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Review Article

Phytosomes: Magnifying Power of Herbal Extract- An Systematic Overview

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ABSTRACT

In the recent days, most of the prevailing diseases and nutritional disorders are treated with natural medicines. Several plant extracts and phyto constituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and bioavailability. So, much work has been directed towards the development of new concept in herbal delivery system i.e., phytosomes which are better absorbed, utilized and as a result produce better results than conventional herbal extracts. Phytosomes often known as herbosomes. The term phyto means plant while some means cell-like. Phytosomes are little cell like structure. Phytosome is composed of phospholipids, mainly phosphatidylcholine, producing a lipid compatible molecular complex with other constituents. Phytosomal complexes were first investigated for cosmetic applications. But phytosome process was developed and patented by Indena, a leading supplier of nutraceutical ingredients like milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng etc. Phytosomes are superior to liposomes due to complex formation ratio of component and phospholipids is 2:1 and 1:1 respectively, much better absorption and stability profile. Development of phytosomes is at the budding stages in India and abroad. It has a lot of potential in the field of medicine, pharmaceuticals and cosmetics.

Key-words: phytosomes, indena, herbosomes, phospholipid.

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Introduction –

Novel herbal drug delivery system opens new wistars for delivery of herbal drugs at right place, at right concentration, for right period of time and also gives scientific angle to verify the standardization of herbal drug. For a long time, herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble phytoconsituents into phospholipids to produce lipid compatible molecular complexes.[42]

Recent developments in herbal medicine provide strong evidence that advances in technology are fueling a greater effectiveness of nature's healing power. Technology is being, used to refine, enhance, and intensify the power of herbal medicines. This is evident in the development of purified standardized herbal extracts. These extracts contain a specified level of active compounds, thus producing not only a more consistent product, but also more consistent results. Now, there is another breakthrough in herbal medicine-the phytosome process[1]. Phytosomes are nanotechnology based dosage forms for delivery of herbal drugs.[41] A phytosome is created by binding molecules of a herbal compound to molecules of phosphatidylcholine, a natural component of lecithin. Phosphatidylcholine is found throughout the human body as an essential component of cell membranes. The reaction of phosphatidylcholine with the herbal compounds creates new molecules known as phytosomes.[1]

Advantages –

- Marked enhancement of bioavailability
- Significantly greater clinical benefits
- Assured delivery to the tissues
- No compromise of nutrient safety[2-6]
- Reduced dose requirement[7]
- Better stability profile[7]

Phosphatidylcholine: The key to phytosome process

Phosphatidylcholine is a very interesting molecule. It contains a water-soluble head (choline component) with two long, fatsoluble tails (phosphatidyl component). Because of this dual solubility, phosphatidylcholine is an extremely effective emulsifier. The emulsifying action of phosphatidylcholine is often used to greatly increase the absorption of fat-soluble vitamins and drugs. Phosphatidylcholine is more than an emulsifier. It is an important constituent of all cell membrane systems. It functions in maintaining the "fluidity" of our cellular membranes. Phosphatidylcholine plays a critical role in all membrane dependent metabolic processes. The new phytosome process applies this technology to plant substances. [1]

Method of preparation –

Phytosomes are prepared by reacting natural or synthetic phospholipids with active components or phytoconstituent. Solvent evaporation method or mechanical dispersion method are generally used. Phospholipid is dissolved in a suitable solvent and active ingredient is added drop by drop while sonicating the solution. Phospholipid complex is sometimes prepared under reflux and stirring conditions to effect complete interaction. Some phospholipid complexes are prepared by adding the phospholipids to the ethanol solution of the hydroalcoholic extract of phytoconstituent under reflux and with stirring. Prepared complex can be isolated by precipitation with nonsolvent, lyophilisation, spray drying or vacuum drying.[8]

Evaluation of phytosomes-

The following are the characterization techniques used for phytosomes in characterizing its physical attributes[43]-

