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Phyto-phospholipid complex vesicles for phytoconstituents and herbal extracts: A promising drug delivery system

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Abstract

The herbal drugs comprising major amount of active constituents with excellent bioactivity *in vitro* but less *in vivo* because of their poor lipid solubility and improper size of the molecules. This results in poor absorption and bioavailability of active constituents from herbal extract. A phyto-phospholipid complex vesicle (Phytosome) is the promising emerging technique applied to pharmaceuticals for the enhancement of bioavailability of herbal extracts and phytoconstituents. Phytosome are advanced forms of herbal formulations contains the bioactive phytoconstituents of herbal extract and has good ability to transition from a hydrophilic into the lipophilic environment of the cell membrane, exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts. They can be formulated in the form of various dosage forms like suspensions, capsules, creams, gels etc. This article overviews recent advance in phytosome technology, their application for various standardized herbal extracts and aims to provide complete scientific information about phytosomes as promising drug delivery system.

Keywords: Phytosomes, Phyto-phospholipid complex, Phospholipid, Herbal Extract

1. Introduction

The plant active molecules from herbal extract applied traditionally in home remedies have been used increasingly to the modern treatment. However, some phytoconstituents have long side chains and high polarity that causes not to be able to pass through lipidic skin by passive diffusion ^[1]. It was observed that most of the phytoconstituents such as the flavanoids, terpenoids and polyphenolics are of highly polar nature or water soluble molecules. These water soluble constituents are poorly absorbed due to their poor lipid solubility, thus unable to cross the highly lipid-rich biological membranes, which results in poor bioavailability ^[2]. Many approaches have been developed for improving the bioavailability such as inclusion of solubility and bioavailability enhancers, structural modification and entrapment with lipophilic carrier ^[3]. The chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Some water soluble extracts when taken orally some constituents may get destroyed in the gastric environment ^[4]. Novel phyto-phospholipid complexation technique named as 'phytosome' plays an important role to increase absorption and improve bioavailability has emerged as one of the leading methods of improving bioavailability of phyto-pharmaceuticals having poor solubility and crossing the biological membranes. Several plant actives in spite having potent *in vitro* pharmacological activities have failed to demonstrate similar *in vivo* response, ^[5] such plant actives have been made more effective systemically by incorporating them with dietary phospholipids forming new cellular structures which are amphipathic in nature. Phytosome is a patent developed by Indena, a leading supplier of nutraceuticals ingredients, to incorporate phospholipids to standardised extract and improve their absorption, bioavailability and utilization ^[6].

1.1. Phyto- phospholipid complex vesicles: Phytosomes

Phytosomes are cell like structure "Phyto" means plant while "some" means cell like and phytosome is a novel approach to drug delivery system which addresses the limitations of the conventional drug delivery systems. Phytosomes contains the bioactive phytoconstituents of herb extracts surrounded by lipids. Phytosomes are developed by incorporating standardized

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plant extract or water soluble bioactive plant constituents into phospholipids to produce lipid compatible molecular complexes called phytosomes and so improve their absorption and bioavailability. Phytosome process produces a cell which is a valuable component of herbal extract which protected from destruction by digestive secretion and gut bacteria. Phytosomes are better able to transform from a hydrophilic environment into the lipid friendly environment of the enterocyte cell membrane and then into the cell finally reaching the blood [7].

Hydrophilic phytoconstituents can be complexed with clinically useful phospholipids to convert into lipid soluble complexes. Such complexes can be used to produce liposome-like vesicles called as phytosomes. In phytosomes, the complexation of phospholipids and water soluble active plant components involve chemical bond formation and therefore becomes more stable [8]. The phytosomes substantially improve the bioavailability of these polar active components. Some of the phospholipids that are reported for phytosome preparation include soy phospholipids, egg lecithin, phosphatidylcholine etc. Phytosomes can easily cross the lipid bio membranes and are reported to increase the bioavailability of poorly lipid soluble extracts by increasing the absorption in gastrointestinal tract. Some of the phytoconstituents incorporated in phytosomes include extracts of ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, olive oil, ginseng, etc. [9].

