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Review Article

A Comprehensive Review Article on Herbosomes

Chetna Chauhan*, Dr. Hariom Sharma, Dr. Rishi Kumar

School of Pharmacy, Raffles University, Neemrana, Alwar, Rajasthan 301705.

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ABSTRACT

Compared to other allopathic treatments, herbal therapies consistently contribute to the improvement of human health. Innovative drug delivery systems will enhance the bioavailability of phyto-pharmaceuticals, which consist of plant extracts complexed with phospholipids and a blend of aprotic solvents. The bulk of biologically active plant compounds have significant in vivo effects. This comprehensive study sourced material on herbosomal techniques for phytopharmaceuticals from the internet databases Google Scholar, PubMed®, and Science Direct. Following the preliminary research on herbosomal techniques for phytopharmaceutical drug delivery conducted by Indena S.P.A. in Italy. The biological mechanism via which phyto- phospholipid traverses membranes and enters the bloodstream has been enhanced, becoming it more sophisticated and accessible than a mere herbal extract. A notable method to enhance the bioavailability of phyto-pharmaceuticals is via herbosome technology, which utilises phyto- phospholipids. Numerous methods of formulation exist, some of which have been patented. Nonetheless, other pharmaceuticals remain in research studies, with some available commercially, such as Silymarin, Ginkgo, Ginseng, Grape Seed, and Curcumin. Herbosomal preparations of herbs are more significant for targeted medicine delivery due to their superior bioavailability compared to normal formulations. This work emphasises the findings of previous research and our discoveries about phyto-phospholipid complexes with additional components.

INTRODUCTION

Herbs are known to be the oldest remedies used by mankind. As safer and more effective alternatives to contemporary synthetic medications, which are through to be full of harmful and unfavorable interactions, plant-derived pharmaceuticals have greatly increased in popularity and accessibility to the medical markets across the world. The primary health care requirement requirements of more than 80% of the population in underdeveloped and developing countries throughout the world by plant pharmaceuticals in traditional forms.

***Corresponding Author:** Chetna Chauhan
Address: School of Pharmacy, Raffles University, Neemrana, Alwar, Rajasthan 301705.
Email ✉: chetnasingh7279@gmail.com
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Currently, around 50% of all medications on the market are made from plants or other natural sources [1, 2]. Specific compounds or a collection of related ingredients from plants are being extracted, separated, and investigated for their many medical uses thanks to advancements in the fields of Phytochemistry and analytical chemistry [3] Historically, India has established traditional systems that are very different from others that accompany with use of herbs [4]. The rising interest in natural products has heightened scientific interest in healthy plants, and it appears that plant- derived goods can still play a significant part in human health. Since ancient times, Phytomedicine has been utilized to cure a variety of ailments. Natural formulation research output has increased in recent years, particularly in Nigeria and Africa as a whole. The formulations of an old system of medicine, such as the African, Chinese, and Indian systems, typically comprise crude extracts of many plants that include undesired and, at times, dangerous compounds in addition to the active principles [5, 6]. Due to the poor oral bioavailability of many plant compounds, due to large molecular weight, minimum water solubility or lipid solubility, poor membrane permeability, particularly those with polyphenolic rings in their structures, and some of the constituents after oral administration destroyed in the stomach due to presence of gastric juice, that's why researchers are becoming increasingly concerned about the bioavailability of active plant compounds [7, 8, 9, 10, 11]. Some methods for increasing bioavailability include nanoparticle formulation, liposomes or herbosomes as phospholipid formulations, micro- emulsion delivery, chemical structure modification, pro-drug delivery, and complexation with cyclodextrins [12, 13 That Novel Herbosome technique; increases the bioavailability of active constituents of herbs incorporating phospholipids invented by Indena S.P.A. Italy. The beneficial or therapeutic uses of herbs were elaborated or written by Ancient Chinese and Egyptian Papyrus. Researchers discovered that people from all over the world were interested in utilizing a comparable for a similar goal [14]. In 1989, polyphenolic extracts were chemically combined with phospholipids including phosphatidylcholine to create the drug phospholipid complexation process. When compared to the bioavailability of pure extract, the combination significantly boosted polyphenolic bioavailability [15]. In recent years, Herbosome a revolutionary approach has been successfully developed to achieve remarkable bioavailability of highly effective herbal drugs with enhanced biological profile and target significant pharmacological response with balanced nutrient safety as compared (Table 1 and Figure. 1) with Liposomal formulation [16].

