ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

Phytosomes as Novel Drug Delivery Methods

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Abstract:- As newly identified phytochemicals increase, studies on their potential medicinal applications in biological contexts will be updated. Nevertheless, these chemicals' limited solubility and susceptibility to degradation limit their use in medicinal and food applications. Currently, learning more about vesicular drug delivery methods may aid in enhancing these features. Because of their exceptional trapping capability, safety, and biocompatibility, vesicles have been demonstrated to be extremely promising delivery methods for a variety of beneficial phytochemicals at a cellular level. Phytosomes, a kind of vesicular drug carrier, combine phytochemicals with phospholipids to produce a complex that enhances compound stability overall and improves the absorption and bioavailability of bioactive compounds. One of the newest, smaller-sized lipid-based vesicles to increase the transport of plant-based nutraceuticals is the nano-phytosome. To guarantee a good safety profile and fulfill repeatability requirements, physical measurements that provide details on the dynamics of release and formulation stability must be thoroughly analyzed. Although there is presently not enough data from clinical trials to make judgments about the biological activities of specific preparations, the overall strength of the evidence supporting these formulations is positive and encourages more study in this area. Clinical trials on standardized products that demonstrate greater effectiveness than unformulated components or extracts will be essential in the future to raise awareness of these technologies.

Keywords:- *Phytochemicals, Phytosomes, Vesicular drug carrier, Clinical trials.*

I. INTRODUCTION

The vesicular drug delivery method known as phytosomes, sometimes known as herbosomes, improves the absorption and bioavailability of low-soluble medications. They are created by reacting phosphatidylcholine (or any other hydrophilic polar head group) with plant extracts in an aprotic solvent. The result is a complex of phospholipids and naturally occurring active phytochemicals bonded in their structures. When compared to common preparations, these formulations have better pharmacological and pharmacokinetic characteristics. Hydrophilic phytoconstituent-choline complexes are entirely covered by the lipid-soluble phosphatidyl part. Their notable advantages include increased drug encapsulation, improved bioavailability, and a higher stability profile (chemical bonds are established between the phytoconstituent and the polar head of the amphiphile molecule).[1,2,3]

Phytosomes have higher bioavailability than herbal extracts because of their enhanced ability to pass through lipid-rich bio-membranes and finally enter the bloodstream. Such novel drug delivery system includes a variety of pharmaceutical carriers, including macro- and micro molecules, polymeric micelles, and particulate systems. The vesicular systems are more firmly required to be the culmination of one or more concentric lipid bilayers. when specific dihydrogen monoxide-sensitive building blocks are exposed to it. These mechanisms help extend a drug's half-life in the body by lowering toxicity and postponing the removal of medications that are quickly metabolized. To increase the bioavailability of plant extracts containing water-soluble elements, the Italian pharmaceutical and nutraceutical companies were the first to discover the complexation of these extracts with phospholipids. They filed a "PHYTOSOME" patent for the invention.[1, 2, 3]

II. ADVANTAGES OF PHYTOSOMES

- Phytosomes are tiny cells that prevent stomach bacteria and digestive secretions from destroying the beneficial ingredients found in plant extracts.
- It guarantees the medicine is delivered to the appropriate tissues properly.
- Using phytosomes to deliver the herbal medication does not have to jeopardize the nutritional safety of the herbal extracts.
- Because the main ingredients have been absorbed to their maximum, the dose needed has been decreased.
- A notable improvement in the drug's bioavailability takes place.
- Because the drug forms vesicles by conjugating with lipids, entrapment efficiency is high and even preset.
- The formulation of phytosomes does not provide any drug entrapment issues.
- Because of the creation of chemical connections between phosphatidylcholine molecules and the phytoconstituents, phytosomes have a superior stability profile.
- Because phosphatidylcholine is a crucial component of a cell membrane, it not only serves as a carrier in the phytosome process but also nourishes the skin.
- In skin care products, phytosomes work better than liposomes.
- Phytosomes show a much higher clinical benefit.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

- In addition to serving as a carrier in the production of phytosomes, phosphatidylcholine also has hepatoprotective properties; thus, when combined with other hepatoprotective compounds, it has a synergistic effect.
- The production of stable emulsions or creams is made possible by their poor solubility in aqueous mediums.
- By making the substance more soluble in bile salt, it makes liver targeting easier.[1, 2, 3]

