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A review on phytosomes as innovative delivery systems for phytochemicals

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Abstract

Nowadays, medicinal herbs and their phytochemicals have emerged as great therapeutic options for many disorders. However, poor bioavailability and selectivity might limit their clinical application. Therefore, bioavailability is considered a notable challenge to improving bio-efficacy in transporting dietary phytochemicals. Different methods have been proposed for generating effective carrier systems to enhance the bioavailability of Phytochemicals. Among them, nano-vesicles have been introduced as promising candidates for the delivery of insoluble phytochemicals. Due to the easy preparation of the bilayer vesicles and their adaptability, they have been widely used and approved by the scientific literature. The first part of the review is focused on introducing pyrosomes technology as well as its applications, with emphasis on principles of formulations and characterization. The second part provides a wide overview of the biological activities of commercial and non-commercial pyrosomes, divided by systems and related pathologies. These results confirm the greater effectiveness of pyrosomes, both in terms of biological activity or reduced dosage, high-lighting curcumin, and Silymarin as the most formulated compounds. Finally, we describe the promising clinical and experimental findings regarding the applications of pyrosomes. The conclusion of this study encourages the researchers to transfer their knowledge from laboratories to the market, for further development of these products.

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Introduction

For several decades, medicinal herbs and their active constituents have been utilized to treat different diseases. There are some major reasons for the increased use of herbal drugs: modern medicine is unable to efficiently cure all the human pathologies, there are increasing interests and attention over the assurance and safety of synthetic drugs, and many natural products are being shown to produce better results than synthetic drugs without adverse effects [1]. However, due to poor oral bioavailability, the clinical application of numerous active compounds of plants is under debate. The weak absorption rate of such constituents may be a result of

low lipid solubility, the existence of multi rings polyphenols in their structures, and high molecular weight. Different solutions have been suggested to face such obstacles, including preparing emulsions, liposomes, and nano-formulation, the adjustment of molecular structure, and administration of prodrugs. Between all approaches, Phyto-phospholipid complexes (named phytosomes) are appeared to be a great method to boost their bioavailability [2]

These formulations exhibit improved pharmacological and pharmacokinetic properties as compared to prevalent preparations. [3] The lipid-soluble phosphatidyl portion completely covers the hydrophilic phytoconstituents-choline complexes. Moreover, a higher absorption rate leads to a lower dosage of active constituents for exerting a biological effect, also for polar phytoconstituents [4]. There is a variety of possible applications of phytosomes that will be discussed in this review

The Phytochemicals

Phytochemicals or plant chemicals are comprised of a wide range of naturally occurring bioactive compounds produced by plants. The term bioactive refers to the ability of these compounds to interact with different components of living organisms, thereby exerting their beneficial effects. [5]Phenolic, alkaloids, carbohydrates, lipids, terpenoids, and other nitrogen-containing compounds are the most structurally different major categories of phytochemicals. Moreover, there are several subcategories of phytochemicals based on differences in biogenesis or biosynthetic pathway. Between all the phytochemicals, only those having an active hydrogen atom (-COOH, -OH, -NH2, - NH, etc.), like polyphenols, can be integrated into a phytosome structure. An active hydrogen atom can form a hydrogen bond between the herbal derivatives and the hydrophilic parts of amphiphilic molecules. Polyphenols are the major group of phytochemicals extensively found in plant-based foods. [6-7] Potential health effects of polyphenols were shown in different diseases including cancer, inflammation, neurodegenerative and cardiovascular diseases, type 2 diabetes, and obesity. Essentially, they are found in conjugated forms composed of sugar residues (one or more) attached to hydroxyl groups; however, the sugar residues may directly attach to an aromaticcarbon. Flavonoids and non-flavonoids are two major subgroups of polyphenols. The current review updates the knowledge on the use of polyphenols through phytosomes, paying attention to their structure, preparation, and the biological activities associated with the use of phytochemicals-loaded phytosome. [8-10]

Vesicular Systems in Phytosome Development

Targeted delivery and sustained release rate are two relevant factors for phytochemical drug carriers. Several kinds of nano-systems would be used in various disease imaging or therapies, or as theranostics.[11] The most used Nano carriers for phytochemicals are the vesicular drug delivery systems, in which active compounds are encapsulated in a spherical structure. Various types of vesicular drug delivery systems such as liposome, niosome, transfersome, and ethosome have been developed [12].

