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Sathish Kumar S
Undergraduate Research Scholar, GRD College of Pharmacy, Thiruvallur, Affiliated to the Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Dhanesh Kumar MR
Assistant Professor, Dept. of Pharmaceutics, GRD College of Pharmacy, Thiruvallur, Affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Suganya K
Assistant Professor, Dept. of Pharmaceutics, GRD College of Pharmacy, Thiruvallur, Affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Saravana Velu K
Undergraduate Research Scholar, GRD College of Pharmacy, Thiruvallur, Affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Udhaya Kumar M
Undergraduate Research Scholar, GRD College of Pharmacy, Thiruvallur, Affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Dhakshesh S
Undergraduate Research Scholar, GRD College of Pharmacy, Thiruvallur, Affiliated to The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Corresponding Author:
Sathish Kumar S
Undergraduate Research Scholar, GRD College of Pharmacy, Thiruvallur, Affiliated to the Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India

Oleosomes: An emerging drug carriers and stability enhancer of natural products

Sathish Kumar S, Dhanesh Kumar MR, Suganya K, Saravana Velu K, Udhaya Kumar M and Dhakshesh S

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Abstract
Oleosomes are submicron oil entities with remarkable interfacial stability, oxidative resistance and biocompatibility. They are made up of a triacylglycerol core covered by a phospholipid monolayer where proteins are embedded. For highly lipophilic substances their architecture allows for solvent-free extraction, self-emulsification and high efficieny. By facilitating targeted delivery techniques like magnetically guided chemotherapy and improving oral bioavailability through lymphatic uptake, oleosomes considerably lower the tumor burden *in vivo*. Recent developments in oleosome research, such as botanical sources, green extraction techniques, interfacial engineering, pharmacokinetics and therapeutic uses in metabolic disorders, cancer, dermatology and regenerative medicine are covered in this review. Strategies like hybrid oleosome-liposome systems and modified oleosins are being used to solve major problems such poor hydrophilic drug loading, allergenicity, and regulatory concerns.

Keywords: Oleosomes, Drug Delivery, Natural Oil, Liposomes, Drug Carrier, Chemotherapy

Introduction
Oleosomes, act as adaptable colloidal carriers for a range of goods in the food, pharmaceutical, cosmetic, and nutraceutical industries. They are structurally composed of a triacylglycerol (TAG) core that is encased in a phospholipid monolayer that contains stabilizing oleosin proteins. Up to 60% of the oil in seeds can be stored in an aqueous environment because to these oleosins. Typically, oleosomes are between 0.65 and 2.0 µm in size, with surface components making about 1-4 weight percent and TAG making up 94-98 weight percent of the droplet. They have a net negative charge at physiological pH, as indicated by their isoelectric point, which is typically between pH 5.7 and 6.6 [1, 2].

Over the course of five days, curcumin exhibits rapid intra-oleosome diffusion without compromising droplet size and may be loaded into rapeseed oleosomes with an encapsulation efficiency of 97-98%. Through improved intestinal absorption and avoiding first-pass metabolism, these oleosomes increase rats' systemic exposure to cannabidiol. Furthermore, in breast cancer models, magnetically responsive, antibody-targeted oleosomes show a roughly 70% decrease in tumor burden, underscoring their potential for translation [3].

The selection of botanicals and interfacial engineering can alter oleosome performance; for example, oleosomes made from high-oleic rapeseed and hazelnut provide excellent oxidative stability, whereas oleosomes made from omega-3-rich chia and flaxseed require additional antioxidants. The qualities of biopolymers, such as salt, pH, and temperature endurance are improved by using layer-by-layer coatings; these features are crucial for topical and medicinal applications [4].

Clinically significant allergens, represented by oleosins (15-26 kDa), are present in peanut and soybean oleosomes. IgE immunoblots/ELISA, basophil activation assays, processing stability tests and cross-reactivity screenings should all be included in an allergenicity test. CRISPR/Cas editing can alter oleosin loci to remove IgE-binding motifs while maintaining the hydrophobic hairpin structure, reducing the risk of allergies in medications. Furthermore, addressing GRAS food usage restrictions, recombinant production of modified low-allergen oleosins in microbial or plant systems may yield allergen-free oleosomes for secure medication administration [5, 6].

