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Phytosome and Liposome: The Beneficial Encapsulation Systems in Drug Delivery and Food Application

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Abstract

Due to poor solubility in lipids, many of bioactive components (Nutraceutical materials) show less bioactivity than optimal state in water solution. Phytosomes improve absorption and bioavailability of biomaterials. Liposomes, spherical shaped nanocarriers, were discovered in the 1960s by bangham. Due to their composition, variability and structural properties, liposomes and phytosomes are extremely versatile, leading to a large number of applications including pharmaceutical, cosmetics and food industrial fields. They are advanced forms of herbal formulations containing the bioactive phytoconstituents of herb extracts such as flavonoids, glycosides and terpenoids, which have good ability to transit from a hydrophilic environment into the lipid friendly environment of the outer cell membrane. They have better bioavailability and actions than the conventional herbal extracts containing dosage. Phytosome technology has increasing effect on the bioavailability of herbal extracts including ginkgo biloba, grape seed, green tea, milk thistle, ginseng, etc., and can be developed for various therapeutic uses or dietary supplements. Liposomes are composed of bilayer membranes, which are made of lipid molecules. They form when phospholipids are dispersed in aqueous media and exposed to high shear rates by using micro-fluidization or colloid mill. The mechanism for formation of liposomes is mainly the hydrophilic-hydrophobic interactions between phospholipids and water molecules. Here, we attempt to review the features of phytosomes and liposomes as well as their preparation methods and capacity in food and drug applications. Generally, it is believed that phytosomes and liposomes are suitable delivery systems for nutraceuticals, and can be widely used in food industry.

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1. Introduction

Since ancient times, the use of traditional plant extracts and natural biomaterials has been proven to be popular for health improving and preserving food products by various methods. During the last century, chemical and pharmacological studies have been performed on various plant extracts to discover their chemical composition and confirm their health benefits [1]. In recent years, good advances have been made on development of novel nutraceutical materials delivery systems for plant actives and extracts [2]. Phytosomes, complex of natural bioactive materials and phospholipids, mostly

phosphatidylcholine, increase absorption of herbal extracts or isolated active ingredients when applied topically or orally. Encapsulation is a process that entraps one substance within another substance, and therefore, produces particles with diameters of a few nm to a few mm. The encapsulated components may be called the base material, the active agent, fill, internal phase, or payload phase. Phytosomes and liposomes are examples of these encapsulating systems that are suitable in food and pharmacokinetic applications. Phytosome is a technology developed by incorporating standardized plant extracts or water soluble phytoconstituents into phospholipids to form complexes that have the ability to increase the extract's bioactivity and antioxidant effects. Phytosome technology has been applied to herbal extracts (ginkgo, milk thistle, and green tea) successfully as well as phytochemicals (curcumin and silybin) with remarkable results both in animals and in human pharmacokinetic studies [3-5]. Several studies have indicated the beneficial role of phospholipids in increasing the bioactivity of some molecules having poor oral absorption. Some of these materials are silybin, curcumin and milk thistle. Efforts were done to prepare phospholipids complex of silybin and to increase its bioavailability and thus therapeutic efficacy. It was observed that the obtained complex has significantly better effect than the pure silybin in protecting the liver and exerting antioxidant activity [6-9]. Another research proved that curcumin-phospholipid complex has better hepato-protective activity, owing to its superior antioxidant property, than free curcumin at the same dose level [10]. Also, they developed the quercetin-phospholipid complex by a simple and reproducible method, and showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride [11]. Greenselect Phytosome proved to be more bioavailable compared to the unformulated extract. The results obtained in *in vitro*, *in vivo* and in human trials suggest that Greenselect Phytosome is effective and safe for various uses. The free radical scavenging capacity of the extract accounts for most of the biological activities. Greenselect Phytosome is also reported to trigger other mechanisms of action:

1. Increasing the antioxidant defense systems [12, 13];
2. Stimulation of alpha1 adrenergic stimulated glucose transport [14];
3. Interference with the formation of pro-inflammatory response function cytokines [15].