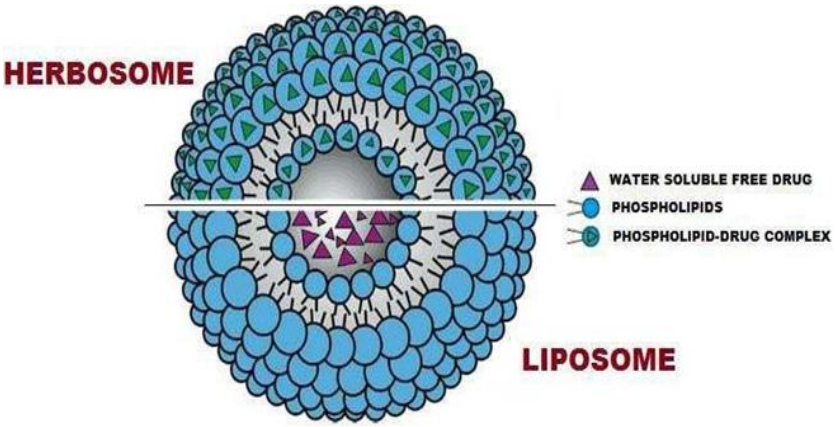

Figure 1. The structure of Liposomes differs from that of Herbosome

Figure 2. Advantages of the Herbosome complex

The term Herbo means “plant” whereas “some” means cell-like [17]. Combining the standardized herbal active extracts with phospholipid in specified quantity to generate herbosome macromolecular complex [18].

Table 1: Difference between Liposomes and Herbosomes

Liposome	Herbosome
In liposomes, the active principle is dissolved in the medium of the cavity or the layers of the membrane. No chemical bonds are formed.	In Herbosome active chemical constituents molecules are anchored through chemical bonds to the polar head of the phospholipids
In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water-soluble molecule.	In Herbosomes, phosphatidylcholine and individual plant compound form a 1:1 or 2:1complex depending on the substance.
Its bioavailability and absorption are lesser.	It’s much better bioavailability and absorption.

2. METHODOLOGY

2.1 Databases

The Science Direct database, PubMed®, and Google Scholar were searched for literature reviews. The following keywords were included in the search strategy: "Phytosome AND Bioavailability," "Phyto-phospholipid complex AND Bioavailability," "Herbosomes AND Drug delivery," "Medicinal plants AND Herbosome AND Drug delivery," and "Herbosome formulations AND Bioavailability AND Clinical trials."

2.2 Inclusion and exclusion criteria

The literature from the phyto- phospholipids complex developed by the Italian company Indena S.P.A. for drug delivery was reviewed. The formulation techniques for the phyto-phospholipids complex were chosen together with

studies on the various phyto-phospholipid formulations used for various diseases or conditions. Articles with keywords in the text were added based on inclusion criteria. Scientific papers that lacked adequate details were eliminated.

2.3 Data screening

Out of several scientific publications that were picked from the database after identification reviewed the articles with pertinent and accurate material, some of them documented articles that didn't fulfil the review's requirements were excluded. Finally, data- rich papers were used and taken into account in addition to the current study.