Composition and Structure

Oleosomes are intracellular lipid droplets that range in size from 0.2 to 2 µm. They are made up of a hydrophobic TAG core and a phospholipid monolayer that is about 9 nm thick and contains phosphatidylcholine and phosphatidylserine. Oleosins are the main stabilizers among the three essential protein groups found in them: caleosins, steroleosins, and oleosins. Charged termini extend into the aqueous environment to provide steric hindrance and electrostatic repulsion, preventing coalescence, while a hydrophobic hairpin anchors into the TAG core. The integrity of the oleosin interface has a major impact on the stability of oleosomes since the removal of the hydrophilic termini reduces the emulsifying power and stability [7].

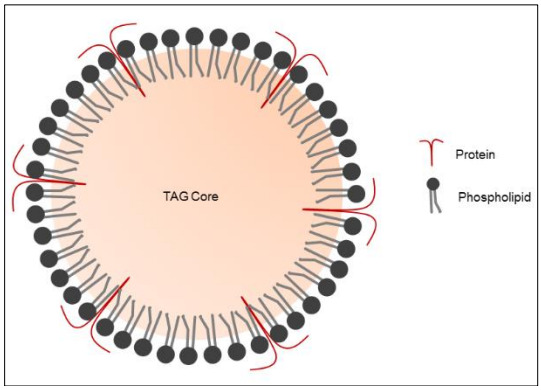

Fig 1: Structural Representation of Oleosomes

When interfaces are preserved, oleosomes with native interfacial proteins and co-encapsulated antioxidants show notable physical and chemical stability that is on par with or better than manufactured emulsions. In culinary, nutraceutical, and pharmaceutical applications, oleosomes are becoming more popular as "clean-label" carriers due to their known components and decreased usage of additional emulsifiers [8].

Extraction Methods for Plant-Derived Oleosomes

(a) Aqueous Extraction

Wet grinding, high-pressure homogenization (HPH) at 50-150 MPa, wash-cream centrifugation, and extraction procedures using water or mild buffers (pH 7-9) assist preserve droplet integrity and produce oil-in-water emulsions. However, these techniques present difficulties in managing effluent and necessitate the use of a lot of water and centrifuges [9].

(b) Assisted Extraction

Although cost, over-hydrolysis hazards, and ultrasonic scale-up are significant factors to take into account, cell-wall-degrading enzymes (e.g.: cellulase, pectinase, protease) and low-frequency (≈20-40 kHz) ultrasound administered prior to moderate homogenization can boost yields, shorten processing times, and improve interfacial protein preservation [8].

(c) Organic Extraction

Conventional oil-mill processing maximizes bulk oil yield while eliminating intact oleosomes, making it suitable for producing neutral oil instead of oleosome-rich dispersions [10].

(d) Mechanical Extraction

Compared to solvent methods, low-moisture single- or twin-screw processes utilize 40-60% less energy and produce less effluent while producing an oleosome-rich cream. The press cake can retain 10-30% oil unless it is compressed again, and shear may shatter some droplets. [10]

Table 1: Different extraction methods for oleosomes

Method	Typical Procedure	Advantages	Drawbacks	References
Aqueous extraction	Wet grind or 50-150 MPa HPH; Water/mild buffer (pH 7-9); wash-cream centrifugation	Droplet integrity is maintained; free of solvent; yields O/W emulsions	Effluent valorisation required; High water consumption; Centrifuge demand is high	[11]
Assisted extraction	Cell-wall degrading enzymes; Low-frequency Ultrasound waves	Less time consuming; High yields in low shear; preservation of membrane proteins; Low water consumption	Enzyme cost; potential over-hydrolysis; ultrasound scale-up	[6, 11]
Organic extraction	Flake → mill → counter-current hexane wash → desolventize	Lipid recovery is high	High solvent usage; No intact oleosomes; Energy intensive	[12]
Mechanical extraction	Low-moisture pressing/extrusion; cream separation	Low energy required; Continuous process	~30% of oil residues; Shear may cause disruption	[11]

