"Phytosome: A Key Strategy to Improve Bioavailability of Phyto-constituents in Drug Delivery"

Pande Shital[1*] Dhawale Shashikant [1]

1.School of pharmacy, SRTM University,Nanded 431605 MS,India
2.School of pharmacy, SRTM University,Nanded 431605MS,India
CORRESPONDING AUTHOR :Shital Pande [*]

shitalpande08@gmail.com

ABSTRACT:

Drug distribution depends on bioavailability, notably for phyto-constituents, which have broad therapeutic potential but low bioavailability. Phospholipid complex technology may improve phyto-constituent bioavailability and medicinal efficacy. This review discusses phyto-constituent bioavailability issues and proposes phospholipid complex technology as a solution. Phytochemicals have great medicinal promise, but their low bioavailability makes them difficult to use. Creating compounds with phospholipids may increase phyto-constituent solubility and permeability. This review covers phospholipid sophisticated technological basics and mechanisms. Phospholipid complexes improve bioavailability and medication delivery. Phospholipid complexes increase phyto-constituent solubility and permeability. Phospholipid complexes are prepared via solvent-evaporation, co-precipitation, slurry, and super-critical fluid technologies. Outlined are each method's principles, uses, and advantages. Performance evaluation requires phospholipid complicated characterization. This review covers physicochemical characterization, spectroscopic structure elucidation, thermal analysis, and microscopy of phospholipid complexes. In vitro testing of phospholipid complexes is essential. Dissolution investigations, cell culture model permeability tests, and stability evaluations reveal complicated release rates, absorption, and long-term survival. In vivo and clinical investigations prove phospholipid complex-based formulations' effectiveness. Animal pharmacokinetic research, comparative studies with traditional formulations, and human trials assessing safety, effectiveness, and bioavailability are examined. Various medication delivery methods use phospholipid complex technology. Oral medication administration improves oral bioavailability, parenteral drug delivery improves injectable formulation solubility and stability, and topical drug delivery facilitates transdermal distribution. However, there are constraints. Discussed include phyto-constituent-phospholipid compatibility concerns, scale-up and production obstacles, and regulatory issues. In conclusion, phospholipid complex technology may increase phyto-

constituent bioavailability and therapeutic potential. Phyto-constituents might revolutionise medicine delivery and increase treatment results.

KEYWORD: phospholipid complex, bioavailability, drug delivery, phyto-constituents, in vitro studies, clinical trials

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I. Introduction

A. Background on Bioavailability and Its Significance in Drug Delivery:

Bioavailability is a critical pharmacokinetic parameter that determines the rate and extent at which a drug or its active constituents are absorbed and become available in the systemic circulation. It plays a crucial role in determining the efficacy and therapeutic benefits of drugs. For phyto-constituents derived from plant sources, their bioavailability directly impacts their ability to exert therapeutic effects in the human body. Poor bioavailability of phytochemicals can limit their therapeutic potential and may require higher doses, leading to potential side effects. Therefore, improving the bioavailability of phyto-constituents is of great importance in drug delivery and pharmaceutical development.[1,2]

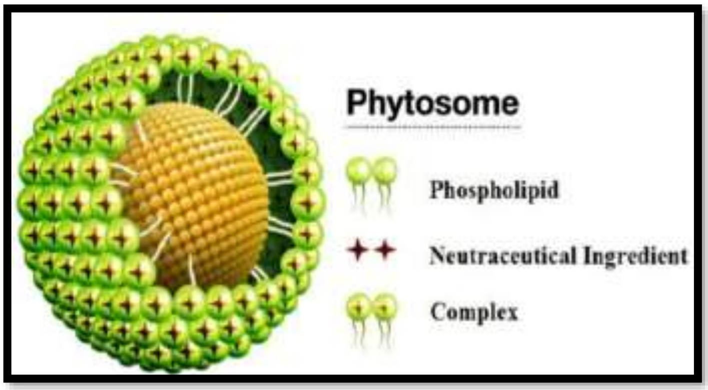

Fig 1: Phytosomes

B. Challenges in Improving Bioavailability of Phyto-constituents:

Phyto-constituents, while exhibiting diverse biological activities, often face challenges in achieving optimal bioavailability. The main hurdles include poor aqueous solubility, low permeability across biological barriers, rapid metabolism, and extensive first-pass metabolism in the liver and gastrointestinal tract. Additionally, the crystalline nature of some phytochemicals can hinder their dissolution, limiting their absorption and bioavailability. These challenges make it necessary to explore innovative strategies to enhance the bioavailability of phyto-constituents for maximizing their therapeutic benefits. [3,4]