2.4 Analysis

By dividing the number of documents chosen by the total number of documents, the published scientific publications with Herbosome complex information on the phytoconstituents were retrieved and subjected to analysis. The fundamental working concept is, that plant extracts phytochemical components, such as flavonoids and terpenoids, give phosphatidylcholine in their complexity. Herbosome is produced when extractor polyphenolic components and a ratio (0.5:1, 1:1, or 1:2) of lipid react in a highly non-polar solvent. Phospholipids' amphiphilic properties include both polar head and non-polar tail regions. A weak hydrogen bond is generated as a result of a complex formation that relays the lipophilic property around the non-polar end of a phospholipid, which connects the polar head of phospholipids and the non-polar end substrate. As a result, Herbosome becomes appropriate for both oral and topical medication administration [18, 19]. General Instructions for Preparing Herbosomeswiththe ratio of Phyto-phospholipid complex 0.5:1, 1:1, 2:1 in a mixture of aprotic solvents such as acetone, dioxane, or Dichloromethane at temperatures of 60°C or 40°C – 50°C for a suitable time, after that concentrate the solution to 5 – 10mL and with the use of spray drying or any other non-solvent method precipitate formed and dried herbosome are stored in an amber-color glass bottle [20, 21, 22] and Figure. 3 show the general steps of preparation of Herbosomes [23].

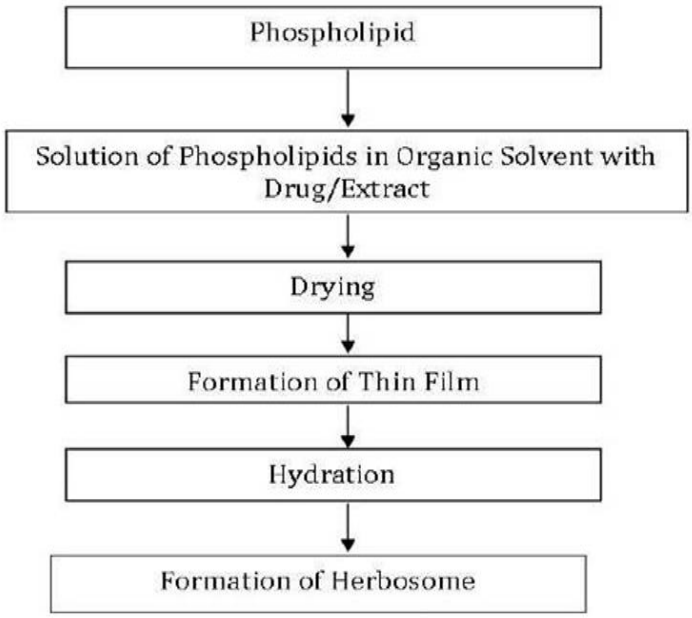

Figure. 3. General Procedure for Herbosome Preparation

3. Different techniques of Herbosome formulation

The following is a technique of the various herbosome formulation processes below in Figure 4.