III. PROPERTIES OF PHYTOSOMES

A. *Chemical Properties*

Phytosomes are a natural substance combined with naturally occurring phospholipids, such as those found in soy. The interaction of stoichiometric quantities of phospholipid with a chosen polyphenol (such as simple flavonoids) in a nonpolar solvent produces this complex. In it has been demonstrated by their spectroscopic and physicochemical data that the primary phospholipid-substrate interaction results from the hydrogen bonds that form between the polar functional groups of the substrate and the phospholipids' polar head, or the phosphate and ammonium groups. They are molecules that are lipophilic and have a distinct melting point. They are also easily soluble in nonpolar solvents, unlike the hydrophilic moiety, and they are only moderately soluble in lipids. Phytosomes take on a micellar shape and form structures resembling liposomes when they are handled with water.

B. *Biological Properties*

Phytosomes are sophisticated herbal preparations that outperform traditional herbal extracts in terms of absorption, utilization, and overall efficacy. Pharmacokinetic investigations or pharmacodynamics testing in experimental animals and human subjects have revealed the higher bioavailability of the phytosome over the non-complexed botanical derivatives. [1,2,3]

IV. REPORTED FORMULATIONS

Hong Jin Tae et al. (2018) investigated the effects of *Centella asiatica* phytosome (CA phytosome) on inflammatory responses by macrophages in an atopic dermatitis (AD) mouse model. The effects of CA phytosome on atopic dermatitis were examined by using a phthalic anhydride (PA)-induced AD mouse model and RAW 264.7 murine macrophages. iNOS and COX-2 protein expression variations and histopathological alterations were assessed using Western blotting; NF-κB activity was measured using EMSA. ELISA was used to determine the levels of TNF-α, IL-1β, and IgE in the blood of AD mice. Histological examination revealed that the CA phytosome prevented inflammatory cells from infiltrating. The application of CA phytosomes suppressed the release of TNF-α, IL-1β, and IgE, as well as the production of iNOS and COX-2 and the activity of NF-κB. Furthermore, CA phytosomes (5, 10, and 20 μg/ml) significantly reduced the generation of NO (one μg/ml) produced by LPS, as well as the expression of COX-2 and iNOS in RAW 264.7 macrophages.

Moreover, the CA phytosome suppressed NF-κB's LPS-induced DNA binding capabilities. This was linked to the cessation of IκBα degradation and ensuing reductions in p65 and p50 translocation into the nucleus.[4]

Camelia Sorina Stancu et al. (2023) reported the preparation of phytosomes with bioactive compounds from hydroalcoholic extracts of ginger rhizomes and rosehip fruits In Vivo with Improved Bioavailability, Antioxidant, and Anti-Inflammatory Effects. Using the thin-layer hydration approach, the phytosomes (PHYTOGINROSA-PGR) were made from freeze-dried GINex, ROSAex, and phosphatidylcholine (PC) in various mass ratios. Structure, size, zeta potential, and encapsulation efficiency were all described for PGR. The findings indicated that PGR is made up of many populations of particles, each of which has a zeta potential of about -21 mV and a size that increases with ROSAex concentration. β-carotene and 6-gingerol had an encapsulation effectiveness of more than 80%. The quantity of ROSAex in PGR is directly correlated with the shielding effect of the phosphorus atom in PC, according to 31P NMR spectra. In cultured human enterocytes, PGR with a mass ratio of GINex: ROSAex: PC-0.5:0.5:1 exhibited the strongest anti-inflammatory and antioxidant properties. Before LPS-induced systemic inflammation, PGR-0.5:0.5:1 was administered by gavage to C57Bl/6J mice, and their antioxidant and anti-inflammatory properties were investigated. PGR-0.5:0.5:1 bioavailability and biodistribution were evaluated in these animals. PGR caused a 65% reduction in the stomach along with a 2.6-fold increase in 6-gingerol levels in plasma and over 40% in the liver and kidneys when compared to extracts. When PGR was administered to animals suffering from systemic inflammation, the antioxidant enzymes paraoxonase-1 and superoxide dismutase-2 were elevated, while the levels of proinflammatory TNFα and IL-1β in the liver and small intestine were reduced. PGR did not cause any toxicity in vivo or in vitro.[5]