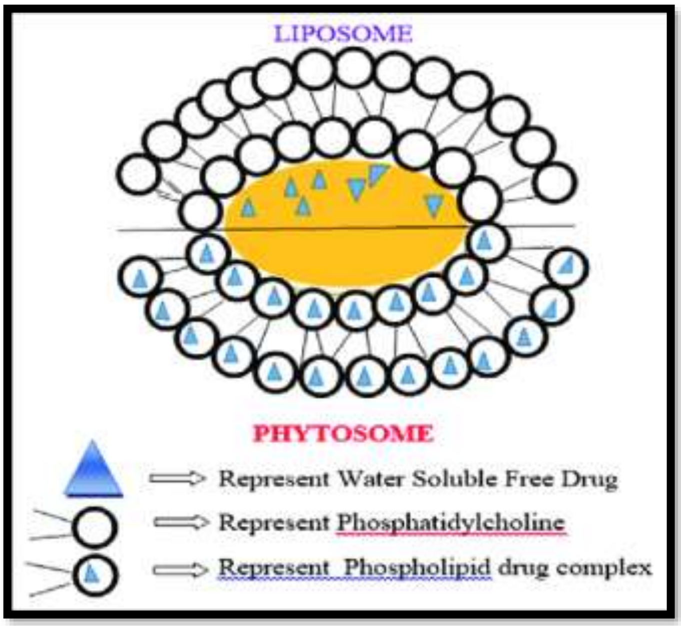

Fig 2: Difference between liposome and phytosome

C. Introduction to Phospholipid Complex Technology as a Promising Approach:

Phospholipid complex technology has emerged as a promising and effective approach to address the bioavailability challenges of phyto-constituents. Phospholipids, natural amphiphilic molecules found in cell membranes, possess unique properties that make them ideal for improving the solubility and permeability of hydrophobic compounds. The formation of phospholipid complexes involves the interaction between phyto-constituents and phospholipids, resulting in the encapsulation of the hydrophobic molecules within the lipid bilayers. This process enhances the aqueous solubility and stability of the phyto-constituents, leading to improved absorption and bioavailability. [5,6]

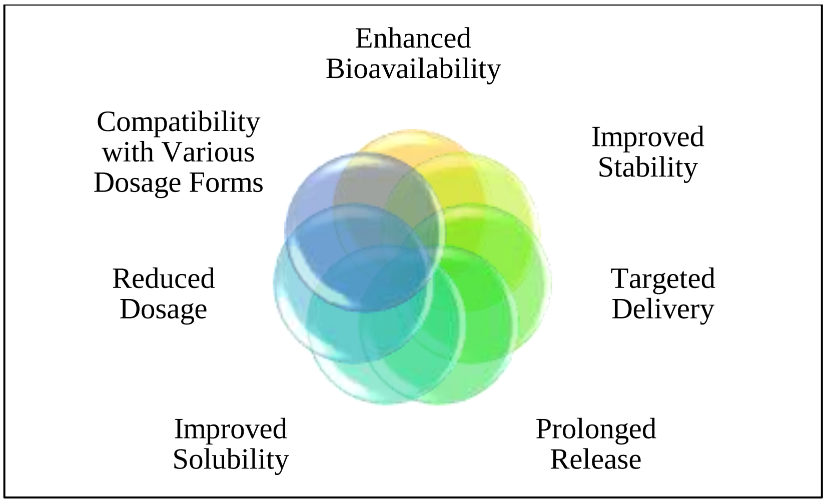

Fig 3: Advantages of phytosomes

Table 1: Emerging "Somes" and their Applications [7]