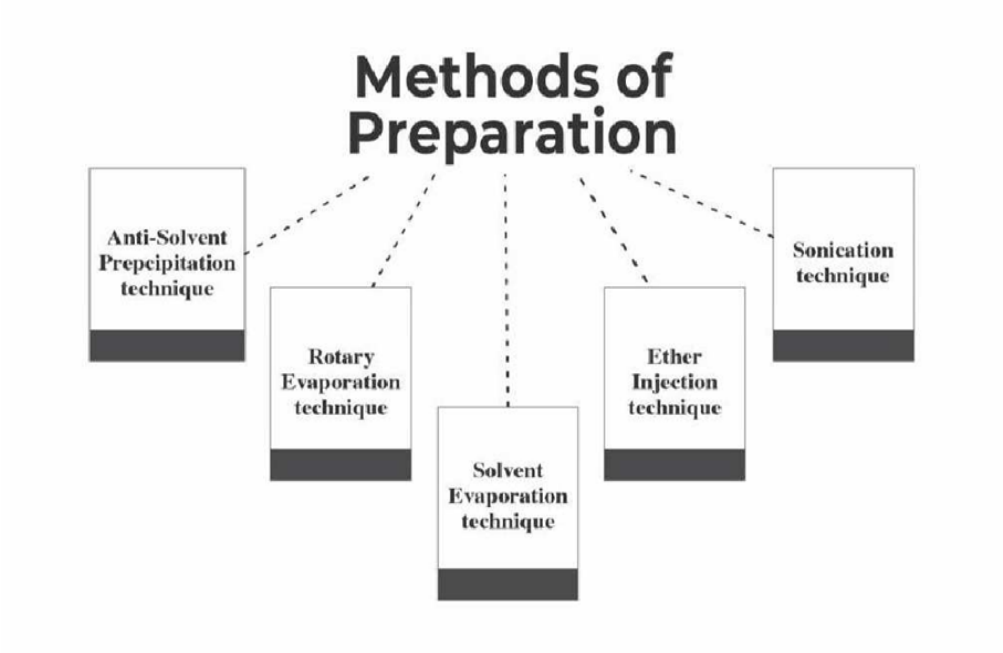

Figure 4. Methods of Herbosome preparation

3.1 Anti-solvent precipitation technique

The fixed amount and quantity of phospholipid combined with herbs extract is a suitable ratio in 100mL round bottom flask and reflux with 20mL of Dichloromethane for 2h (temperature<60°C); Concentrate the mixture to 5- 10mL; Add dissolving agent carefully with continuous stirring, filter and collect the precipitate with store in a desiccator overnight; crush dried precipitate in a mortar. Sieve the powder through mesh size #100 (Figure. 5). The developed formulation is stored in an amber-colored glass bottle in powder form at a temperature of 25°C [13, 24].

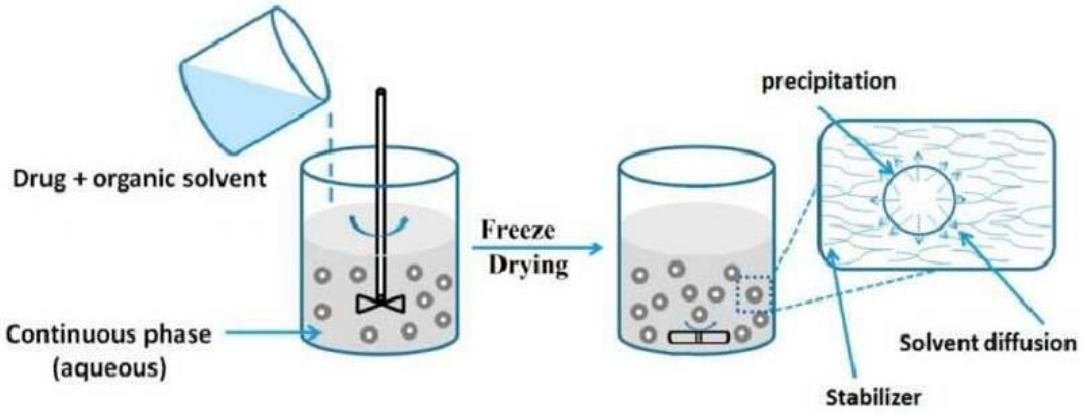

Figure 5. Anti-solvent precipitation technique

3.2 Rotary Evaporation technique

Specified amount/quantity of herb extract mixed with phospholipid dissolved within 30mL of tetrahydrofuran at temperature <40°C, with continuous stirring, add n- Hexane to a thin film of the sample with continued stirring, collect the precipitate, and precipitate in a complex form stored in an amber-colored light-resistant glass bottle at a temperature not exceeding 25°C (Figure. 6)[13].

Figure. 6 Rotary Evaporation technique

3.3 Solvent evaporation technique

The specified quantity of herbal extract with phospholipid mixed (in 100mL round bottom flask.) and refluxed with 20mL of acetone for 2h (temperature 50°C-60°C); Concentrate the mixture to 5-10mL; filter and collect the precipitate; store complex at a temperature 25°C in an amber color glass bottle (Figure 7) [13].