Liposomes are another carrier system composed of bilayer membranes, which are made of lipid molecules such as phospholipids (lecithin) and cholesterol. They form when phospholipids are dispersed in aqueous media and exposed to high shear rates by using micro-fluidization or colloid mill. The mechanism for the formation of liposomes is the hydrophilic-hydrophobic interactions between phospholipids and water molecules. Here we review about introduction, preparation and application of novel delivery systems such as phytosomes and liposomes in pharmaceutical and food industries.

2. Encapsulation in food biotechnology

Like other sciences, encapsulation is used in food science and technology; however, it is in its childhood, and needs more research. Encapsulation can change liquids and other ingredients into powders, making them simpler to process and easier to use. It can also be used to improve the freeze and thaw ability of sensitive ingredients like providing protection against moisture and cross contamination. The carrier material of encapsulates used in food products or processes should be food grade, and able to form a barrier for the active agent and its surroundings. Encapsulation involves the entrapment of food ingredients, enzymes, cells or other substances in tiny capsules.

Applications of this technique have been increased in the food industry since the encapsulated materials can be protected from moisture, heat or other unfavorable conditions. This enhances their stability and maintained viability. Encapsulation in foods is also used to mask unfavorable odors or tastes [16]. Encapsulates might be defined by their particle size, nanoparticles, microcapsules and micro-reservoir. The possible advantages of encapsulating food ingredients could be:

1. Superior handling of the active agent (such as changing of liquid active agent into a powder, which might be dust free and flowing free, and might have a more neutral smell),
2. Immobility of bioactive materials in food processing systems,
3. Improved stability during processing and final product (i.e. low evaporation of volatile active agent and/or no degradation or reaction with other components in the food products such as oxygen or water),
4. Improved safety (such as reduced flammability of the volatiles like aroma, and non-concentrated volatile oil handling),
5. Creation of visible and textural effects (visual cues),
6. Adjustable properties of active components (particle size, structure, oil or water soluble and color),
7. Off-taste decreasing,
8. Controlled release of biomaterials from capsules [17].

Furthermore, encapsulation technique is used for live microorganisms such as beneficial groups of bacteria. Probiotic bacteria are important factors in production of functional foods and have important role in promoting and maintaining human health. In order to reach higher health benefits, probiotic strains should be present in a viable form and

suitable level during the food storage, and throughout the gastrointestinal tract in the body.

The encapsulation techniques for protection of bacterial cells have resulted in greatly enhanced viability of these microorganisms in food products, and protect bacteria against undesirable environmental conditions. Also, encapsulation protects bioactive compounds, such as vitamins, antioxidants, proteins, and lipids. Indeed, it enhances functionality and stability. In the case of harmful bacteria like Salmonella and Escherichia, it can be said that encapsulation of herbal and bioactive natural materials such as turmeric extract improves the antibacterial effect of material, and presence of encapsulated antibacterial ingredients in food products increase their shelf life.

Phytosomes and liposomes are encapsulation systems with wider future applications in food industry. The term "phyto" means plant while "some" means cell-like. Phytosome technology produces a little cell, is able to better transit from a hydrophilic environment into the lipid friendly environment, and it enhances the bioactivity of phospholipids used in phytosome production. Phospholipids are selected from the group consisting of soy lecithin, from bovine or swine brain or dermis, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) in which acyl group may be same or different, and is mostly derived from palmitic, stearic, oleic and linoleic acid.

Selection of flavonoids is done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexin, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolin glucoside, ginkgonetine, isoginkgetin and bilobetin. Phytosomes are amphiphilic substances, having specific melting point, and generally soluble in lipids. Nutraceuticals and bioactive phytoconstituents would be protected more in emulsions stable at aqueous phase. Increasing the emulsion stability results in the higher protection, functional properties and controlled release of core materials [18].

Liposomes are enclosed vesicles formed by lipid materials, such as phospholipids, dispersed in an aqueous medium. One or more bilayers are formed, which have a similar structure to the cell membrane, separating the inner water phase from the outer [19]. Because of their special structure, liposomes have some excellent advantages when used in drug delivery systems. First, the enclosed vesicles can separate the inner phase from the outside one and thus, improve the stability of the encapsulated drug. Liposomes possess a good cell affinity with excellent biodegradability. Liposomes are defined as microscopic spherical shaped vesicles, consisting of an internal aqueous compartment entrapped by one or more concentric lipid bilayers. Liposomes membrane is composed of natural and/or synthetic lipids, which are relatively biocompatible, biodegradable and non-immunogenic [20].