The Liposome

Liposome originated from two Greek words “Lipos signifying fat and Soma meaning body”. Liposomes are phospholipids and cholesterol that made up the spherical shaped vesicles with a diameter of 0.05–5.0 micrometers. They are a very promising carrier for drug delivery in different architectures due to their hydrophobic and lipophilic characters. This drug delivery system attempts to directly target the drug at the desired site of action. Liposomes are biocompatible, biodegradable, stable, and have a unique property that traps both hydrophilic and lipophilic agents into their compartments and provides a controlled-release effect. [13] Liposomes are used in different pathological conditions, such as cancer, inflammation, eye and skin disease, malaria, and osteosarcomas. The liposomes can be designed using various techniques. Overall, most liposome preparatory methods are based on (1) solvation of the lipids in an organic solvent; (2) getting lipid thin film by evaporation; (3) hydration of lipid layer by a hydrophilic solvent; (4) liposome purification (5) and characterize the properties of the final liposome. Also, other synthesis methods can improve the encapsulation of the loaded drug.

The Niosome

Niosomes are nanometric lamellar vesicles that are formed by combining non-ionic surfactant and a helper lipid-like cholesterol. [14]The non-ionic surfactants create a stable bilayer vesicle in hydrophilic systems by using energy (physical agitation and heating). Hydrophobic parts in the bilayer structure are guided aside from the aqueous phase, while the hydrophilic heads stay in contact with the aqueous side. The surfactants used in the preparation of niosomes should be biocompatible, biodegradable, and not immunogenic. Niosomes act like liposomes in vivo and in vitro, extending the circulation of the encapsulated phytochemical, adjusting its organ distribution, and improving bioavailability. The Niosomal formulations are leakier than li

posomes with the same cholesterol value. Previous research has been shown that cholesterol concentration is an important influence factor on vesicle leakage. They are designed to target and control the release of natural compounds. Our group evaluated the niosome encapsulation of different antioxidant phytochemicals [15,16],

The Ethosome

Ethosomes are non-invasive carriers that allow medicinal products to enter deep skin layers and systemic circulation. Ethosomes are soft vesicles customized to improve the delivery of active agents, such as drugs and natural products. They are primarily composed of phospholipids (phosphatidylserine, phosphatidylcholine, and phosphatidic acid), high ethanol concentrations, and deionized water. [17]The high concentration of ethanol makes ethosomes the best choice for skin due to impairment of the skin lipid bilayer. Thus, when ethanol is incorporated into the vesicle membrane, it provides the ability to reach vesicles to the stratum corneum. Therefore, these soft vesicles serve as new vesicular carriers for improved skin delivery. The size of ethosomes may be modified from nanometers to micrometers. Ethosomes have been found to be significantly superior in the quantity and depth of drugs delivered through the skin compared to liposomes and many other commercial transdermal and dermal delivery platforms. [18]

Phytosome Characterization

Nanomaterial measurement approaches are a rapidly growing field, involving effective methods for physical and chemical characterization. [19]Phytosomes have received tremendous attention for phytochemical delivery as a fast-growing class of Nano vesicles. Several techniques were employed to characterize phytosomes size, elemental composition, morphology, and a wide range of other physical characteristics. There are physical properties, which can be investigated by more than one technique. Different limitations and strengths affect the choice of the most appropriate method, while a combinational methodology for characterization is often required. Also, some statistical studies are needed for better application in real world. The main characteristics of phytosomes are (1) size and shape; (2) surface charge; (3) chemical composition; (4) lamellarity and stability; (5) encapsulation efficiency and (6) release behavior. The goal of this chapter is to provide a thorough summary and a systematic overview of all analytical instruments used to characterize phytosomes, including the latest papers [20-21].

Table1 Comparative EvaluationofPhytosome, Liposomes, Niosome, Ethosome and Transfersomes in Nano-Delivery Systems

Characteristics	Phytosome	Liposome	Niosome	Ethosome	Transferso me
Composition	Phospholipids and polyphenolic phytoconstituents	Phospholipids and cholesterol	Non-ionic surfactant and cholesterol	Phospholipid, alcohol, polyglycol and water	Phospholipids and surfactant mixture
Flexibility	Rigid	Rigid	Rigid	Elasticity	Ultra- deformabl e
Main application	Phyto-delivery	Drug and gene delivery	Drug delivery and cosmetics	Skin delivery	Skin delivery
Administration	Oral, parenteral topical, transdermal	Oral, parenteral topical, transdermal	Oral, parenteral topical, transdermal	Topical and transdermal	Topical and transdermal
Key features	High entrapment efficiency along with adepot formation which releases the contents slowly	Biocompatibilty, capacity for self-assembly, ability to carry large drug payloads	Improved dispersion of compounds with solubility issues, high stability, low- cost materials	Enhance permeation of drugs across/ through the skin in an efficient manner	High deforming ability which ensures deeper penetration in skin layers

Limitation	Leaching of the phytoconstituents which reduces the desired drug concentration indicating their unstable nature	Low skin penetration, low stability	Low skin penetration and toxicity of surfactant	Poor yield, coalescence and fall apart on transfer into water, Loss of product during transfer form organic to water media	Toxic effect of surfactant