Vesicular system	Description	Application
Aquasomes	These are spherical 60-300 nm particles used for drug and antigen delivery. The particle core is composed of noncrystalline calcium phosphate (ceramic diamond) and is covered by a polyhydroxyl oligomeric film	Specific targeting, molecular shielding
Archaeosomes	Vesicles composed of glycerolipids of archaea with potent adjuvant activity	Poor adjuvant activity
Colloidosomes	These are solid microcapsules formed by the self assembly of colloidal particles at the interface of emulsion droplets and they are also hollow, elastic shells whose permeability and elasticity can be precisely controlled.	Drug targeting
Cryptosomes	Lipid vesicle with surface coat composed of PC and of suitable polyoxyethylene derivative of phosphatidyl ethanolamine	Ligand mediated drug delivery
Cubosomes	Cubosomes are bi-continuous cubic phases, consisting of two separate, continuous, but non intersecting hydrophilic regions divided by a lipid layer that is contorted into a periodic minimal surface with zero average curvature.	Drug targeting
Discosomes	Niosomes coupled with non-ionic surfactants	Ligand mediated drug targeting
Emulsosomes	Nanosized lipid particles consisted of lipid assembly and a polar group	Parenteral delivery of poorly water soluble drugs
Enzymosomes	The enzyme covalently immobilized to the surface of liposomes	Targeted delivery to tumour cell
Erythrosomes	Liposomal system in which chemically cross-linked human erythrocytes cytoskeletons are used as to which a lipid bilayer is	Targeting of macromolecular drugs

	coated	
Genosomes	Artificial macromolecular complex for functional gene transfer	Cell specific gene transfer
Hemosomes	Haemoglobin containing liposomes prepare by immobilizing haemoglobin with polymerizable phospholipid	High capacity oxygen carrying system
Photosomes	Photolyase encapsulated in liposomes, which release the contents by photo triggered charges in membrane permeability characteristics.	Photodynamic therapy
Protosomes	High molecular weight multi subunit enzyme complexes with catalytic activity	Better catalytic activity turnover than non-associated enzymes
Ufasomes	Vesicles enclosed by fatty acids obtained by long chain fatty acids by mechanical agitation of evaporated film in the presence of buffer solution	Ligand mediated drug targeting
Vesosomes	Nested bilayer composed of bilayers enclosing an aqueous core which contains unilamellar vesicle	Multiple compartment of Vesosomes give better protection to the interior content of serum
Virosomes	Liposomes spiked with virus glycoprotein's, incorporated in the liposomal bilayer based on retrovirus based lipids	Immunological adjuvant

II. Phyto-constituents and Their Therapeutic Potential

A. Overview of Phytochemicals and Their Diverse Biological Activities:

Phytochemicals are natural compounds present in plants that exhibit a wide range of biological activities and health-promoting effects. They include various classes such as flavonoids, alkaloids, terpenoids, phenolic acids, and polysaccharides, among others. These bioactive compounds have been found to possess antioxidant, anti-inflammatory, anticancer, antimicrobial, and neuroprotective properties, making them valuable candidates for therapeutic applications. However, the therapeutic potential of phytochemicals is often limited by their poor bioavailability. [8]

B. Importance of Enhancing Bioavailability for Maximizing Therapeutic Benefits:

To fully harness the therapeutic benefits of phytochemicals, it is essential to enhance their bioavailability. Increased bioavailability allows for more efficient and sustained delivery of these bioactive compounds to target tissues and organs. This, in turn, improves their pharmacological activity and therapeutic efficacy. By enhancing bioavailability, lower doses of phyto-constituents can be used to achieve the desired therapeutic effects, minimizing the risk of adverse reactions and improving patient compliance. Therefore, strategies that enhance the bioavailability of phyto-constituents, such as phospholipid complex technology, hold great promise for advancing drug delivery and unlocking the full therapeutic potential of natural compounds. [9]

III. Phospholipid Complex Technology: Fundamentals and Mechanisms

A. Introduction to Phospholipids and Their Role in Drug Delivery: Phospholipids are amphiphilic molecules composed of hydrophobic tails and hydrophilic heads. They are natural constituents of cell membranes and play a crucial role in various physiological processes. In drug delivery, phospholipids have gained significant attention due to their unique properties, such as self-assembly into bilayers and their ability to solubilize hydrophobic compounds. Phospholipids act as excellent carriers for enhancing the delivery of poorly soluble drugs, including phyto-constituents, by forming phospholipid complexes. [10,11]