Wantida Chaiyana et al. (2023) Investigated the Antioxidant, Anti-Inflammatory, and Attenuating Intracellular Reactive Oxygen Species Activities of *Nicotiana tabacum* Virginia fresh (VFL) and dry (VDL) leaf Extract Phytosomes and Shape Memory Gel Formulation. Using the FRAP test, DCFH-DA fluorescent probe, DPPH and ABTS radical scavenging assays, and phytosomes and/or extracts, the in vitro antioxidant activity and intracellular reactive oxygen species reduction were examined. Using an MTT and a nitric oxide test, the cytotoxicity and anti-inflammatory properties of VDL and VFL phytosomes were investigated, respectively. First, we noted that the dried leaf extract had a much higher total phenolic content than the fresh leaf extract. VDL and VFL extracts had 4.94 ± 0.04 and 3.13 ± 0.01 μg/mL of chlorogenic acid and 0.89 ± 0.00 and 0.24 ± 0.00 μg/mL of rutin, respectively, according to the findings of the HPLC analysis. The phytosomes exhibited high chemical stability, steady size, polydispersity index, and zeta potential values in the VDL and VFL extracts.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

Higher phenolic and flavonoid concentrations in VDL and VDL phytosomes were associated with better DPPH and ABTS radical scavenging actions as well as a decrease in intracellular ROS. The findings indicated that the primary source of their antioxidant action is the phenolic chemicals. The anti-inflammatory properties of the phytosomes were suggested by the inhibition of nitric oxide generation generated by LPS in both VDL and VFL phytosomes. In terms of pH and viscosity, the shape memory gel containing VDL and VFL phytosomes exhibited good physical stability. Regarded as a potentially effective medicinal delivery strategy, the VDL and VFL phytosomes distributed in the shape of memory gels shield the skin from oxidation and reactive oxygen species.[6]

Nikunjana A. Patel et al. (2023) evaluated an anti-inflammatory gel made of *Berberis aristata* root, *Rubia cordifolia* root, and *Boswellia serrata* gum for a synergistic effect in the treatment of acute inflammation using Carbopol 934 and Propylene glycol. The concentration of the polymer (carbopol 934) and the penetration enhancer (propylene glycol) were used as independent variables in the construction of the 3^2 factorial design. The dependent variables were viscosity (m.Pas), the percentage of in vitro release of AKBA, Rubiadin, and Berberine, and a total of nine possible experimental runs were designed and assessed. Expert designers used the overlay plot and desirability technique to choose the optimum gel. The optimized gel had a viscosity of 39568 mPas and included 0.48 mg of berberine, 0.42 mg of rubiadin, and 0.51 mg of AKBA. An in vivo and histopathological analysis demonstrated the good anti-inflammatory efficacy of the produced gel. The group treated with 2% gel showed a similar reduction in edema and infiltration of mononuclear and polymorphonuclear cells as compared to the group treated with Diclofenac sodium. The oedema in the 1% gel-treated group was reduced, but the 1% gel-treated group was not as effective as the 2% gel-treated group in terms of infiltration of mononuclear and polymorphonuclear cells and rupture of connective tissues.[7]

Girendra Kumar Gautam et al. (2019) investigated the phytosomes containing ethanolic extract of leaves of *Bombax ceiba* for hepatoprotective activity. Research on phytosomes can improve medicinal effectiveness and reduce the need for frequent administration. Solvent evaporation is used in the formulation of phytosomes. The various formulations provide ratios of 1:0.5, 1:1.5, 2:1.5, 2:1.1.0, and 2:1.5. Ratio 1:1.5 was used for the final formulation based on the best formulation (F3). A 12-hour, 84.65% release is shown by an in vitro dissolution analysis of the phytosome prolonged release pattern. The DPPH model was employed to look into the synergistic impact of *Bombax ceiba*-phytosome free radical scavenging capability. Finally, phytosomes were produced and enclosed satisfactorily. It captures free radicals more efficiently and has a longer release pattern. The herb known as *Bombax ceiba* is historically used to treat diabetes and has been shown to have hepatoprotective properties.[8]