Table2 Overview of the Analytical Methods Used for the Characterizationof Phytosomes FeaturedinThis Review

Parameter	Techniques
Size,andshape	DLS,SEM,TEM,Opticalmicroscopy,Fluorescencemicroscopy,AFM,Fieldflow fractionation,Nanoparticletrackinganalysis,Scanningionocclusion sensing,FlowCytometry,Size-exclusionchromatography,Centrifugalsedimentation,andDSC.
Surfacecharge	DLS,free-flowelectrophoresis,andlaserDopplervelocimetry.
Chemicalcomposition	FTIR,h1 NMR,GC-MS, LC-MS, DSC, TGA, andThin-layer chromatography.
Lamellarityandstability	31^{P} nuclear magneticresonance,Small-angleX-rayscattering,electronmicroscopymethods,DSC, TGA,DLS,andUV-Vis.
EncapsulationEfficiencyandreleasebehavior	Mini-columncentrifugation,HPLC,UPLC,UV-Vis,dialysis,enzymatic assays,gel electrophoresis,fieldflowfractionation,sample-and-separateapproach,thein-situmethod,andthecontinuousflow.
Optimization	DesignofExperiment(DoE)withBox–Behnkendesign

Abbreviations: DLS, dynamic light scattering; SEM, scanning electron microscope; TEM, transmissionelectron microscopy; AFM, atomic force microscope; DSC, differential scanning calorimetry; FTIR,Fourier-transform infrared spectroscopy; NMR, nuclear magnetic resonance; GC-MS, gas chromatography-mass spectrometry; LC- MS, liquid chromatography-mass spectrometry; TGA, thermal gravimetric analysis;HPLC,high-performanceliquidchromatography;UPLC, ultra-performanceliquidchromatography.

Recent Patented Technologies on the Phytosomes [22-25]

The leading dealer of nutraceutical ingredients developed a patented process for Phytosomes in 2011. Several scientists from academic and industries have found out innovative processes and developed phytosome formulations.

Marketed Phytosomal Products and Challenges to Commercialization Phytosomes are considered as efficient Nano carrier delivery systems. However, there is a long way from product development to a successful commercialization. Despite all advantages, a few final phytosomal products have been introduced into the markets.

After designing an effective formulation, proofing of safety is a primary barrier for the entrance of phytosomes into the market. Phytosomes have biologically neutral structures, so their introduction into the human body is acceptable without any concern about their safety or immunologicalreactions. However,regardingtheirnano size,someparameterssuchasbioaccumulation,biocompatibility,metabolism,and excretionshould bedeterminedbeforetheirmarketing. Sou et al have successfully prepared a curcumin phytosome for intravenousapplication inrats,showed highaccumulationin bonemarrow and spleentissues. Another factor should be considered is the ability of phytosomes to merge withbiological membranes and passively target normal cells. Hence, their actual biologicaleffects should be determined in well-designed animal models as well as in clinicaltrial. In this regard, different studies showed the biological safety of phytosomes. Furtherto this, after designing a phytosome, pharma-

cokinetic and Pharmacodynamic parametersshould be assessed in animals and humans to prove their superiority rather than purePhyto-constituents. Finding the best dosage form to increase the absorption and efficacyoffinal-productisanotherstepinthewayofmarketing. The otherchallengeistheproduction of phytosomes in a large scale. However, during scaling up, the characteristics of the product should be kept. This is related to the practicality of laboratory protocol for in the industrial setup. Although the manufacturing processes of many types of phytosomes are often simple, in regard to pH sensitive phytosomes, their low physicochemical stability makes their industrial production a challenge. Phytosomes like other pharmaceutical products also should have reproducibility and should be checked for their quality during time. Popularity is another factor in a successful commercialization of a product. Taken together, biocompatibility, low-priced and safety of natural products has grown preference of people for this type of therapies in the recent years. Moreover, commercialization of phytosomes is a rapid process due to simple manufacturing process and ease of promotion of phytosomal technology to industrial scale. The enhanced bioavailability of polar phytoconstituents, advantages, and biological activities of phytosome formulations was explored by several pharmaceutical industries.