3. Phytosome and liposome preparation methods

There are some methods for production of phytosomes including anti-solvent precipitation [18, 21, 22], solvent evaporation [11, 23-31], precipitation [32], and anhydrous co-solvent lyophilization [33]. Phytosomes are obtained by reacting 2-3 moles or 1 mole of phospholipid such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine with 1 mole of bioactive components (flavonoids or terpenoids) in an aprotic solvent (dioxane, acetone, methylene chloride, or ethyl acetate). The solvent is evaporated under vacuum or precipitation with non-solvent (aliphatic hydrocarbons), lyophilization (freeze drying) or spray drying; therefore, the complex is isolated [34, 35]. Phytosome production consists of blending biomaterial, inorganic solvent and phospholipid until clear solution creation, solvent evaporation and creating thin layer, hydration and sonication, respectively (see figure 1).

Liposome composition includes natural and/or synthetic phospholipids (phosphatidylethanolamine, phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine), and constitutes the two major structural components of most biological membranes. Liposome bilayers may also contain other constituents such as cholesterol, hydrophilic polymer conjugated lipids, and water [20]. Reverse phase evaporation [36], Hydration lipid film [37], Spray drying [38] and Freeze drying [39] are some of the liposome preparation methods.

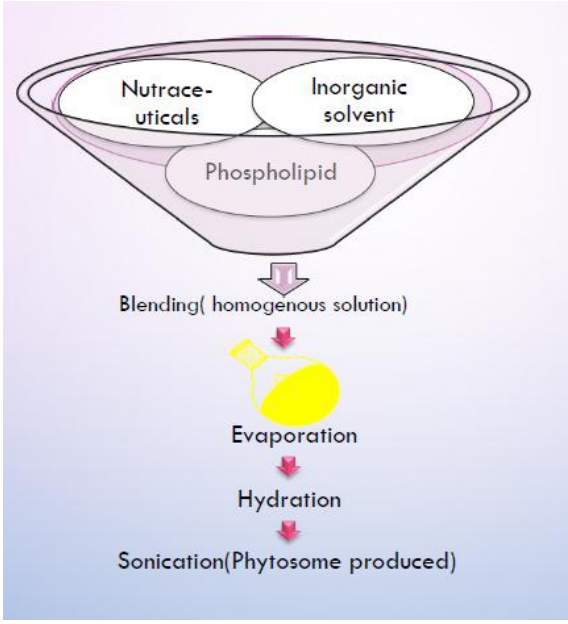


Figure 1. Diagrammatic representation of phytosome preparation.

4. Definition of phospholipids

Phospholipids are lipids that contain phosphorus, a polar and nonpolar part in their structure. Phospholipids can be divided into glycerolphospholipids and sphingomyelins according to the phosphorlipids alcohols.

Glycerophospholipids, which are the main phospholipids in eukaryotic cells, refer to the phospholipids in which glycerol is the backbone. The chemical structure of glycerophospholipids can be classified by the head group, the length and saturation of hydrophobic side chains, the type of bonding between the aliphatic moieties and glycerol backbone, and aliphatic chains. Variation in the head group leads to different glycerophospholipids like phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, and phosphatidylinositol.

Phospholipids are mainly distributed in animals and plants, and the main sources include vegetable oils (such as soybean, cotton seed, corn, sunflower and rapeseed) and animal tissues (such as egg yolk and bovine brain). Egg yolk and soybean are the most important sources for phospholipids production [41]. Phospholipids play important role in sustaining life activity and human good operation. The human body uses phospholipids as emulsifiers.

Together with cholesterols and bile acids, they form mixed micelles in the gallbladder to promote the absorption of fat soluble substances. The human body also uses phospholipids as the surface active wetting agents in the pleura and alveoli of lung, pericardium and joints.