Santosh Marennavar et al. (2024) Reported the Incorporation of standardized *Curcuma longa* into phytosomes and evaluation for in vitro anti-inflammatory and BSL bioassay. Numerous pharmacognostic indicators were used to assess the quality of the plant material. After that, the plant material was macerated in water: ethanol, and then Soxhlet extraction was performed. To find out if plant metabolites were present, phytochemical analysis was performed on the resultant extract. The phytosomes containing extract were effectively prepared using the thin film hydration process. Prepared phytosomes may be used as a natural anti-inflammatory treatment alternative, according to in vitro anti-inflammatory activity. The bioactivity of the produced phytosomes was also validated by the brine shrimp lethality experiment. Future studies on *Curcuma longa* quality analysis and plant identification can benefit from the application of the standardized technique.[9]

Afreen Ansari et al (2023) investigated the Formulation and Evaluation Of the Phytosome Gel Of *Azadirachta indica* leaves. The methanolic fraction of neem leaves was extracted after neem leaf powder underwent a variety of physiochemical analyses; the yield of the extract was 6.34%. Alkaloids, flavonoids, and carbohydrates were detected by phytochemical screening. then the methanolic fraction of the neem leaves were extracted, yielding an extract with a 6.34 percent yield. The dry extract sample's total phenolic compound (TPC) was 0.756 mg/100 mg of gallic acid equivalent, while the total alkaloid content was 0.632 mg/100 mg of atropine equivalent. Phosphatidylcholine and cholesterol were combined in five distinct types of phytosome formulations (4:1), (2:1), (4:3), (1:1), and (1:1.25). Numerous metrics, including yield, drug content, particle size, and encapsulation efficiency, were used to describe these formulations. The drug content ranged from 90.21% to 97.52%, the mean particle size (nm) was around 700 nm, the encapsulation efficiency was between 78.67% and 95.34%, and the overall formulation yield was 86.32% to 98.91%. The drug's excipient compatibility was verified by FT-IR research. The five phytosome formulations were combined with gel and assessed based on a range of parameters. The pH range for all formulations was 6.8 to 7.3, the spreadability was 5.6 to 7.9 cm, the drug content ranged from 98.9% to 101%, the viscosity ranged from 98 to 115 centipoices (cp), and the percentage of permeation ranged from 83.2% to 92.7%. However, F-3 formulation was excellent in terms of drug release kinetics, as seen by its 97.913% drug release percentage, which was in line with the Higuchi Kinetic Model. The F-2 formulation's 95.56% drug release was well-suited for both first-order kinetics.[10]

Archana Arvind Naik et al. (2023) Reported the Formulation Containing Phytosomes of Carotenoids from *Nyctanthes arbortristis* and *Tagetes patula* Protect D-galactose Induced Skin Aging in Mice. Using the lipid film hydration process, phytosomes of the carotenoid-rich extract of the tubular calyx of *Nyctanthes arbortristis* and the petals of *Tagetes patula* were produced, and these phytosomes were then added to the gel basis. The gel formulation's stability was assessed per ICH recommendations. Using an

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

aging model produced by d-galactose, the formulation's efficacy was assessed. For 42 days, albino mice were given 100 mg/kg of d-galactose to cause skin aging. For 42 days, the gel composition was administered topically. Subsequently, histological analyses of treated skin samples and the calculation of biochemical indicators, such as glutathione and malondialdehyde (MDA), were used to assess the impact of formulation on skin aging. RT-PCR was also used to measure COL type I and elastin gene expression in skin tissues. It became apparent that the percentages of crocin and lutein entrapped (%w/w) in phytosomes were 60.20% and 50.81%, respectively. Crocin and lutein, two carotenoids with improved stability, were shown to be present in the formulation at a rate of 99.98% w/w to 99.85% w/w after three months, according to accelerated stability experiments. In comparison to the untreated group, the formulation containing phytosomes of carotenoid-rich extracts from *Nyctanthes arbortristis* and *Tagetes patula* petals demonstrated strong antiaging activity by significantly enhancing the skin's dermal and epidermal layers and increasing its GSH levels. By considerably improving the skin's dermal and epidermal layers and raising its GSH levels, the formulation including phytosomes of carotenoid-rich extracts from *Nyctanthes arbortristis* and *Tagetes patula* petals showed substantial antiaging action as compared to the untreated group.[11]