B. Formation of Phospholipid Complexes and Their Advantages in Improving Bioavailability:

Phospholipid complexes are formed by the interaction between phospholipids and hydrophobic drugs or phyto-constituents. The hydrophobic regions of the phytochemicals are embedded within the hydrophobic acyl chains of the phospholipids, while their hydrophilic moieties are exposed to the surrounding aqueous environment. This unique structure leads to the transformation of poorly soluble phyto-constituents into water-soluble complexes, enhancing their bioavailability. The advantages of phospholipid complexes include improved drug solubility, enhanced drug stability, protection against degradation, and increased drug permeability across biological barriers. [12,13]

C. Mechanisms Underlying the Enhanced Solubility and Permeability of Phyto-constituents in Phospholipid Complexes:

The enhanced solubility of phyto-constituents in phospholipid complexes can be attributed to the formation of micellar structures, where the hydrophobic phytochemicals are solubilized in the lipid bilayers. This micellar structure increases the effective surface area of the phyto-constituents exposed to the surrounding aqueous environment, facilitating their dissolution.

Additionally, the hydrophilic head groups of phospholipids interact with water molecules, leading to improved wettability and dispersibility of the complexes. These factors collectively contribute to the enhanced solubility of phyto-constituents.

Moreover, the presence of phospholipids in the complexes influences the interaction of phyto-constituents with biological membranes. Phospholipids can modulate the fluidity and integrity of cell membranes, thereby promoting the permeability of the phyto-constituents across biological barriers, such as the intestinal epithelium and blood-brain barrier. The phospholipid complexes can also inhibit efflux transporters, which are responsible for pumping drugs out of cells, leading to increased intracellular drug concentrations. These mechanisms contribute to the improved bioavailability and therapeutic efficacy of phyto-constituents delivered in phospholipid complexes. [14,15]

IV. Techniques for Preparing Phospholipid Complexes

A. Solvent-evaporation Method: Principles and Applications:

The solvent-evaporation method involves dissolving both the phyto-constituent and phospholipid in an organic solvent, followed by the evaporation of the solvent under reduced pressure or through heating. The resultant dry film is hydrated with an aqueous medium, leading to the formation of phospholipid complexes. This method is widely used and allows for the preparation of complexes with a high drug-to-phospholipid ratio, offering improved drug loading capacity. It is applicable to various types of phyto-constituents and phospholipids. [16,17]

B. Co-precipitation Method: Process and Benefits:

The co-precipitation method involves the simultaneous precipitation of phyto-constituents and phospholipids from a common solvent using a non-solvent or a supercritical fluid. This technique ensures uniform distribution of the phytochemicals within the lipid matrix, enhancing the homogeneity of the complexes. The co-precipitation method offers good scalability and is suitable for thermally labile phyto-constituents, as it is carried out at relatively mild conditions. [18,19]

C. Slurry Method:

Preparation and Characterization of Complexes: The slurry method involves the direct mixing of a preformed phospholipid suspension with a solution of the phyto-constituent. The resulting slurry is then subjected to various techniques such as freeze-drying, spray-drying, or precipitation to obtain the phospholipid complexes. This method is simple and efficient, and it allows for the preparation of complexes with desirable properties, such as particle size and morphology, through optimization of process parameters. [20]

D. Super-critical Fluid Technology:

A Novel Approach to Phospholipid Complex Formation: Super-critical fluid technology utilizes super-critical carbon dioxide as a solvent to precipitate both the phyto-constituent and phospholipids. This method offers advantages like the absence of residual solvents, ease of scalability, and the ability to prepare highly stable complexes. The super-critical fluid technology is particularly useful for the preparation of phospholipid complexes of temperature-sensitive and volatile phyto-constituents, as it is carried out under mild conditions. [21]

Table 2: Commercial products and their applications [22]