Semalty et al. [18] prepared naringenin-phosphatidylcholine complex by taking naringenin with an equimolar concentration of PC. The equimolar concentrations of PC and naringenin were placed in a 100 ml round bottom flask, and refluxed in dichloromethane for 3 h on concentrating the solution to 5-10 ml, and then 30 ml of n-hexane was added to get the complex as a precipitate followed by filtration. The precipitate was collected and placed in vacuum desiccators [25].

Preparation of silybin-phospholipid complex used ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, and a silybin phospholipid complex was formed [9].

5. Difference between liposomes and phytosomes

The basic difference between liposomes and phytosomes is that, in liposomes, the active biomaterial is dissolved in the medium contained the cavity or in the layers of the membrane, whereas in phytosomes, it is an integral part of the membrane, being the molecules stabled through chemical bonds to the polar head of the phospholipids (see figure 2). Liposomes are used in cosmetics to deliver water-soluble materials to the skin. A liposome is formed by mixing a water-soluble substance with phosphatidylcholine, and no chemical bond is formed; the phosphatidylcholine molecules surround the water-soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surroundding the water-soluble compound. In contrast with the phytosome technology, the phosphatidyl-choline and the plant active components from a 1:1 or a 2:1 complex (depending on the substance) are compared to liposomes. Phytosome is characterized by a high bioactive/lipid ratio with stoichiometry in the range of 1:1-1:3 between the active and the phospholipid formulation aid. This difference results in phytosomes absorbed much better than liposomes; they are also superior to liposomes in skin care products.

In liposomes, the active material is dissolved in the core of the complex, and there is no chemical bonding between the lipid and the guest substance; however, in phytosomes, the polar group of phospholipids interact with hydrogen bonds, and form a unique arrangement that is confirmed by spectroscopy [18, 42-47].

6. Advantages of phytosomes

1. Phytosomes enhance the absorption of hydrophilic polar phytoconstituents through oral topical route, and increasing the bioavailability;
2. They improve active constituent absorption and reduce the dose requirement;
3. Besides phosphatidylcholine acting as a carrier, they act as a hepato-protective;
4. Because chemical bonds are formed between phosphatidylcholine molecule and phytoconstituents, phytosomes show good stability profile;
5. Phytosomes improve skin absorption of phytoconstituents, and are widely used in cosmetics for their more skin penetration and high lipid profile;
6. Phytosomes also have the nutritional benefits of phospholipids;
7. The phytoconstituent in phytosomes can easily permeate the intestinal walls and is better absorbed;
8. Drug entrapment is not a problem with herbosome as the complex is biodegradable;
9. They improve the solubility of bile to herbal constituent;
10. They intensify the effect of herbal compounds by improving absorption, enhancing biological activity, and delivering to the target tissue; therefore, phytosomes are suitable for a delivery system;
11. They transit from the cell membrane and enter the cell easily;
12. Duration of action is increased [1, 40, 45, 48-50].

7. Plant extract in foods

While nearly all plant foods contain health promoting phytochemicals, the following are the most phyto-dense food sources: soy, tomato, broccoli, garlic, flax seeds, citrus fruits, melons, cantaloupe, watermelon, pink grapefruit, blueberries, sweet potatoes, chili peppers, legumes, beans, and lentils.

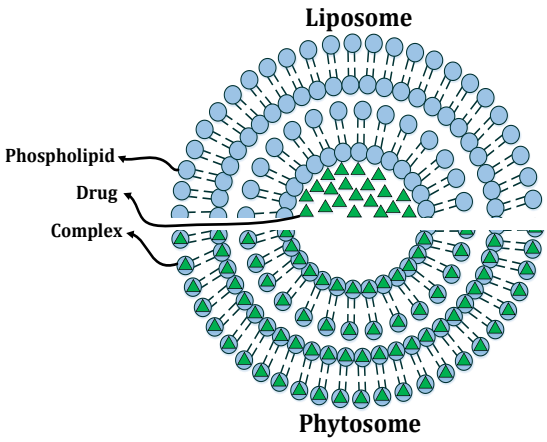


Figure 2. Difference between phytosome and liposome. The molecular organization of phytosome (lower segment) and liposome (upper segment)

Also these herbal materials are important: green tea, red grapes, papaya, carrots, kale, nuts, seeds, eggplant, artichoke, cabbage, brussels sprouts, onions, apples, cauliflower, dried apricots, pumpkin, squash, spinach, mangos, and shiitake mushrooms. There is increasing interest in using plant extracts by the food industry as natural preservatives. Lipid oxidation and microbial growth in food can be controlled [51].