Rudra Pratap Singh et al. (2015) reported the preparation and evaluation of the phytosome of Lawsone. Using the antisolvent precipitation method, many phytosome complexes of lawsone with molar ratios of 1:1, 1:2, 2:1, and 2:2 of lawsone and soy lecithin have been generated. The phytosome was described using FTIR, DSC, and SEM. The antifungal activity of lawsone's phytosome was assessed using ketoconazole, against the fungus Candida albicans. The skin of rats was used for the in-vitro penetration investigation. In male Wistar rats, the anti-inflammatory activity was assessed. Lawsone appeared to be intercalated in the lipid layer and the phytosome complex of the plant exhibited irregularly sized vesicles made of soy lecithin, according to SEM and DSC data. After three days, the phytosome complex (1:1) antifungal activity displayed the largest zone of inhibition when compared to the phytosome complex (1:2), plant medication, and ketoconazole. Research on the ex-vivo permeation of lawsone phytosome gel via excised rat skin revealed 92.91% cumulative drug penetration during a period of six hours. At 4 hours, the gel containing the phytosome of lawsone exhibited a statistically significant reduction in inflammation as compared to the gel containing plant medication.[12]

Ugwu Calister et al. (2020) Evaluated the Formulation of *Morinda lucida* based phytosome complexes for malaria treatment. After being dried, leaves were extracted using methanol-based maceration. On the extract, a phytochemical study was performed. The extract and phospholipon 90 H were combined in different ratios, either with or without surfactants, to produce phytosomes. Every formulation was evaluated both *in vitro* and *in vivo*.

High concentrations of terpenoids, flavonoids, and tannins were found in the phytochemical examination. The traditional antimalarial drug artesunate and the 1:1 extract combination had the strongest anti-plasmodium suppressive efficacy, 97% and 93%, respectively. A higher antimalarial impact of 1:1 complex at 800 mg/kg equivalent to/similar to the normal medication was established by *in vivo* anti-plasmodium experiments.[13]

Akash Chouhan et al. (2021) reported the Evaluation of Phytosomes of *Swertia perennis*. Because flavonoids are a component of hydroalcoholic extract, aerial portions of *Swertia perennis* exhibited antioxidant activity. The amount of flavonoids was reported as milligrams of quercetin equivalent per 100 milligrams of dry extract (mg QE/100mg). Based on these findings, flavonoid components were detected in the hydro-alcoholic extract (1.021 mg QE/100 mg). A variety of formulations, including extract and cholesterol, were used to create the phytosomes, which were then assessed for drug excipient compatibility, entrapment effectiveness, and particle size analysis, as well as an in vitro drug release investigation. A variety of phospholipid formulations, including extract and cholesterol, were used to create the Phytosomes, which were then assessed for drug excipient compatibility, entrapment efficiency, and particle size analysis, as well as in vitro drug release research. Entrapment efficiency is a crucial metric in the description of phytosomes. When the values of the regression coefficients were compared, it was discovered that the Higuchi release kinetics were followed by the drug release from formulations, as evidenced by the greatest "r2" value of 0.964.[14]

Deepak Tripathi et al (2023) reported the Formulation and Evaluation of Naringin Loaded Phytosomes for Improving Bioavailability. Lecithin was used as the lipid molecule in the solvent evaporation procedure to create naringin phytosomes. The phytosomes' particle sizes ranged from 651 nm to 2235 nm, and their polydispersity index fluctuated between 0.357 and 0.629. In the SEM scan, the phytosomes were discernible as hard, round vesicles. It turned out that the phytosome vesicles had a smooth, uniform surface. The formation of persistent phytosomes was demonstrated by clear, sharp endothermic peaks in DSC, which were caused by interactions between the extract and lecithin molecules. The release clearly showed the impact of medication concentration.[15]

Sucilawaty Ridwan et al. (2023) evaluated the development of cream preparation containing phytosome from *Phyllanthus emblica* fruit extract. Three techniques were used to generate the phytosome: solvent evaporation, antisolvent, and thin layer production method. The Fourier Transform Infra-Red (FTIR), Transmission Electron Microscope (TEM), polydispersity index, particle size, and entrapment effectiveness of the phytosome were assessed. A cream with 1% phytosome content was created. Over 28 days, the cream's stability was assessed at 40 ℃ room temperature. Diffusion tests were used to assess the penetration of the total phenolic content of cream-containing phytosome and cream-containing extract without phytosome