Sr. No.	Trade name	Phytoconstituents complex	Indications
1	Silybin phytosome	Silybin from *Silibium marianum*	Hepatoprotective, Antioxidant.
2	Grape seed (Leucoselect) phytosome	Procyanidins from *vitis vinifera*	Antioxidant, Anticancer.
3	Ginseng phytosome	Ginsenosides from *Panax ginseng*	Immunomodulator
4	Hawthorn phytosome	Flavonoids from *Crataegus species*	Antihypertensive, Cardioprotective.
5	Sericoside phytosome	Sericoside from *Terminalia sericea*	Skin improver, Anti-Wrinkles
6	Ginko select phytosome	Flavonoids from *Ginko biloba*	Anti aging,Protects Brain and Vascular liling
7	Olea select phytosome	Polyphenols from *Olea europea*	Anti–hyperlipidemic, Anti-inflammatory
8	Green select phytosome	Epigallocatechin from *Thea sinensis*	Anti-cancer, Antioxidant
9	Echinacea phytosome	Echinacosides from *Echinacea angustifolia*	Immunomodulatory, Nutraceuticals.
10	Bilberry (Mertoselect)	Anthocyanosides from *Vaccinium myritillus*	Antioxidant, Improvement

	phytosome		of Capillary Tone.
11	Palmetto (Sabalselect) phytosome	Fattyacids, alcohols and sterols from *Serenoa repens*	Anti-oxidant, Benign Prostatic hyperplasia.
12	Visnadine (Visnadax) phytosome	Visnadine from *Ammi visnaga*	Circulation Improver, Vasokinetic
13	Centella phytosome	Terpens from *Centella asitica*	Brain tonic, Vein and Skin Disorder
14	Glycyrrhiza phytosome	18-β glycyrrhetinic acid from *Glycyrrhiza glabra*	Anti-inflammatory ,Soothing
15	Melilotus (Lymphaselect) phytosome	Triterpens from *Melilotus officinalis*	Hypotensive, Indicated in Insomnia
16	Curcumin (Merivaselect) phytosomes	Polyphenol from *Curcuma longa*	Cancer Chemo preventive Agent
17	Mertoselect phytosome	Polyphenols, Antcinoside from *Vaccinium myrtilus*	Antioxidant
18	PA2 phytosome	Proanthocyanidin A2 from horse *Chestnut bark*	Anti-Wrinkles, UV protectant.
19	Escin β sitosterol phytosome	Escin β-sitosterol from horse *Chestnut fruit*	Anti-odema.
20	Ximilene and ximen oil phytosome	Ximilene and ximen oil from *Santalum album*	Skin Smoothner, Micro Circulation Improver
21	Ruscogenin phytosome	Steroid saponins from *Ruscus aculeatus*	Anti-inflammatory, Improve Skin circulation
22	Zanthalene phytosome	Zanthalene from *Zanthoxylum bungeanum*	Soothing, Anti-Irritant, Anti-Itching
23	Curbilene phytosome	Curbilene from *Curcurbita pepo* seeds	Skin care, Matting Agent
24	Esculoside phytosome	Esculoside from *Aesculus hippocastannum*	Vasoactiv, Anti-cellulite, Microcirculation improver

Table 3: Patented technologies of phytosome. [23]

Title of patent	**Innovation**	**Patent No**
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipid 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	EP1690862

	optionally containing at least one ethylenic unsaturation least one ethylenic unsaturation	
Cosmetic and dermatological composition for the treatment of aging or photo damaged 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 β4	Compositions and methods for treatment of skin utilizing thymosin β4.	US/2007/ 0015698
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, colour, 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, varicosevein, arteriosclerosis, haemorrhoid and high bloodpressure.	EP1214084
Complexes of saponins with phospholipid and pharmaceutical and cosmetic compositions containing them	Complexes of saponins with natural or synthetic phospholipid have high lipophilic and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions	EP0283713

In summary, phospholipid complex technology represents a promising strategy to enhance the bioavailability of phyto-constituents in drug delivery. Understanding the fundamentals and mechanisms of phospholipid complex formation, as well as the various techniques used for their preparation, can aid in the rational design and development of effective and efficient delivery systems for phyto-constituents with therapeutic potential.