1.2 Advantages of Phytosome Vesicles [10-12]

- a) They transport from the cell membrane and enter the cell easily.
- b) Noticeable enhancement in the bioavailability of drug occurs.
- c) Phytosomes insures increased duration of action for herbal drugs.
- d) Phytosomes enhance the absorption of hydrophilic polar phytoconstituents through oral, topical and other route and increases the bioavailability.
- e) Phytosomes produces a little cell where the valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.
- f) Phytosomes persuades proper delivery of drug to the respective tissues.
- g) The nutrient safety of the herbal extracts need not be compromise by assigning the herbal drug as means of phytosomes.
- h) Dose requirement has been reduced due to the maximum absorption of principle constituents.
- i) They improve absorption of biologically active constituent and reduce the dose requirement.
- j) Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituents show good stability profile of phytosomes.
- k) Phytosomes improve transdermal absorption of phytoconstituents, and are widely used in cosmetics for their more skin penetration and high lipid profile.
- l) The phytoconstituent in phytosomes can easily permeate the intestinal walls of tissue and is better absorbed.
- m) The complex is biodegradable and drug entrapment is not a problem with phytosome.
- n) 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 drug delivery system.
- o) Entrapment efficiency is high because drug itself is in conjugation with lipids in forming vesicles.

- p) There is no problem in drug entrapment while formulating phytosomes.
- q) Phosphatidylcholine used in formulating phytosome besides acting as a carrier also nourishes the skin as it is an essential part of a cell membrane.
- r) Phytosomes are also better to liposomes in skin care products.
- s) Phytosomes proves to be of significantly greater clinical benefit.
- t) Phosphatidylcholine used in preparation of phytosomes, acting as a carrier and also acts as a hepatoprotective as a result it imparts a synergistic effect when hepatoprotective substances are use.
- u) Their low solubility in aqueous media allows the formation of stable semisolid dosage form.
- v) Facilitates the liver targeting by increasing the solubility in bile salt.

1.3. Properties of Phytosomes

1. Physico-Chemical properties: Phytosomes is a complex between a natural product and phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal structure. This can be conclude from the comparison of the NMR of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active content, producing a lipophilic envelope, which shields the polar head of the phospholipid and active constituents [13].

2. Biological properties: Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects [14].

1.4 Prospects of Phytosome Technology

When compared with conventional herbal formulation, phytosomes have following prospects

- They enhance the absorption of lipid insoluble polar botanical extract through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
- As the absorption of active constituent(s) is improved, its small dose can produce desired results.
- Phytosomes show better stability profile due to formation of chemical bonds between phosphatidylcholine molecule and botanical extract.
- Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and then into the cell, and thus can be used for systemic targeting.
- Phytosome are widely used in cosmetics due to their more skin penetration and have a high lipid profile.
- By enhancing the solubility of bile to herbal constituent, phytosomes facilitates the liver targeting [15].

2. Methods of preparation for phytosomes

2.1 Anti-solvent precipitation technique

The specific amount of plant extract and phospholipid were taken into a 100 ml round bottom flask and refluxed with 20 ml of dichloromethane at a temperature not exceeding 60°C for 2 h. The mixture is concentrated to 5-10 ml. Hexane (20ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. Powdered complex was placed in amber colored glass bottle and stored at room temperature [16].

2.2 Rotary evaporation technique

The specific amount of plant material and phospholipid were dissolved in 30 ml of tetrahydrofuran in a rotary round bottom flask followed by stirring for 3 hours at a temperature not exceeding 40°C. Thin film of the sample was obtained to which n-hexane was added and continuously stirred using a magnetic stirrer. The precipitate obtained was collected, placed in amber colored glass bottle and stored at room temperature [17].

2.3 Solvent evaporation technique

The specific amount of plant material and phospholipids were taken into a 100ml round bottom flask and refluxed with 20ml of acetone at a temperature 50-60° C for 2h. The mixture is concentrated to 5-10 ml to obtain the precipitate which was filtered and collected. The dried precipitate phytosome complex was placed in amber colored glass bottle and stored at room temperature [17].

2.4 Ether-injection technique

In this technique, the drug lipid complex is dissolved in an organic solvent. This mixture is then slowly injected into a heated aqueous agent, resulting in the formation of vesicles. The state of amphiphiles depends on the concentration. When the concentration is less, amphiphiles introduce a monomer state but as the concentration is increased, variety of structures may be formed, that is, round, cylindrical, disc, cubic, or hexagon type [18].

3. Characterization of phytosomes

3.1 Physical attributes

The following are the characterization techniques used for Phytosomes in characterizing its physical attributes [19].

a) Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) provides the details about internal composition and can show many characteristics of the phytosomes, such as morphology, crystallization, stress or even magnetic domains. Scanning electron microscopy (SEM) focuses on the phytosomes surface and its composition provides morphological details.

b) Particle size and zeta potential

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).

c) Entrapment efficiency

The entrapment efficiency, capability of the drug to be entrapped in phytosomes can be measured by the ultracentrifugation technique. It gives an idea about the %

drug that is successfully entrapped into the phytosomes.

d) Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry.

e) Surface tension activity measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

f) Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM.

g) Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method.

