, solvent injection, ethanol injection, microfluidization and membrane-based methods can provide different control over size and encapsulation.[7,23,28]

Roleofsoylecithinandcholesterol

Soy lecithin was selected in the dissertation as the primary phospholipid because of its amphiphilic character and bilayer-forming capacity. Cholesterol was included as a membrane-stabilizing component. In general,lipid composition influences bilayer packing, membrane fluidity, permeability and retention of hydrophobic compounds. The ratio between phospholipid and cholesterol is therefore a critical formulation variable rather than a fixed universal value.

The dissertation investigated changes in phospholipid and cholesterol concentrations and used particle size, PDI, zeta potential, entrapment efficiency and stability as practical optimization criteria. This approach is consistent with the broader principle that liposome development requires simultaneous consideration of composition and process parameters rather than optimization of a single response.

6. CriticalQualityAttributesandCharacterization

Particlesizeandpolydispersityindex

Particle size is a major determinant of dispersion behavior, physical stability and biological performance. Dynamic light scatteringiswidelyused for hydrodynamic size and PDImeasurement in colloidal systems.[29] A lower PDI generally indicates a narrower size distribution, although interpretation should consider the measurementmethod,sampleconcentrationandformulationcomposition.Inthedissertation,theoptimized formulationshowed aparticlesize ofapproximately152.4 ± 6nmand a PDIof approximately0.22, indicating a nanoscale dispersion with comparatively narrow size distribution.

Zetapotential

Zeta potential provides information related to the electrokinetic behavior of dispersed vesicles and can help in assessing colloidal stability. The dissertation reported a zeta potential of approximately −34.7 mV for the optimized formulation. This negative surface potential was interpreted as providing electrostatic repulsion between vesicles. Zeta potential should nevertheless be considered together with steric effects, lipid composition, ionic strength and storage conditions rather than used as a stand-alone predictor of long-term stability.[29]

Entrapmentefficiencyanddrugloading

Entrapment efficiency quantifies the fraction of the added lutein ester associated with the liposomal system. Because lutein ester is strongly lipophilic, partitioning into the hydrophobic bilayer can favor high incorporation. The dissertation reported approximately 81.4% entrapment efficiency for the optimized formulation. The observed value should be interpreted in the context of the separation method, analytical recovery and formulation composition, because incomplete separation of free drug or analytical losses can influence the calculated result.

Morphologyandstructuralevaluation

Electron microscopy can provide complementary information on vesicle morphology and structural integrity. The dissertation used SEM/TEM as morphological tools and reported intact vesicular structures for the optimized formulation. Morphological data are particularly useful when interpreted alongside particle-size measurements because microscopy and dynamic light scattering measure different physical aspects of a dispersion.

Drug–excipientcompatibility

FTIR spectroscopy was used in the dissertation to compare characteristic lutein ester bands in the pure material,physical mixtureandoptimizedformulation.Thereportedspectraretainedtheprincipal characteristic bands without major disappearance or substantial shifts, supporting the absence of an obvious chemical incompatibilityunderthe conditions tested. FTIRis best viewed as a compatibility-screeningtool and does not by itself establish complete chemical stability or molecular-level absence of interaction.

Invitro release

Thedissertation evaluatedrelease usinga dialysis-membrane approach in phosphate buffer at 37± 0.5 °Cwith sampling over 24 h. The optimized liposomal formulation exhibited approximately 78% cumulative release at 24 h, whereas free lutein ester released approximately 92% within 6 h under the reported test conditions. The slower release from the liposomal system is consistent with diffusion through and partitioning within the

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lipid bilayer.
Mathematical modeling showed the highest reported coefficient of determination for the Higuchi model (R^2 = 0.986), followed by the Korsmeyer–Peppas model (R^2 = 0.981), first-order (R^2 = 0.945) and zero-order (R^2 = 0.912). The reported Korsmeyer–Peppas exponent of n = 0.58 was interpreted as indicating anomalous/non-Fickian transport. Higuchi-type behavior is commonly associated with diffusion-controlled release from matrix-like systems.[30–33] However, kinetic-model fitting should be treated as supportive mechanistic evidence rather than definitive proof of the molecular release mechanism.