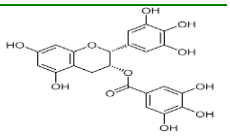
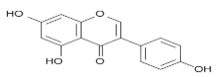
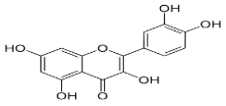
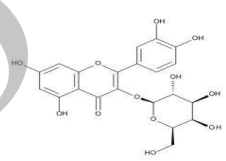
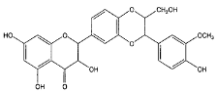
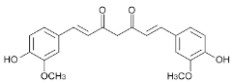
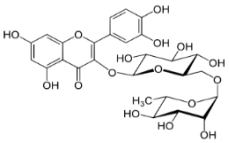
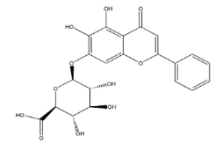
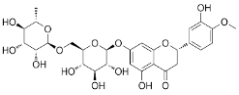
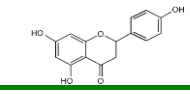
The plant extract has shown to be more effective than BHT (butylated hydroxytoluene) in enhancing the quality parameters of the fermented sausage, suggesting the use of the plant in sausage industry to enhance its total quality [52]. One of the phenolic compounds investigated is sumac; more research displayed sumac as showing significant antimicrobial effects on the total microbial and Salmonella counts in minced meat for one week, so it is an important factor in meat preservation [53].

8. Researches on manufactured phytosomes and their benefits

Moscarella et al. [55] prepared silybin phytosome, and treated 232 patients with chronic hepatitis (viral, alcohol or drug induced) with a dose of 120 mg either twice daily or thrice daily for up to 120 days; liver function returned to normal state faster in the patients treated with silybin phytosome compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo).

Yanyu et al. [9] prepared silymarin phytosome, and studied its pharmacokinetics in rats. They indicated that the bioavailability of silybin in rats was increased significantly after oral administration of the prepared silybin phospholipid complex due to an impressive improvement of the lipophilic property of silybin phospholipid complex and the biological effect of silybin.

Table 1. Some flavonoids used in phytosomes production

No.	Flavonoids	Plant	Structure
1	EGCG	Green tea (Camellia sinensis)	
2	Genistein	Soy Tea	
3	Quercetin	Apple Grape Lemon Tomato Onion Honey	
4	Isoquercetin	Onion Buckwheat Hyptis fasciculate	
5	Silibinin	Silybum marianum	
6	Curcumin	Curcuma longa	
7	Rutin	Plant species, carpobrotus edulis	
8	Baicalein	Scutellaria baicalensis	
9	Hesperidin	Orange	
10	Naringenin	Orange	

Naik et al. [56] reported that Ginkgo biloba phytosome treatment increase of superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase activities in all the brain regions compared with those treated only with sodium nitrite that killed animals after 30 minutes of administration. However Ginkgo biloba phytosomes were administered to wistar rats at 50 $mgkg^{-1}$ and 100 $mgkg^{-1}$ for 7 and 14 days. Chemical hypoxia was induced by administration of sodium nitrite (75 $mgkg^{-1}$) 1 h after the last administration of treatment.