1. Entrapment efficiency:- Determined by ultracentrifugation technique.

2. Transition temperature:- Determined by differential scanning calorimetry.
3. Vesicle size and Zeta potential:- Determined by dynamic light scattering.
4. Surface tension activity measurement:- by ring method Du Nouy ring tensiometer.
5. Spectroscopic evaluation:- to confirm the formation of complex between phytoconstituents and the phospholipid moiety as well as to study the corresponding interaction between the two. The widely employed methods are listed below-
   a. ^{1}H NMR b.^{13}C NMR c.FTIR

In-vivo studies are performed on Beagle dogs, rodents, wistar rats to compare pharmacokinetics parameters between pure extracts and its phospholipid complex.

Formulation of phytosomes –

Phytosome® complexes can be formulated both orally and topically. In order to obtain the best performances of this technogical innovation both in terms of formulating manageability and enhanced bioavailability (as appropriate disintegration and dissolution time of oral forms, for instance) Indena suggests the most appropriate manufacturing procedures to obtain effective formulations.[9,10,11]

1. **Soft gelatin capsules:-**
   Soft gelatin capsules represent an ideal solution to formulate Phytosome® complexes.
   The Phytosome® complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena recommend a granulometry of 100% <200 µm to best perform capsule production. According to Indena experience, not all the Phytosome® complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules; for this reasons preliminary feasibility trials should be performed to select the most suitable vehicle.

2. **Hard gelatin capsules:-**
   The Phytosome® complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the Phytosome® complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process, however, it is possible to increase the amount of powder which can be filled in a capsule, but precompression might affect the disintegration time. Indena recommend to carefully monitor the related parameters during product/process development. A preliminary dry granulation process is advisable define the best manufacturing process.

3. **Tablets:-**
   Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties. However, due to the limited flowability, potential stickiness and low apparent density of the Phytosome® complex, a direct compression process can be applied only for low unitary doses; note that whenever a direct compression process is applied, the Phytosome® complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/ drying) on the stability of the phospholipid complex.

4. **Topical dosage forms:-**
   The Phytosome® complex can be formulated topically as well. The ideal process to incorporate the Phytosome® complex in emulsion is to disperse the phospholipidic complex in a small amount of the lipidic phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The Phytosome® complexes are dispersible in the main lipidic solvents employed in topical formulations. In case of formulations containing a limited amount of lipids, the

Phytosome® complex might also by dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C.

Commercial products –

1. **GreenSelect® Phytosomes:-**
   GreenSelect® Phytosome is a proprietary, caffeine free extract from green tea, that is 1 part GreenSelect®green tea to 2 parts phophatidylcholine. This allows for greater absorption of epigallocatechin gallate, or EGCG, one of the primary components known to support healthy metabolism. Green tea has demonstrated the ability to promote resting energy expenditure and thermogenesis in a number of clinical studies. A 90-day study involving GreenSelect® Phytosome revealed its ability to support healthy weight management and body composition in subjects following a calorie-restricted diet.[39]

2. **Silymarin Phytosome®:-**
   The well known soothing activity of Silymarin has been shown to be increased by more than 6 times in Silymarin Phytosome® in experimental models. The improvement in the activity of the Phytosome® form, compared to the free active principles, is due to a higher affinity of the complex for skin phospholipids. This not only improves the absorption of the compounds exerting the biological activity, but also increases the duration of the activity as the complex slowly releases the active principle.[31-38]

3. **Sericoside Phytosome®:-**
   Many trials have been performed and Sericoside has shown to have skin restructuring, capillary protecting activity, wound healing and anti-oedema properties. This is due to a remarkable reduction of capillary permeability exerted by the active ingredient. Significant anti-inflammatory qualities have been demonstrated by Sericoside and the Phytosome® form as well.[24-30]