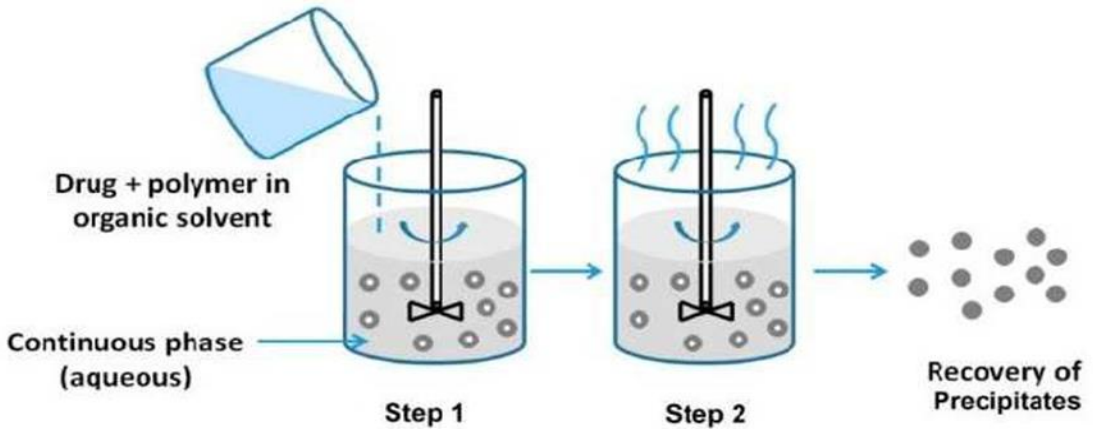

Figure. 7 Solvent evaporation technique

3.4 Ether-injection technique

Dissolve the drug-lipid complex in an organic solvent. Inject this mixture slowly into a heated aqueous agent Formation of amphiphilic vesicles having different structures [13].

3.5 Sonication technique

Put the correct amount of phospholipid and cholesterol in a flask with a flat bottom, dissolved in 10mL of chloroform, and then sonicate the mixture in a bath sonicator using a rotating evaporator at 40°C white under decreased pressure will remove organic solvents. In a rotary evaporator, after completely removing the thin solvent, a layer is created that is hydrated with the polyphenolic extract of the medication. In an amber-colored container, the phospholipid mixture was sonicated [25].

4. Evaluation and Characterization of Herbosome

Characterization and Identification of herbosomes can be done with particle shape, particle size, distribution of particles, and percentage of active drug molecules adhering capture volume, and release of drug (percentage) along with considering the following factor such Physical size, Cell permeability, Percent entrapped solutes, Chemical composition, Quantity and purity of the starting materials. A variety of techniques have been employed for the study and characterization of Herbosomes[26] [27]. Visualization includes optical microscopy for the evaluation and characterization of with complex suspended with water and drops on a glass slide, observed and evaluated with different magnification [28, 29]. The internal structure by transmission Electron Microscopyis done with a centrifuged sample, a thin film on the carbon-coated copper grip [28]. Scanning Electron Microscopy is used for surface texture information, surface morphology, size, and shape [28].

4.1 Measurement of Particle size

The sample was diluted with distilled water, then measured the particle size. Photon correlation spectroscopy (PCS) is also utilized for determined the particle size [29, 30]. Dynamic light scattering (DLS) coupled with a computerized inspection system and Photon correlation spectroscopy (PCS) is utilized for the determination of size and zeta potential. Surface tension is measured by the ring method in a dunuoy ring tensiometer in aqueous [31, 32]. Spectroscopic evaluation by Nuclear Magnetic Resonance (NMR), Fourier Transformed Infrared Spectroscopy (FT-IR), Entrapment efficacy, X-ray diffraction study employed for structure elucidation along with electron distribution [33].

% Entrapment efficacy = (Amount of drug in sediment/Total amount of drug added) x 100

Drug content by thoroughly dissolving a precisely weighed quantity of Phyto- phospholipid dispersion in 10mL of methanol, the drug concentration of the Phyto- phospholipid complex was ascertained. After the appropriate dilution, the absorbance was measured using spectroscopic techniques at an appropriate wavelength, and the drug content was calculated using a formula [32, 33].

% Drug content = Actual drug content in Phyto-phospholipid complex/theoretical yield x100

In-vitro drug release by Franz diffusion cell method or dialysis bag and different kinetic models; for in-vitro release of drug content is adopted for finding the mechanisms. Also, an in-vitro dissolution test was employed for finding drug release [34].