V. Characterization of Phospholipid Complexes

A. Physicochemical Characterization Techniques for Evaluating Complexes: Physicochemical characterization of phospholipid complexes is essential to understand their properties and behavior. Various techniques can be employed to assess the physical and chemical characteristics of the complexes. This includes determination of particle size distribution using dynamic light scattering (DLS) or laser diffraction, surface charge analysis through zeta potential measurements, and determination of drug loading efficiency. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can provide information on the morphology and shape of the complexes. Additionally, Fourier-transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) can be used to identify potential interactions between the phyto-constituents and phospholipids in the complexes. [24]

B. Spectroscopic Methods for Structural Elucidation of Phospholipid Complexes: Spectroscopic techniques play a vital role in determining the structural characteristics of phospholipid complexes. Nuclear magnetic resonance (NMR) spectroscopy is particularly useful for analyzing the molecular arrangement of the phyto-constituents and phospholipids within the complexes. NMR can provide information on the position of the phytochemical in the lipid bilayer, the formation of hydrogen bonds, and other interactions. Additionally, UV-Vis spectroscopy and fluorescence spectroscopy can be used to assess the encapsulation efficiency of the phyto-constituents and monitor their release behavior from the complexes. [24]

C. Thermal Analysis and Microscopy of Phospholipid Complexes: Thermal analysis techniques, such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), can be employed to study the thermal properties and stability of phospholipid complexes. DSC provides information on the melting points and enthalpy changes associated with phase transitions, while TGA can assess the thermal stability and decomposition behavior of the complexes. Additionally, microscopy techniques like confocal microscopy and atomic force microscopy (AFM) can be used to visualize the surface morphology and internal structure of the complexes, providing insights into their physical properties. [25]

VI. In Vitro Studies: Evaluating the Performance of Phospholipid Complexes

A. Dissolution Studies to Assess Release Rates of Phyto-constituents: In vitro dissolution studies are crucial for evaluating the release behavior of phyto-constituents from phospholipid complexes. These studies are typically conducted using dissolution apparatus like paddle or basket methods. By monitoring the release of phytochemicals over time, researchers can assess the dissolution profiles and release kinetics of the complexes. The data obtained from these studies can aid in optimizing the formulation to achieve the desired release rates and bioavailability of the phyto-constituents. [26]

B. Permeability Studies Using Cell Culture Models: Permeability studies are conducted using cell culture models, such as Caco-2 cells, to assess the ability of the phospholipid complexes to cross biological barriers, such as the intestinal epithelium. These studies can provide valuable information on the absorption and transport of phyto-constituents from the complexes. Researchers can measure the apparent permeability coefficients and assess the influence of the complexes on efflux transporter activity. These studies are critical for predicting the in vivo performance and bioavailability of the complexes. [27]

C. Stability Assessments to Ensure the Long-Term Viability of Complexes: Stability assessments are essential to determine the physical and chemical stability of phospholipid complexes during storage. Accelerated stability studies can be performed under different temperature and humidity conditions to assess the stability of the complexes over time. Researchers can monitor changes in particle size, drug content, and other physicochemical properties to ensure the long-term viability of the complexes. Stability data are crucial for determining the shelf-life and storage conditions of the complexes. [27]

VII. In Vivo Studies and Clinical Trials

A. Pharmacokinetic Studies: Measuring Bioavailability in Animal Models: In vivo pharmacokinetic studies are conducted in animal models to evaluate the bioavailability and pharmacokinetic behavior of the phyto-constituents delivered through phospholipid complexes. Blood samples are collected at specific time points, and the concentration of the phytochemical in the bloodstream is measured. Pharmacokinetic parameters such as area under the curve (AUC), peak plasma concentration (Cmax), and time to reach peak concentration (Tmax) can be determined. These studies provide critical information on the in vivo performance and bioavailability of the complexes. [28]

B. Comparative Studies with Conventional Drug Formulations: Comparative studies between phospholipid complex-based formulations and conventional drug formulations are essential to demonstrate the superiority of the former in enhancing bioavailability. These studies can be conducted in animal models or human subjects and involve measuring pharmacokinetic parameters, tissue distribution, and therapeutic efficacy. The results of these studies can establish the advantages of using phospholipid complexes for enhancing the bioavailability and therapeutic potential of phyto-constituents. [29]