Xenobiotics and Oleosomes

Oleosomes, which have a variety of physicochemical characteristics, emerge as a flexible platform for the encapsulation of different xenobiotics. Highly lipophilic substances like CBD and moderately lipophilic substances like curcumin exhibit nearly full loading efficiency, improving their oral bioavailability and photostability via lymphatic transport. However, new research shows that the CBD-to-lipid ratios have a major impact on the encapsulation efficiency (EE); efficiency drops noticeably from approximately 90 to 99% when the ratio exceeds 1:1. Only around 8% of CBD is released after 120 minutes, according to *in vitro* digestion tests, underscoring the protective function of thick oleosin-phospholipid interfaces. [13].

When administered via nano-oleosomes, sildenafil citrate has demonstrated a four-fold increase in skin deposition, suggesting that it may be effective in treating chemotherapy-induced hand-foot syndrome. When prepared in a hyaluronate-stabilized gel-core oleosome, berberine, another alkaloid with therapeutic promise, has shown efficacy in a vitiligo mouse model. Additionally, in breast cancer models, magnetic, antibody-conjugated oleosomes containing the alkylating chemical carmustine reduced tumor growth by around 70%, while chitosan-coated oleosomes containing propranolol effectively eliminated Candida biofilms while retaining high drug entrapment. These results highlight oleosomes' capacity to transport a variety of substances, showing great promise in pharmacological and nutraceutical settings [14, 15].

Therapeutic Applications

Table 2: Various therapeutic applications of oleosome-based formulations

Clinical Condition	Encapsulated Drug/Cargo	Result	Reference
Hand-foot syndrome	Sildenafil (nano-oleosome cream)	Decreased erythema and pain	[14]
Wound healing	FGF-1 fused oleosome protein	~98% healing	[16]
Vitiligo	Berberine	Complete repigmentation	[15]
Vaginal candidiasis	Propranolol	Complete fungal clearance	[17]
Breast cancer	Carmustine (magnetic, antibody-targeted oleosomes)	Massive reduction in tumour volume	[18]
Photo protection	Oleosome-based UV-filter blend	SPF 30 using 80% less active	[19]

Oleosomes and Other Lipid Nanocarriers

Oleosomes are plant-derived lipid droplets that have an oleosin-protein-stabilized phospholipid monolayer that gives them stability and a protective structure. Without the use of synthetic surfactants, this design enables oleosomes to self-emulsify, offer antioxidant advantages, and release lipophilic actives like vitamins and curcumin. They are appropriate for oral administration of lipophilic chemicals because of their lipid-protein interface, which slows down digestive hydrolysis. Entrapment efficiencies (EEs) for lipophilic actives can surpass 90-98%, according to recent research. Storage trials have demonstrated prolonged peroxide-induction periods of more than 120 days at room temperature, which are ascribed to tocopherols and oleosins. Compared to the costs of purified phospholipids for liposomes, the production costs of oleosome concentrates are expected to be between $15 and $20/kg [20, 21].

Oleosomes are a more environmentally friendly option than synthetic carriers because of their high natural encapsulation, extended oxidative shelf life, and lower production costs. However, problems like size heterogeneity and aggregation risk call for stabilization methods like homogenization and surface coating. Table 3 provides comparative evaluations of oleosomes and other lipid nanocarriers [22].

Table 3: Comparative evaluations of oleosomes and other lipid nanocarriers

Carrier	Origin	Entrapment Efficiency	Stability	References
Oleosomes	Natural, Plant-derived	90-98%	Peroxide-induction times > 120 d at 25 °C	[3, 23]
NLCs	Synthetic blend of solid + liquid lipids	80-95%	Oil separation occurs above 30 °C	[24]
SLNs	Synthetic (hydrogenated lipids + surfactants)	60-85%	Solid matrix slows leakage	[25]
Liposomes	Synthetic/semi-synthetic phospholipid bilayers	60-95%	Susceptible to oxidation/hydrolysis	[26]

Pharmacokinetics of Oleosomes

Absorption

Skin and stomach absorption is improved by natural phospholipid-protein interfaces and seed fatty acid compositions. Compared to oils or emulsions, oral administration of rapeseed oleosomes considerably improved CBD absorption metrics in rats. When compared to solutions, topical administration of sildenafil-loaded oleosomes enhanced skin penetration and deposition. Coconut oleosomes also demonstrated persistent interfacial proteins and polydisperse droplets with negative zeta potential, indicating their efficacy as cutaneous delivery methods [14].

