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Strategies to encapsulate natural extracts in lipid based nanocarriers†

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Abstract: Numerous photosynthetic organisms possess bioactive properties, with algae standing out especially for their distinctive characteristics that arouse the interest of diverse industries. For instance, pharmaceutical industry has a great interest in features like neuroprotective, anti-glycemic and cytotoxic properties found in some algae species. Nonetheless, it is imperative to design efficient systems capable of releasing the bioactive compounds present in these extracts. In this regard, nanoparticles have attracted considerable attention across various fields, particularly in drug delivery applications. Lipid-based nanoparticles have emerged as a promising solution, offering numerous advantages. These nanoparticles exhibit high biocompatibility and biodegradability, making them suitable for use in biological systems. Additionally, they possess the ability to encapsulate both hydrophilic and hydrophobic drugs, thereby expanding their versatility. One remarkable attribute of lipid-based nanoparticles is their capability to cross the blood-brain barrier, a crucial physical barrier responsible for regulating the entry of chemicals into the brain and maintaining central nervous system homeostasis. Overcoming this barrier presents a significant challenge in the treatment of central nervous system disorders. Therefore, the objective of this study is to provide an overview of the latest advancements in the nanoencapsulation of natural extracts using lipid-based vesicular delivery systems.

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1. Introduction

Numerous photosynthetic organisms possess bioactive properties, and among them, algae have gained significant attention due to their distinctive characteristics that capture the interest of diverse industries. The pharmaceutical industry recognizes the potential of algal species that exhibit neuroprotective, anti-glycemic, and cytotoxic qualities [1–4], among other properties for the development of new products. However, to effectively utilize these bioactive species and their compounds, efficient systems for their release must be developed. Nanoparticles, especially lipid-based nanoparticles, have emerged as promising solutions for various applications, including drug delivery [5,6].

Lipid-based nanoparticles offer several advantages that make them attractive for use in biological systems. Firstly, they exhibit high biocompatibility, ensuring minimal immunogenicity [7] and allowing the bioactive molecules to be more available to the body after ingestion. Biomolecules can reach their target organs at an effective concentration when they are nano encapsulated, which increases circulation half-lives and improves bioactive stability [5], by using for instance the modification of nanoparticle surface by techniques such as PEGylation, a covalent surface modification with polyethylene glycol, an inert substance not easily digested [8,9]. The blood-brain barrier crossing capacity of lipid-based nanoparticles is one of their most noteworthy features, especially because treatment of central nervous system disorders presents a substantial challenge in overcoming this barrier [10]. In addition, the use of lipid-based vesicular delivery systems allows to overcome challenges associated with the direct application of algae extracts, such as stability issues and undesired organoleptic characteristics.

The up-to date importance of this subject, together with the known characteristics of the algae extracts, led to an overview of the latest advancements in the nanoencapsulation of natural extracts using lipid-based vesicular delivery systems.

2. Discussion

Algal polysaccharides present versatile chemical characteristics and significant bioactive potentialities, which have been extensively described. Thus, they are excellent biomaterials for nanocarriers design. The applications of these algae compounds as drug delivery systems have been reported in a recent review [11]. However, the reports of lipid-based delivery systems aiming to encapsulate bioactive compounds of algae are relatively scarce, a few of the latest is presented in **Table 1**.

Table 1. Selected studies on lipid-based encapsulation of bioactive algal extracts/compounds.

Entrapment technique	Bioactive compounds	Experimental	Major outcomes	Ref.
Nanoemulsion	Phytosterol/alga oil (microalgae derived oil)	Ultrasound emulsification	-Minimize the fishy off-flavor - Maximize oxidative stability	[12]
	Coffee oil /alga oil (microalgae derived oil)	Surfactant: 20% Span 80 80% Tween 80	-Protection effect on ultraviolet A-induced skin damage -Growth inhibition of melanoma cells	[13]
	β-carotene/*Dunaliella salina*	Whey protein or soybean lecithin as emulsifiers	-Increased β-carotene and retinol bioavailability in rats.	[14]
	Fucoxanthin/*Sargassum. angustifolium*	Ultrasonic treatment using fucoidan, gum Arabic, and sodium caseinate as natural emulsifiers *vs* tween 80	-The best encapsulation efficacy was obtained from the tween 80-stabilized nanoemulsion, followed by sodium caseinate, fucoidan, and gum Arabic nanoemulsions.	[15]
Nanoliposome / Phytosome	*Sargassum boveanum*	Optimal conditions with 0.5% lecithin, 30°C process temperature, and 1,313 ppm of the phenolic compounds	- Good stability - Control the release of phenolic compounds at different pH values. -The antioxidant activity of the algal extract has maintained.	[16]
	Protein hydrolysates/*Spirulina platensis*	Thin-film hydration method, with lecithin and cholesterol	- Biocompatibility of the peptides -Accelerated wound healing process- increased the population normal human fibroblast cells.	[17]
	Codium tomentosum	Highest % of complexation: time—1 h, temperature—59 °C, and phosphatidylcholine:extract—1:1)	-FTIR and DSC studies confirmed the phyto–phospholipid complex formation -Phytosomes had low particle size and polydispersity -Increase octanol–water partition coefficient	[18]

Some studies have reported that nanoemulsion have several benefits. Recent studies on nanoemulsion as encapsulation technique highlight not only the increase of the efficiency of antioxidant stability [15], but also the capacity to minimize the unpleasant off-flavors associated with algae extracts and compounds [12]. In other study, the nanoemulsion increased β-carotene and retinol bioavailability in rats [14]. Finally, a nanoemulsion developed with coffee residues and commercially available alga oil was investigated as a protective agent against UVA-induced skin damage and showed its efficiency by significantly inhibiting the B16-F10 melanoma cell line growth (IC_{50} value of 26.5 μg/mL). Additionally, the nanoemulsion was efficient in ameliorating several skin conditions such as erythema, and melanin formation in rats [13] .

Similarly, researches have demonstrated the advantages of other lipid-based encapsulation, based on the development of nanolyposomes. For example, nanoliposomes of soybean lecithin loaded with of *Spirulina platensis* peptides have been demonstrated to reduce the wound healing period. The results of the study showed that the complex did not exert toxicity on Human Foreskin Fibroblast (HFFF-2) ells and in vivo tests in mice, improving wound healing through increased wound contraction, epithelialization, and increased fibroblast population [17]. In another study, the stability of algae phenolic compounds, extracted from *Sargassum boveanum* entrapped in nanoliposomes was confirmed [16]. Authors reported an optimal experimental conditions of 0.5% lecithin, 30 °C of temperature and 1.313 ppm of the phenolic compounds leading to an entrapment rate of 45.5%. The nanoliposome achieved good stability, the capacity to maintain antioxidant activity and to control the liberation of phenolic compounds at different pH values. Finally, a preliminary report on the inclusion of a bioactive extract fraction from *Codium tomentosum* into phytosomes demonstrated that the complex was successfully synthesized, with a low particle size and a high octanol-water partition coefficient [18].

In conclusion, we can say that the use of lipid-based vesicular delivery methods to nanoencapsulate algae extracts offers considerable potential for addressing the restrictions associated with the direct application of bioactive substances. Biocompatibility, biodegradability, and the ability to encapsulate both hydrophilic and hydrophobic compounds are all advantages of lipid-based nanoparticles.

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