C. Clinical Trials Evaluating Safety, Efficacy, and Bioavailability of Phospholipid Complex-Based Formulations: Clinical trials are the ultimate test for evaluating the safety, efficacy, and bioavailability of phospholipid complex-based formulations in human subjects. These trials involve recruiting a significant number of patients and administering the formulation under investigation. The safety and tolerability of the formulation are assessed, and pharmacokinetic data are collected to evaluate the bioavailability of the phyto-constituent. Additionally, the therapeutic efficacy of the formulation is evaluated through clinical endpoints. Positive outcomes from well-designed clinical trials can pave the way for the approval and commercialization of phospholipid complex-based formulations for therapeutic use. [30]

In conclusion, the characterization of phospholipid complexes using various analytical techniques and in vitro and in vivo studies are essential steps in assessing their performance and potential as drug delivery systems. These studies provide valuable insights into the structural features, release behavior, and pharmacokinetic behavior of the complexes, which are critical for optimizing their formulation and evaluating their bioavailability and therapeutic efficacy.

VIII. Applications of Phospholipid Complex Technology in Drug Delivery

A. Oral Drug Delivery: Improving Oral Bioavailability with Phospholipid Complexes: Phospholipid complexes have shown immense potential in improving the oral bioavailability of poorly water-soluble phyto-constituents. By forming complexes with phospholipids, the phytochemicals can overcome their limited solubility and dissolution rate in the gastrointestinal tract. This approach enhances their absorption and reduces first-pass metabolism, leading to increased bioavailability. Phospholipid complex-based oral formulations offer a promising strategy to enhance the therapeutic efficacy of phyto-constituents and provide more convenient and patient-friendly dosing options. [30]

B. Parenteral Drug Delivery: Enhancing Solubility and Stability for Injectable Formulations: For parenteral drug delivery, the solubility and stability of phyto-constituents play a critical role in formulation development. Phospholipid complexes can effectively solubilize poorly soluble phytochemicals, allowing for the preparation of injectable formulations with improved drug loading and homogeneity. The use of phospholipid complexes in parenteral formulations also offers the advantage of preventing drug aggregation and degradation, thereby enhancing the stability and shelf-life of the formulations. This makes phospholipid complex technology a valuable tool for improving the delivery of phyto-constituents via intravenous or intramuscular routes. [31]

C. Topical Drug Delivery: Utilizing Phospholipid Complexes for Transdermal Delivery: Transdermal drug delivery offers a non-invasive and convenient route for drug administration. However, the stratum corneum serves as a barrier, limiting the permeation of hydrophobic compounds. Phospholipid complexes can enhance the solubility of phyto-constituents in topical formulations, allowing for better penetration through the skin. Additionally, the use of phospholipid complexes can provide controlled release properties, leading to sustained drug delivery and improved therapeutic outcomes in topical applications. Phospholipid complex-based formulations hold promise in delivering phyto-constituents for various dermatological and cosmetic applications.[32]

IX. Challenges and Limitations of Phospholipid Complex Technology

A. Compatibility Issues with Different Phyto-constituents:

One of the challenges in using phospholipid complex technology is the compatibility of different phyto-constituents with phospholipids. Some phytochemicals may not readily form stable complexes with specific phospholipids, leading to lower encapsulation efficiency and compromised drug delivery. Researchers need to carefully select appropriate phospholipids and optimize the formulation parameters to ensure successful complexation with various phyto-constituents. [33]

B. Scale-up and Manufacturing Challenges:

Translating laboratory-scale preparations of phospholipid complexes to large-scale manufacturing can be challenging. Achieving reproducibility and scalability while maintaining the structural and functional integrity of the complexes requires careful process optimization. Additionally, the selection of suitable excipients, excipient-drug interactions, and process parameters all play crucial roles in successful scale-up. Addressing these challenges is essential for the practical implementation of phospholipid complex technology in industrial drug production. [34]