Table 2. Available PHYTOSOME® complexes on the market. PHYTOSOME® and all other trademarks are owned by Indena S.p.A. Milan, Italy [54]

	Trade name	Phytoconstituents complex	Daily dose	Biological activity
1	Aesculus hippocastanum	Saponins	3% gel	Anti-edema, vasoactive properties
2	Bilberry (irtoselect) Phytosome	Anthocyanosides from Vaccinium myrtillus	-	Anti-oxidant, improvement of capillary tone.
3	Casperome™	Banksia serrata gum Resin	-	Higher systemic availability and improving tissue distribution of boswellic acids
4	Centella phytosome	Terpenes from centella asiatica	-	Brain tonic, vein and skin disorder
5	Curcumin (Merinoselect) Phytosomes	Polyphenol from Curcuma Longa	200-300 mg	Cancer chemo preventive agent improving the oral bioavailability of curcuminoids, and the plasma
6	Curbilene phytosome	Curbilene from Curcurbita pepo seeds	-	Skin care, matting agent
7	Echinacea phytosome	Echinacosides from Echinacea angustifolia	-	Immunomodulatory, nutraceuticals.
8	Echinacea purpurea	Echinacea purpurea (L.) Moench - Root	-	Immunomodulator
9	Ginkgo select phytosome	Flavonoids from ginkgo biloba	120 mg	Anti-aging, protects brain and vascular liling
10	Ginseng phytosome	Ginsenosides from panax Ginseng	150 mg	Nutraceutical, immune-modulator
11	Grape seed (Leucoselect) phytosome	Procyanidins from vitis Vinifera	50-300 mg	Nutraceutical, anti-oxidant, anticancer.
12	Greenselect phytosome	Polyphenols, catechins	320 mg	Nutraceutical, weight management, healthy blood lipids, healthy inflammatory response, anti-oxidant capacity
13	Hawthorn phytosome	Flavonoids from crataegus species	100 mg	Anti-hypertensive, cardio-protective
14	Melilotus (Lymphaselect) Phytosome	Triterpenes from Melilotus Officinalis	-	Hypotensive, indicated in insomnia
15	Mirtoselect phytosome	Polyphenols, Anti-cinoside from Vaccinium myrtillus	-	Anti-oxidant
16	Oleaselect TM Phytosome	Olive fruit and leave extracts	-	More bioavailable than crude extract
17	Leucoselect® Phytosome	Procyanidins	300 mg	Reduces oxidative stress and improves plasma anti-oxidant defenses
18	PA2phytosome	Proanthocyanidin A2 from horse Chestnut bark	-	Anti-wrinkles, UV protectant
19	Palmetto (sabalselect) Phytosome	Fatty acids, alcohols and sterols from Serenoa Repens	-	Anti-oxidant, benign prostatic hyperplasia
20	Ruscogenin phytosome	Steroid saponins from ruscus aculeatus	-	Anti-inflammatory, improves skin circulation
21	Sericoside phytosome	Sericoside from Terminalia Sericea	-	Anti-wrinkles, soothing, edensifyer
22	Silybin phytosome	Silybin from Silybum marianum	-	Hepato-protective, anti-oxidant
23	Vaccinium myrtillus	Anthocyanoside	-	Anti-oxidant, anti-inflammatory, diabetic retinopathy
24	Visnadine (visnadine) Phytosome	Visnadine from Ammi Visnaga	-	Circulation improver, isokinetic
25	Ximilene and ximen oil Phytosome	Ximilene and ximen oils from Santalum album	-	Skin smoother, micro- circulation Improver
26	Zanthalene phytosome	Zanthalene from zanthoxylum bungeanum	-	Soothing, anti-irritant, anti-itching

Maiti et al. [10] reported that phytosomes of curcumin (flavonoid from turmeric, Curcuma longa) and naringenin (flavonoid from grape fruit, vitis vinifera) showed higher antioxidant activity than pure curcumin in all dose levels tested.

Mukherjee et al. [57] prepared hesperetin phytosome with hydrogenated phosphatidylcholine, and studied its antioxidant activity and pharmacokinetics in CC14 intoxicated rats. Finally, they reported that phytosome has shown high antioxidant activity. Also pharmacokinetic studies showed the better bioavailability of phytosomes than the parent molecule at the same dosage. Pierro et al. [58] prepared green tea phytosome and studied its effects in 100 obese males and females (divided into 2 groups of 50 each). Group 1 was given hypocaloric diet with green tea phytosome but Group 2 was given only hypocaloric diet. After 90 days, parameters like weight, body mass index (BMI), low density lipid, high density lipid, total cholesterol, triglycerides, insulin, growth factor, and cortisol were determined. Finally, they found that all parameters were improved in both groups but there was more

weight loss in the green tea phytosome group than in the diet only group (14 kg loss versus 5 kg loss). Also no adverse effects were reported.