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

technology. The most effective technique for creating phytosomes was the antisolvent approach, which produced particles with sizes, polydispersities, and entrapment efficiencies of 66.99±0.01%, 298.53 nm±12.04, and 0.323±0.01, respectively. The creation of a spherical phytosome was also verified by evaluation utilizing TEM and FTIR spectroscopy. The organoleptic, pH, and viscosity of the cream did not significantly alter when it was stored at room temperature. Cream with phytosome technology exhibited a higher diffusion % than cream-containing extract without phytosome technology, according to the permeation test conducted through Spangler's membrane and skin snake. The study's findings demonstrated that the antisolvent approach could be used to create phytosomes from *Phyllanthus emblica* fruit extract, and that phytosome-containing cream could be used to increase permeation.[16]

Prasuna Sundari Pingali et al. (2014) reported the formulation and evaluation of capsules of Ashwagandha phytosomes. Phytosomes were produced by a process in which standardized plant extract was bound to phospholipids, producing a lipid-compatible molecular complex. Ashwagandha phytosome complexes were characterized by particle size, zeta potential, scanning electron microscopy (SEM), Fourier transform infrared spectroscopy, and in vitro drug release. The results showed that the average particle size and zeta potential of optimized Ashwagandha phytosomes formulation were 98.4nm and −28.7 mV. In vitro drug release studies revealed that the cumulative % drug release of capsules of Ashwagandha phytosomes was found to be 76.8%. The antioxidant activity of Ashwagandha phytosomes was evaluated by the reducing power method. The results showed that the phytosome complex exhibited more antioxidant activity compared to the extract. Hence it was concluded that Ashwagandha phytosomes serve as a useful novel drug delivery system and provide more bioavailability than conventional formulations.[17]

Manish Dubey et al. (2020) investigated the Formulation and Evaluation of Phytosome Tablets of Leaves and Stem of *Cucumis sativus*. After the plant material was extracted, ethyl acetate and water produced the maximum yield. It yielded percentage yields (w/w) of 15.48 for ethyl acetate and 1.28 for chloroform. Three distinct techniques were used to prepare the phytosomes. Antisolvent precipitation was chosen as the best of the three techniques due to its ability to produce particles with a smaller size and better entrapment effectiveness. The improved formulation of the phytosome was synthesized and characterized. A high entrapment efficiency was observed. Using a scanning electron microscope for visualization, excellent surface morphology was discovered. The measurement of zeta potential was -16.85 mv. It displayed a decent value by the standard. The findings of the XRD and DSC analyses showed that the improved formulation was an amorphous, stable formulation. It was determined that increasing the phospholipid concentration led to an increase in mean particle size.

A tablet containing a phytosomal complex was made. Good features were discovered after a thorough analysis of several characteristic parameters, including bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio. Weight variation, hardness, friability, and disintegration time were judged to be within an acceptable range by the official assessment parameters. In 120 minutes, the phytosome tablet's dissolution time was 91.12% after PCS6 formulation.[18]

Manish Dubey et al. (2020) investigated the Formulation and Evaluation of Phytosome Tablets of *Mangifera indica* leaves. Several quality control criteria were applied to the dried and powdered components. The following solvent extraction methods were used: methanol, chloroform, petroleum ether 60–80 ºC, Ethyl acetate, Butanol, and Water. The percentage yield (w/w) of ethyl acetate of *Mangifera indica* was found to be 25.48 whereas Chloroform was 0.28. Three techniques have been used to manufacture phytosomes: solvent evaporation, rotational evaporation, and antisolvent precipitation. After a comparison of results obtained with the three methods, antisolvent precipitation was selected as it resulted in minimum particle size and higher entrapment efficiency. The preparation of phytosomal complex tablets and the assessment criteria—weight variation, hardness, friability, and disintegration time—were determined. A dissolution time study was conducted to track the drug's percentage release. The entrapment efficiency of the optimized formulation of *Mangifera indica* was found to be 91.5%. Zeta potential was found to be -19.40mv for the optimized formulation of *Mangifera indica*. Optimized formulation showed a less intense and broader peak from 2θ values 14.9416 to 44.6383. X-ray diffraction pattern of the phytosome of the extract showed peaks from 2θ value 15.1080 to 72.5498 indicating an amorphous form. The dissolution time study of Phytotab MI tablet has been done at different time intervals. PMI5 formulation was found better than other formulations.[19]