5. Formulations of Herbosome

Herbosome formulations are developed for orally and locally use to get the most effective formulations by this novel technology each in terms of formulating manageableness and increased bioavailability [10].Table 2 showed the commercial formulation available in the market [35]. The herbosomes are often spread in oily vehicles (vegetable or semi-synthetic oil) to get the viscous solution to be filled in soft gelatin capsules [36]. The most suitable dosage form is soft gelatin capsules for herbosomes. The novel structural configuration of herbosomes in an oily solution filled in soft gelatin capsules. Several primary trials are required or performed with vehicles because not all the novel herbosomes formulation act or showed in the same way when it is entrapped with oily solvents in soft gelatin capsule dosage form [10]. The Garlic soft gelatin capsules formulation is approachable in the market and administered orally. Curcumin soft gelatin 500 mg capsules are given by oral route [13]. The Herbosomes composition is often developed in hard gelatin capsules yet. Hard gelatin capsule filled with novel herbosomes in small density powder from developed with volumetric method usually less than 300mg for size #‘0’capsules. With an automatic/Semiautomatic/Manually hard gelatin capsule filling method, a preliminary dry granulation method is recommended to outline the most effective producing process. Also, Ashwagandha administers orally with the strength of 500mg. Neem hard gelatin capsules of 250mg are given by oral route [10]. The dry granulation method is preferred to get tablets with higher doses and with appropriate technological and biopharmaceutical properties. However, sometimes flow property of granules, potential adhesiveness, and density are very helpful for herbosome complex formulation. For low doses of medicaments, the direct compression method is applied with 60- 70% excipients to increase the formulation properties of tablets[10]. Carica papaya herbosomal tablets 500mg are administered by oral route Shatavari pill 250mg are given by oral route. Neem tablets of 300mg are given by oral route [37]. The Herbosomes composition is often developed locally yet. For external preparation phospholipid dispersed as an emulsion form at low temperature in lipidic solvents. In the case where the quantity of lipids is restricted then formulation at a low temperature of less than 40°C [10] spread into the watery part numerous kinds of Herbosomes are applied locally like Curcuma longa Herbosomes [38], Mitomycinecherbosome [39], Ashwagandha Herbosomes [40], ginger Herbosomes[41] and many more.

Table 2: Commercial Marketed Formulation

Commercial Marketed	Uses	Reference
Silybinphytosome	Hepatoprotective, Antioxidant	[35]
Ginkgophytosome		
	Protect the brain and vascular lining,	
Ginsengphytosome	ant-aging agent	
Hawthronphytosome	Immunomodulatory	
Grapeseedphytosome	Cardioprotective, antihypertensive	

Curcuminphytosome	Antioxidant, anticancer	
Escin β-sitosterolphytosomes	Antioxidant, anti-inflammatory	
Centellaphytosome	Anti-oedema	
	Skin disorder	

The benefits of Herbosomes increase a drug's transdermal and dermal absorption, increasing its bioavailability and yielding therapeutic benefits that are considerably stronger [42]. Delivery of a wide range of complex and unique plant parts. The complex system is operational, integrated, and ready for immediate financial advantage [43]. Herbosomes are resistant to gut microbes' actions and maintain their stability in stomachic discharge [44]. A better justification for stability the dose of phytoconstituents decreased. Enduring therapeutic impact Biochemical membranes are more permeable to Phyto-constituents. The Patented technology has a high level of commercial acceptance [42, 45]. The drawbacks include It has a short half-life. The breakdown, dissociation, and resolution of phospholipids happen very fast. The cost of manufacture is rather high. [43, 44].