Distribution

By offering robust interfacial activity and preserving membrane integrity, sunflower oleosomes improve colloidal stability in biological fluids and facilitate extended residence at target epithelia. They exhibit size-dependent behavior that promotes dispersion stability whether they are complete particles or membrane fragments. [27]

Metabolism

The low oxidation state of native droplets and co-extracted antioxidants can help stop carrier lipids and actives from oxidatively degrading too soon. Over a 120-day timeframe, phenolic co-extracts were found to considerably reduce oxidation in sunflower systems. Additionally, processing can modify the release of peptides and the antioxidant potential of soybean oleosomes during digestion, which could have an impact on the metabolic environment. [28]

Excretion

Elevated mesenteric lymph node and lymph fluid CBD levels with rapeseed oleosomes suggest that highly lipophilic medicines can benefit from lymphatic transport utilizing oleosome carriers, which may reduce first-pass hepatic exposure [29].

Toxicity

Topical oleosome systems have demonstrated good safety in skin models, and compositions generated from plants are biocompatible. Gel-core oleosomes for berberine were successful with no systemic toxicity *in vivo*, while sildenafil-oleosome gels improved distribution while preserving skin integrity [14, 15].

Challenges in Oleosomes Formulation

Oleosome-based carriers have a number of drawbacks that limit their application in pharmaceuticals, despite their benefits such oxidative stability and solvent-free processing. They are not appropriate for hydrophilic drug administration, which frequently requires intricate techniques like ion-pairing or the use of gel matrices, because their hydrophobic triacylglycerol (TAG) core favors lipophilic substances. Encapsulation efficiencies (EEs) rarely surpass 15-20% even with these techniques, which stands in stark contrast to almost full loading for lipophilic substances like curcumin and CBD. Although there isn't

enough *in vivo* data, hybrid oleosome-liposome structures that combine the adaptability of liposomes with the interfacial proteins of oleosomes have been proposed as a solution [12, 13].

Hyaluronate gel-core oleosomes, which increased skin penetration and retention of berberine with acceptable safety outcomes, are an example of a hybrid platform that improves features like mucoadhesion and mechanical strength while maintaining biocompatibility. Additionally, bionic oleosomes promise far greater payload capacity and improved stability under a variety of circumstances because they are designed for optimum core oil composition and interfacial architecture [28].

Another major worry is allergenicity, especially with oleosomes from soybeans and peanuts that can include IgE-binding proteins. The creation of hypoallergenic fractions and recombinant oleosome shells that alter immunogenic components are examples of mitigation initiatives in progress. Consistency also requires addressing issues including batch-to-batch variation in fatty acid composition, antioxidant levels, and residual allergens brought on by seed cultivar and extraction circumstances. To ensure that oleosomes can compete with fully synthetic lipid-based nanocarriers in pharmaceutical applications, strict raw material controls and in-process analytics must be implemented in order to comply with good manufacturing practices (GMP) [30].

Conclusion

Future research on oleosomes is focused on enhancing their use as targeted drug carriers. Key developments include engineering "designer" oleosomes through genome editing of oleosin proteins to incorporate cell-penetrating peptides, and creating stimuli-responsive coatings using biopolymers. There are opportunities to explore underutilized plant species for novel lipid profiles that may aid in drug development. Regulatory frameworks must be established to guide clinical applications, including compliance with GMP and specific testing for allergenicity and toxicology. Sustainability remains a priority, with methods like enzyme-assisted extraction showing environmental benefits. Overall, oleosomes hold significant promise as biocarriers, necessitating interdisciplinary collaboration for advancement from agricultural byproducts to therapeutic applications.

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