7. EvidencefromPreviousLuteinLiposomeResearch

The dissertation literature review describes a progression from early lipid-based lutein systems to increasingly specialized liposomal platforms. Early work investigated lutein proliposomes and liposomes for improving dispersibility and stability. Comparative studies of carotenoid-loaded liposomes reported that lutein could be incorporated into phospholipid membranes and that lipid composition and lutein concentration influenced membrane organization, retention and stability.[24,25]
Later studies summarized in the dissertation investigated approaches such as supercritical-fluid-assisted processing, polypeptide-decorated nanoliposomes, cationic liposomes, chitosan-coated systems, stigmasterol-stabilized liposomes and brain-targeted surface-modified liposomes. These studies collectively illustrate that formulation performance can be modified by processing method, lipid composition and surface engineering. Importantly, most of these studies concern lutein rather than specifically lutein ester, supporting the dissertation's identification of a formulation-development gap for lutein ester-loaded liposomes.
The literature also indicates that lipid encapsulation can improve the stability and antioxidant performance of lutein-containingsystems.
Tanandcolleaguesreportedliposomaldeliveryofcarotenoids,includinglutein,and subsequent work examined protection of lutein by liposomal encapsulation.[24–26] These studies provide a scientific basis for using a phospholipid bilayer as the carrier environment, while also demonstrating that formulation composition must be optimized rather than assumed to be interchangeable across carotenoids.

8. Dissertation-BasedFormulationFindings

Thedissertationinvestigatedluteinester-loadedliposomes usingsoylecithinandcholesterol,preparedbythin-film hydration followed by probe sonication. Preliminary formulations varied the quantities of lecithin and cholesterolwhilemaintainingtheluteinesterquantity. Theformulationwasoptimizedusingparticlesize,PDI , zeta potential, entrapment efficiency and physical stability as principal criteria.

Parameter	Optimizedformulationfinding
Particlesize	Approximately152.4±6nm
Polydispersityindex	Approximately0.22
Zetapotential	Approximately−34.7mV
Entrapmentefficiency	Approximately81.4%
Cumulativerelease	Approximately78%at24h
Releasemodel	Higuchimodel;R^2=0.986
Korsmeyer–Peppasexponent	n=0.58
Storageevaluation	Refrigeratedstorage;gradualchangesover90days

The dissertation contains an internal inconsistency in naming the optimized batch: one results section refers to F4, whereas the summary identifies F7 as the optimized formulation. The numerical characteristics reportedfor the optimized formulation are otherwise presented consistently around approximately 152.4 nm particle size, 0.22 PDI, −34.7 mV zeta potential and 81.4% entrapment efficiency. For a journal manuscript, the final batch designation should be reconciled against the original laboratory record and formulation table before submission. This correction is important because a journal-ready manuscript should contain one unambiguous formulation code throughout.
The stability study reported gradual increases in particle size from 152.4 nm at day 0 to 168.3 nm at day 90and PDIfrom 0.22 to 0.28,together with gradual reductions in zeta potential and entrapment efficiency. These changes suggest some time-

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dependent evolution of the dispersion, although the dissertation considered the formulation to retain acceptable physicochemical characteristics during refrigerated storage. Formal stability conclusionsshouldbelimited to thetestedstorage conditionandstudyduration and shouldnotbeextrapolated to long-term shelf life without appropriate stability data.

Theformulationfindings are consistent withthecentral deliveryhypothesis: ahighlylipophiliccarotenoid can be incorporated into a phospholipid vesicular system, producing a nanoscale aqueous dispersion with measurable drug retention and sustained release. Nevertheless, the present data demonstrate formulation feasibility and in vitro performance; they do not by themselves establish enhanced in vivo bioavailability or therapeutic efficacy.

9. Formulation Development Considerations

Quality-by-designperspective

A systematic development program should define the target product profile and identify critical material attributes and critical process parameters. For lutein ester liposomes, relevant variables include phospholipid identity and concentration, cholesterol level, drug-to-lipid ratio, organic-solvent composition, film-formation conditions, hydration conditions, sonication energy and time, temperature, and storage environment.Responses should include particle size, PDI, zeta potential, entrapment efficiency, drug content, release behavior and stability.