3.2 Spectroscopic Evaluation [20]

The spectroscopic evaluations are widely employed in order to confirm the formation of complex between phytoconstituents and the phospholipids moiety as well as to study the corresponding interaction between the two.

a) ¹H-NMR

The complex formation between the active phytoconstituents and the phosphatidylcholine molecule can be estimated by this method.

b) ¹³C-NMR

In the ¹³C NMR of the phytoconstituents and the stoichiometric complex with the phosphatidylcholine when recorded the phytoconstituents carbons were invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonance of the fatty acid chains retains their original sharp line shape.

c) FTIR

The formation of the complex can be confirmed by IR spectroscopy, comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times.

3.3 In-vitro and in-vivo evaluations

Models of *in-vitro* and *in-vivo* evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the Phytosomes [21].

4. Phytosome formulations

Phytosome complexes can be converted and formulated in different kinds of dosage forms used both orally and topically. Various products can be designed in order to obtain the best performances of this technological innovation both in terms of formulating manageability and enhanced bioavailability.

4.1 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% <math><200\ \mu\text{m}</math> 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 [22].

4.2 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 careful monitoring the related parameters during product/process development. A preliminary dry granulation process is advisable, defines the best manufacturing process [22].

4.3 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 flow ability, 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 [23].

4.4 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 be dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C [24].

Table 1: Difference between Phytosome and Liposome

Phytosome	Liposome
Phytosome is a unit of a molecules bounded together	Liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them.
Phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or 2:1 molecular complex depending on the substances compl exed. Involving chemical bonds,so they better absorbed and shown better bioavailability.	In Liposome no chemical bond is formed. The phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water soluble compound.
Phytosome complex can somewhat be compared to an integral part of the lipid membrane. Where the polar functionalities of the lipophilic guest interact via hydrogen bonds with the polar head of a phospholipids (i.e. phosphate and ammonium groups). Forming a unique pattern which can be characterized by spectroscopy.	In Liposome active principles are dissolved in the central part of the cavity. When no possibility of molecular interaction between the surrounding lipid and hydrophilic substance.
Phytosome act with the solvent having a reduced dielectric constant such as Acetone, Dioxane, Methylene chloride, Hexane and Ethyl acetate etc.	Liposomal drug complex is formed in the presence of water or buffer solution.

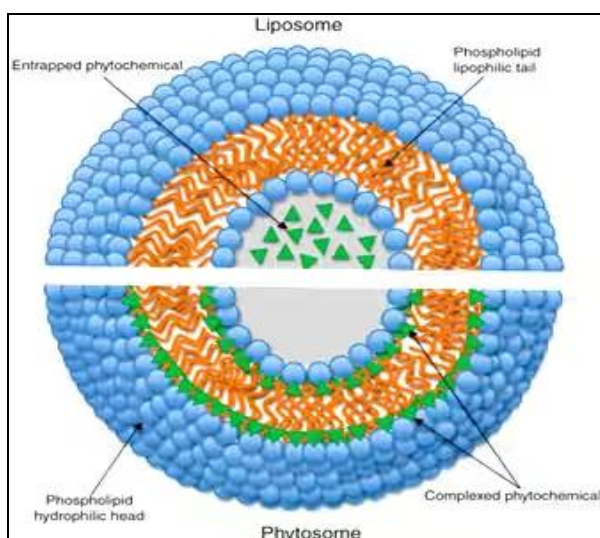


Fig 1: Phytosomes vs Liposomes

5. Applications of phytosome and commercially available phytosome technology

• Silymarin Phytosomes

Most of the Phytosomal studies are focused on Silybum marianum (milk thistles) which contains premier liver protectant flavonoids. Yanyu *et al.* (2006) prepared silymarin phytosome and studied its pharmacokinetic in rats. In the studies, the bioavailability of silybin in rat was increased remarkably after oral administration of silybin-phospholipid complex due to an impressive improvement of the lipophilic properties of silybin-phospholipid complex and improvement of biological effect of silybin.¹⁷ Tedesco *et al* (2004) reported Silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [25].

• Curcumin Phytosomes

Maiti *et al.* (2006) developed the phytosomes of curcumin

(flavonoid from *Curcuma longa*, turmeric) and naringenin (flavonoid from grape fruit, *Vitis vinifera*) in two different studies. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose level tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may due to decrease in the rapid elimination of the molecule from body [26].

- **Quercetin-phospholipid phytosomal complex**

Maiti *et al.* (2005) developed the quercetin-phospholipid Phytosomal complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride [27].