6. Biological Applications and Their Utilization

Many plant compounds including flavonoids, terpenoids, saponins, and alkaloids that are weakly lipid-soluble, are polyphenolic in origin [42]Numerous of these substances, particularly flavonoids, have been shown to have a variety of therapeutic effects, including anti- inflammatory, liver-protective, antioxidant, Cardioprotective, antidepressant, anti-allergic, and anticancer properties [46, 47, 48, 49, 50]. Bioavailability; among its many pharmacological properties are anti-tumor, anti-inflammatory, anti-nociceptive, anti-obesity, and thermoregulatory actions [51] possess that Evodiamine is a quinolone alkaloid found in the plant Evodia rutaecarpa offers anti-tumor potential, that had a greater in-vitro dissolution rate, better absorption, a longer duration action with a higher bioavailability and T1/2 from 1772.35 µg h- 1L-1 in 1.33 hours to 3787.24 µg h-1L-1 in 2.07 hours respectively. By creating the phospholipid complex of Ginkgo biloba extract, [52] were able to show the pharmacokinetic profile of kaempferol, quercetin, and isorhamnetin following oral treatment in rats shown in table 3, and when compared to the Tmax of kaempferol, quercetin and isorhamnetin were shown to be lower in phospholipid complex from compared with crude extract results increase in bioavailability.

Table 3: Pharmacokinetic profile of kaempferol, quercetin and isorhamnetin

Chemical constituents (G. biloba)	Cmax	AUC
Kaempferol	180.23 to 323.56	1.95
Quercetin	179.21 to 724.89	2.42
Isorhamnetin	195.96 to 672.29	2.35

New bioavailable phospholipid complexes derived from olive fruit or leaf extract used to create the Oleaselectphytosomepossess increases in oral bioavailability as compared with the uncomplexed extract [53]. Bioavailability studies Conducted of oxymatrine on rats with an oral phospholipid complex dose of 100mg/kg resulting in an increase in the average value of Cmax from 0.164 µg/mL and T max was 2.17hours and 1.71 hours in complex form along with increased AUC with a value 9.43 µg h ml-1 [54]. Curcumin's pharmacokinetic profile was shown to be improved by by preparing a phospholipid complex investigated on rats, plasma concentration increased from 0.5g/mL to 1.2g/mL in complex formation, with a half-life increased from 1.45 to

1.96, Cmax from 0.5 to 1.2µg/mL, Tmax from 0.75 hours to 1.5 hours in case of the complex with enhanced bioavailability up to 125.8% [55]. The bioavailability of silybin- phospholipid complex in comparison to silybin-N- methylglucamine was assessed by with C maxfrom 104.29 ng/mL to 126.72 ng/mL from 10 min to 05 min respectively shown enhanced bioavailability and a longer plasma therapeutic level [56]. Antioxidant activity herbosomal complex formation was formulated by using Soya lecithin and cholesterol in a different ratio by using solvent evaporation method with Nano herbosomes of Eleocarpus ganitrus for antioxidant activity shows improved drug delivery of same phytoconstituents having low aqueous solubility [57]. Silipide, a phytosome from the Silybummarianum plant by against liver damage brought by high doses of CCl4 and paracetamol in rats [58]. Phytosomes are created by encapsulating Calendula officinalis extracts. On Vero cell lines, reactive oxygen species analysis was carried out using an in-vitro anti -oxidant test. The result showed that the cell viability of plant extract and Au-loaded phytosome were around 35 percent and 81 percent respectively [59]. Anti - diabetic activity;naringenin herbosome was prepared by solvent evaporation method with 1:0.5, 1:1, 1:2, and 1:3 ratio, after characterization, treatment with naringenin herbosome of diabetic rats compared with conventional naringenin was shown to reduce the elevated blood glucose level with a reduced level of cholesterol, triglycerides, and blood urea nitrogen level [57]. Anti-tumor conducted a study on the methanolic extract of Terminalia arjuna bark and its phytosome in order to examine its anti-proliferative activity on the human breast cancer cell line MCF-7 by MTT test, the extract's and its phytosome IC50 values were 25 g/ml and 15 g/ml, respectively, indicating that they have a stronger anti -proliferative impact than the free drug [60]. Employed luteolin is phytosome to down-regulate the Nrf2 expression and sensitize cancer cells MDA-MB 231cells (human breast cancer cell line) to the chemotherapeutic drug Doxorubicin. The activity of detoxifying enzymes and transporters on Doxorubicin would be prevented by the presence of luteolin phytosome, which would make cells more susceptible to the drug [61]. Topical application novel herbosomes formulation developed by using PEG-Poloxamer for external application for cold injury equipped with PEG-3350 and Poloxamer-188 has excellent entrapment efficiency >90% and <300nm by Higuchi release kinetics [62]. Rutin, one of the most popular flavonoids in Rutagraveolens is used to treat capillary fragility, hypertension, ultraviolet radiation-induced cutaneous oxidative stress, hepatic and blood cholesterol, cataract, and cardiovascular disease. The impenetrable stratum corneum was shown to be more permeable to Rutin phytosomes than to its free form. Skin absorption of Rutin phytosomes was 331.33 percent, compared to 13 0.87 percent for Rutin [63]. The plant extract and saponinphytosomal complex (Panax ginseng M.) showed greater activity in vasal protection, capillary permeability, and UV radiation protection. It has a moisturizing effect on the cutis, making it more elastic as a result of a fibroblastic stimulation at the dermal level, with an increase in proteoglycan and collagen production. It is also useful in the development of dermatological and cosmetic pharmaceutical formulations [64]. Wound healing Sinigrin found in plants of the Brassicaceae family, to repair wounds oh HaCaT cells when tested both alone showed 71 percent healing rate and as part of phytosome complex showed 100 percent healing rate. On the A-375 melanoma cells, Sinigrin phytosomes also exhibit improved anti-cancer activity [65]. Wrightia arborea leaves and their phytosomes were studied for their comparative effects. The ethanolic extract alone could only cure 65.63 percent of the lesion, but the phytosomes demonstrated healing of around 90.40