Naik et al. [59] found that grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, Vitis vinifera) of varying molecular size, complexed with phospholipids. They indicated that total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma increased through a network of mechanisms that extend beyond their great antioxidant potency, offering marked protection for the cardiovascular system and other organs.

Kuamwat et al. [60] developed Gallic acid phospholipids complex in different ratios to improve the lipophilic properties of Gallic acid and for overcoming its poor absorption because of less lipophilicity. They analyzed its properties by ultraviolet visible spectrometry (UV), infrared spectrometry (IR), differential scanning calorimeter (DSC), solubility, dissolution, etc. Finally, they reported that Gallic phospholipids complex form a new compound was an effective scavenger of DPPH radicals with strong antioxidant activity. Zhang et al. [61] prepared a novel drug delivery system, curcumin phytosome loaded chitosan microspheres (Cur-PS-CMs) by combining polymer and lipid-based delivery systems. They reported that the new Cur-PS-CMs system combined the advantages of chitosan microspheres and phytosomes, which show better effects of promoting oral absorption and prolonging the retention time of curcumin than single Cur-PSs or Cur-CMs. The PS-CMs significantly prevented the degradation of bound curcumin in rat plasma, and prompted absorption of curcumin compared with natural curcumin, Cur-PSs, and Cur-CMs. Therefore, the PS-CMs can be used as a sustained delivery system for lipophilic compounds with poor water solubility and low oral bioavailability.

Husch et al. [62] showed that lecithin formulation significantly improves the absorption of BAs and promotes their tissue penetration, demonstrating for the first time the achievement of tissue concentrations of the compounds in the range of their anti-inflammatory activity. Taken together, these results provide a rationale for investigating the clinical potential of Casperome™ in a variety of conditions where preclinical evidence of action for BEH has been reported.

Habbu et al. [63] prepared Bacopa phospholipid complex characterized and evaluated for its possible enhancement of anti-amnesic activity as compared to Bacopa extract (BE) in natural aging induced amnesic mice. They concluded that Bacopa phospholipid complex has shown improved anti-amnesic as compared to Bacopa extract at the dose studied. This might be because of better absorption of bacopasides from the complex. Omar Ali et al. [64] investigated the protective effects of curcumin, silybin phytosome and alpha-R-lipoic acid against thioacetamide induced cirrhosis in five groups of rats, and represented the antioxidant and antifibrotic capabilities of these supplements against chronic liver diseases caused by ongoing hepatic damage.

Bhattacharyya et al. [65] prepared phospholipid complex of chlorogenic acid and evaluated its effect against oxidative stress produced in the rat skin due to UVA exposure. Compared to the conventional formulation, the complex showed better protection when UVA irradiation was performed after 4 h of topical application; thus, they concluded that chlorogenic acid-phospholipid complex has good protection against UVA radiation for long duration. Wu et al. [66] developed a formulation to improve the oral absorption of baicalin by combining a phospholipid complex and self-emulsifying micro-emulsion drug delivery system, termed BA-PC-SMEDDS. Baicalin-phospholipid complex was prepared by a solvent evaporation method and evaluated by complexation percentage. Physico-chemical properties of baicalin-phospholipid complex were determined. Phospholipid complex with self-emulsifying micro-emulsion drug delivery system creates a good balance for lipophilicity and hydrophilicity of drugs, which is critical for oral absorption. Drugs with a phenolic hydroxyl group should have a high complexation percentage with phospholipid complex and good oral absorption by phospholipid complex with self-emulsifying micro-emulsion drug delivery system.