Rather than selectingan optimumfroma small number oftrial batches alone,future studies coulduse aformal design-of-experiments strategy to quantify main effects and interactions. Such an approach would beespecially useful for determining whether increases in phospholipid concentration improve entrapment at the expense of particle size, or whether cholesterol improves retention while altering membrane rigidity and release kinetics.

Analyticalconsiderations

Reliable quantification of lutein ester is essential because entrapment efficiency, drug content and release data all depend on analytical recovery. UV-visible spectroscopy provides a practical screening method because lutein has strongvisible-region absorption, but chromatographic methods such asHPLCcan provide improved specificity when degradation products, isomers or complex lipid matrices are relevant. Analytical method validation should address specificity, linearity, accuracy, precision, range, robustness and solution stability before the method is used to support publication-quality quantitative claims.

Stabilityandpackaging

Lutein-relatedcompoundsaresensitivetoenvironmentalconditions,makingprotectionfromlight, oxygen and heat important. The dissertation appropriately emphasizes light-protected storage. A more comprehensive development programshouldevaluatephysicalstability,chemical assay,degradationproducts,lipidoxidation, vesicle-size distribution and drug leakage under long-term, accelerated and photostability conditions as appropriate. ICH stability principles can provide a framework for study design, although the exactrequirements depend on the intended product category and regulatory pathway.[34–36]

10. ResearchGapsandFutureDirections

Several research gaps remain before lutein ester-loaded liposomes can be considered a fully developed pharmaceutical or nutraceutical product. First, the dissertation is primarily an in vitro formulation study, so in vivo pharmacokinetic confirmation is needed to determine whether improved dispersion and sustained release translateintogreatersystemicortissueexposure.Second,therelationshipbetweenliposomaldeliveryand retinal lutein accumulation requires direct investigation rather than inference from physicochemical characterization alone.

Third, the distinction between lutein and lutein ester should remain explicit in future research. Much of the published liposome literature concerns free lutein, whereas the formulation investigated in the dissertation specifically uses lutein ester. Hydrolysis, digestion, intestinal uptake and conversion therefore deserve dedicatedstudy. Fourth,scale-up shouldbeevaluatedbecauselaboratorythin-filmhydrationcanbedifficultto translate directly into large-scale manufacturing with identical vesicle characteristics. Continuous orintensified processes may provide improved control over batch-to-batch variability.

Finally, future work should integrate formulation science with biologically relevant endpoints. Potentialstudies include simulated gastrointestinal digestion, cellular uptake, permeability, antioxidant assays using validated protocols, pharmacokinetic studies, tissue-distribution studies

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and, where scientifically justified, ocular models. These studies should be designed to answer specific translational questions rather than simply generating additional characterization data.

11. Conclusion

Lutein ester combines substantial biological interest with formulation challenges arising from high lipophilicity, poor aqueous solubility and sensitivity to environmental degradation. Liposomes offer a rational lipid-based strategy because their phospholipid bilayers provide a compatible environment for hydrophobic carotenoids while enabling dispersion in an aqueous vehicle. The dissertation demonstrates the feasibility of preparing lutein ester-loaded liposomes using soy lecithin, cholesterol, thin-film hydration and probe sonication. The reported optimized formulation showed nanoscale particle size, comparatively narrow size distribution, a negative zeta potential and approximately 81.4% entrapment efficiency, together with sustained in vitro release and acceptable refrigerated stability over the investigated period.

The literature and dissertation findings together establish a strong formulation-development rationale but should be interpreted within the limits of the available evidence. Improved physicochemical properties and in vitro release do not automatically establish improved oral bioavailability, retinal delivery or clinical efficacy.

Futurestudiesshouldthereforeemphasizevalidatedquantitativeanalysis,systematicformulationoptimization, gastrointestinal and pharmacokinetic evaluation, long-term stability, scale-up and reproducibility. With these additional investigations, lutein ester-loaded liposomes may provide a useful platformfor further development of lutein-based nutraceutical and pharmaceutical delivery systems.

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