percent [66]. Recent years have seen the development of a number of therapeutically more effective Phyto-phospholipid complexes from various plant extracts/active compounds.

7. Future Directions

Herbosomes enhance the in-vivo bioavailability of herbal drugs, which despite positive in-vitro results fail to deliver a similar response in-vivo. A key method for enhancing the pharmacokinetic and pharmacodynamics characteristics of plant elements with high therapeutic potential but low bioavailability is the complexing of herbal medicine molecules with dietary phospholipids. The Phytophospholipid complex, which was first created for cosmetic use, has now undergone substantial research and development to serve as a cutting-edge drug delivery method with systemic activity. The potential of Phyto-phospholipid complexes for therapeutic applications has increased due to the widespread replacement of the conventional methods for producing them with hydrophilic solvents like ethanol instead of hazardous organic solvents like tetrahydrofuran and dichloromethane. As a common practice, the solvent evaporation approach has been used often to produce Phyto- phospholipid complexes. There aren't many studies showing a connection between increased in-vivo and in-vitro pharmacokinetic characteristics and the pharmacological effects of medicinal molecules in their phospholipid complexed forms. Another issue that requires further research and attention is the stability of the Phyto- phospholipid complexes. Regarding their marketability and lifespan, the data supporting the stability of the Phyto – phospholipid complexes during storage are lacking. Due to its simple process of novel herbosome formulation and improved commercialization scale; profitable for the pharmaceutical industry. The herbosomes components are relatively safe and stable.

8. CONCLUSION

An good opportunity and renewed hope have been offered by the phyto-phospholipid complexation technique for the purpose of enhancing the in-vivo bioavailability of herbal medications. These medicines, although having optimistic in-vitro findings, have not been able to elicit a comparable reaction in-vivo. Polyphenolic plant components, such as flavones and others, have enormous therapeutic potential; however, their use in the treatment of serious diseases such as cancer, hepatic ailments, and rheumatic problems has been a source of controversy for a long time. This is because polyphenolic plant components are unable to pass through the lipoidal barrier. A novel formulation of herbosome that has a favourable herbal medicine process and overcomes hurdles to the creation of a dosage form for increased combination bioavailability is being developed. There have been many patent endorsements granted to these newly discovered substances. The Herbosome presents a promising future since it enables the development of medicine delivery systems that may be applied topically or taken orally. There is a wide variety of herbosome products available on the market; however, these products do not yet include all of the phytoconstituents that have the amazing ability to treat severe disorders. More research might be done in order to develop herbosomes that are extremely specific to their target.

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