4. **GBDF Phytosome®:-**
   GBDF Phytosome® inhibits cAMP phosphodiesterase thus improving lipolysis in fat cells and the capillary blood flow, because cAMP is able to stimulate the pre-capillary arterioles rythmic contractions. Moreover the number of open capillaries increases. These activities, complemented by the soothing ones observed, are important for the management of cellulite. The improvement in the activity of the Phytosome® form, compared to the free active principles, is due to a higher affinity of the phospholipidic complex to the skin phospholipids. This not only improves the absorption of the compounds exerting the biological activity, but also increases the duration of the activity as the complex slowly releases the active principle.[19-23]

5. **Ginselect® Phytosome®:-**
   At least two interacting mechanisms of action can be observed.The hydration of the superficial corneous layer is related to the liposomial-like properties of the phospholipids of the complex. Ginselect® Phytosome® possesses a transdermic action which can be ascribed to the ginseng saponins present in the phospholipidic complex. This is demonstrated by the objective improvement in the cutaneous elasticity and tone, further confirmed by the subjective scores after long term application. This action could be related to increased blood perfusion "with dilatation of capillaries and arterioles, leading to improved delivery of nutrients to the skin"4. This seems to be also confirmed by the regional increase of cutaneous temperature of the hemiface after application of Ginselect® Phytosome® in female subjects older than 40 years.[15-18]

6. **Leucoselect™ Phytosome®:-**
   Improves the bioavailability of grape procyanidins, which are widely recognized to exert a protective activity on the cardiovascular system.[14]

7. Siliphos®:-

Prevents liver damage of different etiology. It is the most absorbable form of silybin known upto now, as it allows silybin to reach the target organ, the liver, in concentrations which are reported to be effective as antihepatotoxic.[13]

Other current commercially available products are given below in table:-[12 & 40]

Trade name	Active principle formulated with phytosome technology
Boswellia extract	Boswellic acids from Boswellia serrata's resin
Centella asiatica selected triterpenes	Selected triterpenes from Centella asiatica's leaf
Escin β-Sitosterol	Escin and β-sitosterol from Centella asiatica's seed
GINKGOSELECT®	Ginkgoflavonglucosides, ginkgoterpenes, bilobalide and ginkgolides from Ginkgo biloba's leaf
VIRTIVA®	Ginkgoflavonglucosides, ginkgoterpenes and phosphatidyleseine from Ginkgo biloba's leaf
Ginkgo Biloba Dimeric Flavaonoids	Biflavones from Ginkgo biloba's leaf
Ginkgo biloba terpenes	Ginkgoterpenes, bilobalide and ginkgolides from Ginkgo biloba's leaf
18β-glycyrrhetinic acid	18β-glycyrrhetinic acid from Glycyrrhiza glabra's root
Hawthorn	Vitexin-2''-O-rhamnoside from Crategus' flowering top
Proanthocyanidin A2	Proanthocyanidin A2 from Aesculus hippocastanum's bark
Resveratrol	Resveratrol from Polygonum cuspidatum's rhizome
MERIVA®	Curcuminoids from Curcuma longa's seed
VISNADEX®	Visnadin from Ammi visnaga's umbel without fruit
Echinacea Phytosome	Echinacosides from Echinacea angustifolia
Olive oil Phytosomes	Polyphenols from Olea europaea oil
Palmetto berries Phytosomes	Fatty acids, alcohols and sterols
Super Milk thistle ExtractTM	Silybin from Silymarin Food Product
Bilberry Phytosomes	Extract of Bilberry which provides anthocyanosides

Conclusion –

The poor absorption and the poor bioavailability associated with the polar phytoconstituents limits its use. These hindrances can be tackled by formulating an appropriate drug delivery system. Phospholipid based drug delivery system have been found promising for better and effective delivery of drug and can enhance the rate and extent of drug absorption across the lipoidal biomembrane. Phytosome are one of the phospholipid based drug delivery system with a better absorption and stability profile as compared to other phospholipid based drug delivery system like liposome. Presently phytosomes are used primarily in cosmetics to deliver water soluble substances to the skin. The technology can effectively deliver the product by topical and oral route. Technology is having a lot of commercial application. Phytosomes enables pharmaceutical manufacturers to provide new pharmaceutical products using water soluble drugs and provides new developments in medical industry.

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