Sunil S Jalalpure et al. (2022) evaluated the *Moringa oleifera* loaded phytosome for its in vitro antioxidant activity. The plant material was extracted by maceration and then Soxhlet extraction using a solvent mixture of ethanol and water. The resulting extract was put to phytochemical analysis. Through the use of thin film hydration, new phytosomes were created. The prepared phytosomes' entrapment effectiveness and particle size were examined. The antioxidant activity of the improved formulation (F3) was tested *in vitro*. Using methanol: water as the mobile phase and quercetin as the standard, thin-layer chromatography was carried out. The plant is green, has a fragrant scent, a somewhat bitter taste, upright stems, thick gray bark, and white blooms, according to the organoleptic test. The results demonstrate that the following Physicochemical parameters have for Moisture content, Total, Acid Insoluble, Water-Soluble Ash, Aqueous, Alcohol, and Petroleum Ether extractive values: 8.5, 10.5, 5, 12.5, 12.5, and 2.5% respectively. The presence of phenols, steroids, alkaloids, glycosides, and terpenoids was confirmed by the phytochemical analysis. The compatibility

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

research attests to the medications' and excipients' compatibility. Out of four distinct phytosome formulations with varying ratios, formulation 3 demonstrated a reduced particle size of 141 nm and an 81% entrapment effectiveness. For this reason, formulation 3 is tested for additional antioxidant activity. Formulation 3 demonstrated encouraging antioxidant activity with an IC50 value of 17.82 µg/ml when compared to normal ascorbic acid, which has an IC50 of 33.53 µg/ml. The findings suggest that *Moringa oleifera* has promising antioxidant qualities.[20]

Heni Rachmawati et al. (2015) reported the development of a silymarin-containing phytosome in order to improve the bioavailability of silymarin with sufficient safety and stability. This system comprised of a solvent-evaporation-prepared silymarin-phospholipid complex that was integrated using the thin-layer approach to generate phytosome vesicles with different phospholipid and silymarin molar ratios and concentrations. Sonication caused the phytosome's vesicle size to decrease. The findings showed that the optimal phytosomal characteristics were obtained with a formula containing 2% silymarin-phospholipid complex and a molar ratio of 1:5. The mean vesicle diameter was 133.534 ± 8.76 nm, the polidispersity index was 0.339 ± 0.078, the entrapment efficiency was 97.169 ± 2.412 %, and the loading capacity was 12.18 ± 0.30 %. After undergoing a freeze-thaw stability test, the preparation stayed stable. Differential scanning calorimetry and infrared spectroscopy analysis verified the existence of both chemical and physical interactions between silymarin and phospholipid during complex formation. The results of the freeze-thaw stability test, drug content measurement, and Transmission Electron Microscopy examination showed well-formed and distinct vesicles.[21]

Cysilia K Hindarto et al. (2017) investigated the *In vivo* evaluation of luteolin-loaded phytosome. The thin film hydration approach was used to synthesize luteolin into luteolin-loaded phytosomes (LLP). Rats administered oral LLP suspension underwent in vivo assessments to determine their plasma levels of luteolin, and the results were compared with rats in the control group that received pure luteolin suspension. With an average particle size of 105.3 nm, a PDI of 0.735, a zeta potential of -34.4 mV, and an entrapment effectiveness of 91.12%, round-shaped LLPs were verified. According to *in vivo* experiments, the plasma level of luteolin increased 3.54 times (AUC = 5426 µg. min/mL) when compared to the control group. Because the formulation of phytosomes effectively boosted luteolin absorption, they offer a potential delivery strategy for medications with limited lipid solubility.[22]