- **Phytosomes of grape seed extract**

It is composed of oligomeric polyphenols (grape proanthocyanidins or Procyanidin from grape seed extract, *Vitis vinifera*) of varying molecular size complexed with phospholipids. The main properties of Procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system and other organs through a network of mechanism that extend beyond their antioxidant effect [28].

- **Phytosomes of ginkgo biloba leaves**

Studies have shown that ginkgo phytosomes (prepared from standardized extract of *Ginkgo Biloba* leaves) produced better results compared to the conventional standardized extract from plant (GBE, 24% ginkgo flavones glycoside and 6% terpenes lactones). In a bioavailability study conducted with healthy human volunteers the level of GBE constituents (flavonoids and terpenes) from the Phytosomal form peaked

after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the Phytosomal GBE produced a 2-4 times greater plasma concentration of terpenes than did the non-Phytosomal GBE. Its major indication is cerebral insufficiency and peripheral vascular disorders and it can also ameliorate reduced cerebral circulations. Its improved oral bioavailability and good tolerability makes it the ideal ginkgo product even for long term treatment. Studies have also proved the improve efficacy of ginkgo phytosomes over the conventional standardized extract in protecting rat isolated hearts against ischemia [26].

- **Phytosomes of green tea**

Green tea leaves (*Thea sinensis*) is characterized by presence of a polyphenolic compound epigallocatechin 3-O-gallate as the key component. These compounds are potent modulators of several biochemical process linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. Green tea also furnishes us with a number of beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, hypocholesterolemic, and cardioprotective effects [27].

- **Phytosome of olive (*Olea Europaea*) oil**

A commercially available phytosome- Oleselect phytosome is available in the market based on olive oil polyphenols (Pandey and Patel, 2010). It is a strong antioxidant, anti-inflammatory and anti-hyperlipidemic (Rajendra, 2011). It inhibits the oxidation of LDL cholesterol and is cardioprotective [28].

6. Some patented technologies related to phytosomes

There are a number of innovative processes and formulation research studies in the field of phytosomes carried out by a number of academic scientists as well as by industrial laboratories. Some patents for phytosomes and other related technologies along with their applications and innovations are listed bellowed: [29, 30]

Table 2: Some Patented Technologies Related To Phytosomes

Title of patent	Innovation	Patent No.
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability.	EP/1844785
Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions	Compositions containing fractions deriving from Ginkgo biloba, useful for the treatment of asthmatic and allergic conditions	EP1813280
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	Fatty acid monoesters of sorbityl furfural selected from two diff series of compounds in which side chain is a linear or branched C3-C19 alkyl radical optionally containing at least one ethylenic unsaturation	EP1690862
Cosmetic and dermatological composition for the treatment of aging or photodamaged skin	Composition for topical treatment of the skin comprises a substance that stimulates collagen synthesis and a substance that enhances the interaction between extracellular matrix and fibroblasts Cosmetic or dermatological composition for topical treatment	EP1640041
Treatment of skin, and wound repair, with thymosin beta 4	Compositions and methods for treatment of skin utilizing thymosin β 4.	US/2007/0015698
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for making the same.	WO/2004/045541
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in treatment of circulation problems such as phlebitis, varicose veins, arteriosclerosis, hemorrhoids and high blood pressure	EP1214084
Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions Containing them	Complexes of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions	EP0283713

7. Conclusion

Phytosomes are novel compounds comprising lipophilic complexes of components of various plants like *Silybum Marianum*, *Ginkgo Biloba*, ginseng etc. with natural phospholipids. Preparation of phytosomes is usually carried out by non-conventional method. Phytosomes are used as medicament absorption of phytosome in gastrointestinal tract is appreciably higher resulting in increased plasma level than the individual component. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application. Phytosomes forms a bridge between the conventional delivery system and novel delivery system. Phytosomes enables pharmaceutical manufacturers to provide new pharmaceutical products using water soluble drugs and provides new developments in pharmaceutical industry. The technology can effectively deliver the product by topical and oral route.

Initially the phytosome complexes are used in cosmetics, but now a days they are popularly utilised in therapies such as antioxidants, cardiovascular, anti-inflammatory, hepatoprotective and anti-cancer as drug delivery system. Phyto-phospholipid complexing technique became an important revolution for herbal medicines that can't demonstrate a remarkable effect at *in vivo* tests instead of good *in vitro* results. Phytosomes technology emerged as a promising drug delivery system for improving efficacy, quality and target ability of active plant constituents and herbal extracts.

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