Table 3: Plant Extracts and the Relative Range of Doses Used in Clinical Studies in Different Pathological Condition

Plant Species	Dose (mg/Day)	Application
Boswellia serreta	200–4500	Central and peripheral nervous system
	250–500	Gastrointestinal system
	250–500	Musculoskeletal system
	500	Respiratory system
Camellia sinensis	150–300	Metabolic syndrome
	300	Genitourinary system
Citrus x bergamia	500–1000	Metabolic syndrome
Curcuma longa	2000	Gastrointestinal system
	900–2000	Genitourinary system
	2000	Integumentary system
	500–2000	Musculoskeletal system
	800–1000	Metabolic syndrome
	800–1000	Central and peripheral nervous system

Title	Novelty/Innovation
Phospholipid complex of curcumin havingimproved bioavailability	Phospholipid complexes of curcuminprovide ahigher systemic level of parent agent than uncomplexed curcumin.
Phospholipid complexes of olive fruits or leavesextract having improved bioavailability	Olive fruits/leaves extracts bioavailability enhancedusing phospholipids complexes
Compositions comprising *Ginkgo biloba* derivativesfor the treatment of asthmatic and allergic conditions	Compositions of the fraction gained from *Ginkgobiloba* for the treatment of asthma and allergic conditions
Treatment of skin, and wound repair, with thymosinβ-4	The formulation developed containing Thymosinβ4 for wound healing

Oral compositions for the treatment of cellulite	Oral and cosmetic pharmaceutical Formulation containing *Centella asiatica* triterpenes, extracts of *Vitis vinifera*, and *Ginkgo biloba* flavonoids in the free or complexed form with phospholipids
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	The selected fatty acid monoesters of sorbitylfurfural are lipophilic agents for specific anti-hydroxyl radical activity
Cosmetic and dermatological composition for thetreatment of aging or photodamaged skin	The topical cosmetic or dermatological preparation containing at least one collagensynthesis- stimulating agent for anti-wrinkle treatment
Soluble isoflavone composition	Isoflavone compositions enhanced the solubility, texture characteristics, taste, and color of the formulation
An anti-oxidant preparation based on plant extracts for the treatment of circulation andadiposity problems	The formulation developed having the plant extracts possessing the anti-oxidant activity for thetreatment of phlebitis, hemorrhoid, arteriosclerosis, varicose vein, and elevated bloodpressure
Phospholipid complexes prepared from extractsof Vitis vinifera as anti- atherosclerotic agents	Vitis vinifera extract phospholipid complexes for theprevention and treatment of atherosclerosis.
Bilobalide phospholipid complexes, their applications, and formulations containing them	Complexes with synthetic or natural phospholipidsand Bilobalide (a sesquiterpenes found in the Ginkgobiloba leaves) are revealed, as well as their formulation and application in inflammatory conditions and for the treatment of neuritic processes. This compound exhibited higher bioavailability than free Bilobalide, hence it is applicable for parenteral and topical administration.

Table 4: Phytosomes Related Patents on the Developed Technologies

Conclusion

With the rise in the number of recently discovered phytochemicals, research will be brought up to date on their medical benefits in a biological environment. However, low solubility and sensitivity to degradation restrict the application of these compounds in food and pharmaceutical products. At this stage, gaining insight into vesicular drug delivery systems could help to improve these characteristics. Vesicles are shown to be very promising delivery systems for various beneficial phytochemicals at a cellular level, because of their remarkable entrapment capacity, biocompatibility, and safety.

Among vesicular drug carriers, phytosomes form a complex between phytochemicals and phospholipids, which results in the improvement of absorption and bioavailability of bioactive molecules, together with improved overall compound stability. Liposomes, transfersomes, niosomes, and ethosomes are the most used Nano carriers for phytochemicals, which are characterized by different dimensions, release efficiency, or preferential target (eg, transfersomes and ethosomes for topical application). Similarly, nano-phytosomes are one of the newest lipid-based vesicles with lower dimensions, a development to further boost the transport of plant-based nutraceuticals. Each formulation must be adequately characterized to ensure a high safety profile and meet reproducibility standards, through analysis of physical measures that give information on both dynamics of release and formulation stability. This review provides an overview of biological activities of phytosomes both for commercial and non-commercial products. The set of collected studies shows a general advantage in the use of these formulations to improve the bioavailability of bioactive phytochemicals, allowing a reduction in dosage, compared to non-formulated compound, or greater biological activity. All the considered human systems are characterized by the presence of at

least a clinical study. However, the superiority of the formulation has only rarely been investigated in comparison with its components in clinical trials. Exceptions are studies on the bioavailability of quercetin288 and bergamot292 and a comparison between the anti-adhesive activity of urine of subjects following oral consumption of cranberry extract; 241 in all the cases, the formulations gave higher values. Among the sources of phytochemicals Curcuma longa and Silybum marianum have collected most of the clinical evidence, with positive effects, except for silibinin in the management of prostate cancer, which yielded only marginal results. Overall, clinical studies are currently insufficient to draw conclusions on biological activities of individual preparations, but the overall evidence for these formulations is encouraging and invites the researchers to continue investigations in this field. In the future, clinical studies on standardized products that show superior efficacy compared to non-formulated components or extracts will be fundamental to drive attention to these technologies.

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