9. Liposome and phytosome in food safety and technology

In addition to improved fermentation, liposomes were tried in preserving cheeses. Addition of nitrates to cheese milk to suppress the growth of spore forming bacteria is questioned due to health concerns, and natural alternatives are under study [20]. Liposomes become localized in the water spaces between the casein matrix and the fat globules of curd and cheese; therefore, it preserves potency and increases effectiveness [67]. Liposome enhances the effect of natural preservatives, including antioxidants such as vitamin E and C; this finding is undoubtedly important due to recent dietary trends, which tend to reduce the addition of artificial preservatives and increase the portion of unsaturated fats in the diet. Liposome surface can be made sticky so that it remains on the leaf for longer times and does not wash into the ground. Mohammadi et al. [69] prepared vitamin D_3 nanoliposome by thin layer method and they found high encapsulation efficiency. Also, they showed that various amounts of lecithin to cholesterol had no significant effect on encapsulation efficiency. Bashiri et al. [70], prepared beta carotene nanoliposome by thin layer method and reached high encapsulation efficiency. They reported that encapsulation of beta carotene cab helps to preserving in foods during the processing. Tiz chang et al. [71]

prepared nisin nanoliposome by heating method and achieved optimal formulation. They reported that agitation rate and time have influence on particle size. Also, they reached high encapsulation efficiency of 30%.

Pezeshki et al. [72] prepared vitamin A palmitate nanoliposomes from various concentrations of lecithin to cholesterol by thin film hydration and sonication methods. They fortified sterilized and pasteurized low fat milk with vitamin A palmitate nanoliposome, and reported that nanoliposomes had no effective preserving role and was similar to control the sample.

Babazadeh et al. [73] prepared rutin phytosome and fortified milk, apple and orange juices with rutin nanophytosome. They represented that nanophytosome increases the stability, and that the pH of the products remained constant during the sterilization and pasteurization. Cui et al. [74] researched on the antibacterial activities of liposome encapsulated Clove oil. They demonstrated that the essential oil exhibited favorable antimicrobial activity for *E. coli* and *S. aureus*, and the stability of Clove oil liposome was better than clove oil alone. Also they showed that liposome encapsulated Clove oil has no effect on *E. coli* that does not secrete PFTs because antimicrobial component cannot reach bacteria; however, it showed efficient antimicrobial activity for *S. aureus* in tofu.

10. Conclusion

Over the past decades, great advances have been made on the development of bioactive materials delivery systems for plant actives and extracts. Encapsulation is an advantageous method for various delivery and food processing systems. Nanocapsules, phytosomes, liposomes and ethosomes have been reported for this aim. Phytosomes are advanced form of herbal extracts that result from the reaction of stoichiometric amount of phospholipids with standardized herbal extracts or polyphenolic substances (flavonoids, terpenoids, tannins, and xanthones) in nonpolar solvents. Phospholipids are mainly employed to make phytosomes. Phospha-tidylcholine is derived from soybean phosphatidyl-choline. On the other hand, phosphatidylethan-olamine or phosphatidylserine can also be used for phytosome production. They are absorbed better than conventional herbal extracts. In addition, they have improved pharmacokinetic and pharmacological characteristics, which can be used in the treatment of various diseases. Phytosomes aid to explore maximum therapeutic capability of phytoconstituents of polar nature, exhibiting remarkable therapeutic efficacy. They have many significant advantages over other conventional formulations that cause them important delivery system. The Phytosome formulation methodology is simple, and can be easily upgraded to a commercial scale by pharmaceutical, nutraceutical or cosmetic manufacturers. This review attempted to display that developing biomaterials into phytosome improves their solubility, permeability and bioavailability. Phytosomes have many different therapeutic benefits like hepato-protective, anti-cardiovascular, anti-inflammatory, immune-modulator, anticancer and antidiabetic activities. Most recent developments include encapsulating foods in the areas of controlled release, carrier materials, preparation methods and sweetener immobilization. New markets are being developed, and current research is under way to reduce the high production costs and lack of food grade materials.

11. Future perspective

In food science and technology, use of carriers is lower than in other sciences, but it can be said that many of food technologies problems such as lipid oxidation, short shelf life, microbial spoilage, necessary materials deficiencies, etc. need to more attention. Therefore, encapsulation systems such as phytosomes and liposomes will have important role in food technologies progressing. Finally, one can conclude that food products supplementation with nutraceutical capsulated materials helps to the health of people and reduce needs of drug.

12. Conflict of interest

Authors declare that there is no conflict of interest.

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