W. W. Nandayasa et al. (2023) evaluated the design of an optimal formulation for quercetin and vitamin C nano-phytosomes. Using a 2-level-5-factor design experiment, the thin layer hydration approach is used to create nano-phytosomes. For data analysis, a total of thirty-two experimental formulations were employed. Globule size was employed as a dependent factor, while the ratios of quercetin to soy lecithin (X1), cholesterol (X2), speed (X3), temperature (X4), and time (X5) were utilized as independent factors. A program called Design Expert12® was used to analyze the data. Transition Electron Microscopy (TEM) study, FTIR analysis, zeta potential, entrapment efficiency, polydispersity index, globule size analysis, and physicochemical assessment were all used to characterize the optimal formula. The ideal mixture contained 1: 1: 1.046: 0.105 mol of quercetin, vitamin C, lecithin, and cholesterol; stirring speed: 763.986 rpm; stirring time: 59 min; and temperature: 51.73 ℃. This resulted in an average globule size of 59.26 nm, PDI value: of 0.66; zeta potential: of 35.93±0.95 mV; and average SPAN value: of 0.61. Quercetin's entrapment effectiveness was found to be 91.69±0.18% in this formulation, whereas vitamin C's was 90.82±0.13%. The shape of the globules and the interactions between the medications, cholesterol, and soy lecithin to produce nano-phytosomes were revealed by the TEM and FITR analyses.[23]

Effionora Anwar et al. (2018) reported the Formulation and Evaluation of a Phytosome-Loaded Maltodextrin-Gum Arabic Microsphere System for the Delivery of *Camellia sinensis* Extract. The green tea leaf extract from Camellia sinensis is rich in epigallocatechin gallate (EGCG), a polyphenol. The thin-layer hydration approach was used to create the phytosome. In addition to various quantities of 97% phospholipids including 30% phosphatidylcholine (lipoid P 30), such as 2% (F1), 3.5% (F2), and 4% (F3), it was created with green tea leaf extract, which is equivalent to 3% of EGCG. Maltodextrin and gum arabic were used as a carrier to construct the chosen phytosomes into a microsphere, after which their stability and dissolution profile were assessed. With a spherical shape, a Dmean volume of 42.58 nm, a polydispersity index of 0.276, a zeta potential of -48.2 ± 1.78 mV, and an entrapment efficiency of 50.61±0.93%, the findings indicated that formula F3 was the best one. Following a 4-hour dissolving test, the total cumulative quantity of EGCG was 85.21%. Furthermore, it showed good physicochemical stability through organoleptic, water content, and physicochemical properties study which was conducted for 6 weeks at various temperatures. In conclusion, phytosome-loaded maltodextrin and gum arabic microsphere of green tea leaf extract could increase the stability of EGCG.[24]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24NOV049

Table 1 Marketed Phytosome Products with Their Therapeutic Application and Dose[25]

Sl. No.	PHYTOSOME PRODUCT	DAILY DOSAGE	APPLICATION
1.	Leucoselect ® phytosome	50–100 mg	Unique systemic antioxidant. For most people under fifty, this is the best option. Particularly for diabetes, varicose veins, the eyes, the lungs, and heart disease prevention.
2.	Greenselect ® phytosome	50–100mg	Systemic antioxidant. The greatest option to prevent cholesterol damage and cancer
3.	Ginkgoselect ® phytosome	120 mg	The best option for the majority of those over 50. Protects the vascular lining and brain
4.	Silybinphytosome	150 mg	Best option if extra antioxidant protection is needed for the skin or liver
5.	Panax ginsengphytosome	150mg	As a Food Product

V. CONCLUSION

Phytosomes is a technology that is patented. They can go from hydrophilic environments into the lipid-friendly enterocyte cell membrane and then into the cell itself, ultimately entering the bloodstream. Phytoconstituents have restricted solubility and are susceptible to degradation. Vesicular drug delivery techniques' exceptional capacity to capture particles, safety, and biocompatibility all help to increase these attributes. It has been shown that vesicles are incredibly promising cellular delivery vehicles for a range of advantageous phytochemicals. They are vesicular drug carriers that create a complex between phytochemicals and phospholipids to enhance the absorption, bioavailability, and overall stability of bioactive molecules. Since they are more absorbed than conventional phyto chemicals or botanicals, the innovative medication delivery technologies known as phytosomes offer better bioavailability and effects. A lipid-compatible molecular complex known as a phytosome is produced by binding the standardized plant extract or its contents to phospholipids, particularly phosphatidylcholine. Compared to traditional herbal extracts, the pharmacokinetic and pharmacodynamic profile of phytosomes is improved.

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