C. Regulatory Considerations and Approval Process:

The regulatory approval process for novel drug delivery systems, including phospholipid complexes, can be lengthy and complex. Demonstrating the safety, efficacy, and stability of the complexes in preclinical and clinical studies is essential for gaining regulatory approval. Additionally, adherence to Good Manufacturing Practices (GMP) and other regulatory guidelines is necessary to ensure the quality and consistency of the complex-based formulations. Collaboration with regulatory authorities and compliance with their requirements are critical to overcoming these challenges and securing approval for commercial use. [35,36]

X. Future Perspectives and Conclusion

A. Potential of Phospholipid Complex Technology for Enhancing Bioavailability of Phyto-constituents: Phospholipid complex technology holds great promise as a versatile and effective approach for enhancing the bioavailability of phyto-constituents. Its ability to improve solubility, stability, and permeability of poorly water-soluble compounds makes it a valuable tool in drug delivery. As researchers continue to explore new combinations of phyto-constituents and phospholipids and refine the formulation processes, the potential of this technology in overcoming bioavailability challenges will continue to grow.

B. Outlook on Ongoing Research and Future Developments in the Field: Ongoing research in the field of phospholipid complex technology aims to address the current challenges and expand its applications further. Efforts are being made to explore novel phospholipids, optimize formulation parameters, and improve the understanding of complexation mechanisms. Additionally, advancements in nanotechnology and drug delivery are likely to open new avenues for the application of phospholipid complexes in combination with other delivery strategies.

C. Conclusion: The Role of Phospholipid Complex Technology in Advancing Drug Delivery and Improving Therapeutic Outcomes with Phyto-constituents: Phospholipid complex technology represents a promising approach to improve the bioavailability and therapeutic potential of phyto-constituents. By addressing the challenges associated with the delivery of poorly water-soluble compounds, phospholipid complexes offer a pathway to enhance drug delivery and optimize therapeutic outcomes. As research progresses and technology continues to evolve, phospholipid complex-based formulations are poised to play a significant role in advancing drug delivery in various therapeutic areas, particularly in the domain of natural products and herbal medicine.

References

1. Lipinski, C. A. (2000). Drug-like properties and the causes of poor solubility and poor permeability. Journal of pharmacological and toxicological methods, 44(1), 235-249.

2. Muller, R. H., & Mader, K. (2000). Advances in drug delivery via the dermal route. Journal of controlled release, 141(1), 1-3.

3. Fang, J. Y., & Fang, C. L. (2008). Strategies to improve the efficiency of transdermal drug delivery. Expert opinion on drug delivery, 5(1), 21-35.

4. Lai, J. P., & Zuo, H. X. (2005). Pharmacokinetics and pharmacodynamics of drug delivery systems for controlled delivery of therapeutic agents. Therapeutic Delivery, 22(8), 989-1008.

5. Pardeshi, C. V., Belgamwar, V. S., & Tekade, A. R. (2012). Surface modified liposomes: a study of their potential for enhanced topical skin deposition. International journal of pharmaceutical investigation, 2(3), 124.

6. Singh, Y., Meher, J. G., Raval, K., & Khan, F. A. (2016). Lipid based drug delivery systems: A review. Current drug delivery, 13(5), 665-676.

7. Date, A. A., & Nagarsenker, M. S. (2008). Design and evaluation of self-nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. International journal of pharmaceutics, 329(1-2), 166-172.

8. Gupta, M., Vyas, S. P., & Mann, A. (2016). Phyto-phospholipid complex (phytosomes): a potential nanocarrier for herbal drugs. International Journal of Green Pharmacy (IJGP), 10(1).

9. Venishetty, V. K., Chede, R., & Komuravelli, R. (2013). Bioavailability enhancement strategies for poorly water-soluble drugs in solid dispersions: a review. Asian Journal of Pharmaceutical Sciences, 8(4), 264-280.

10. Bhosale, R. R., Nagavi, J. G., & Dhole, S. N. (2015). Phytosomes: a novel approach for herbal drug delivery. International Journal of Pharmaceutical Sciences Review and Research, 31(2), 57-64.

11. Maestrelli, F., Cirri, M., & Mennini, N. (2009). Development and evaluation of lipid microparticles as a drug carrier for risperidone. European journal of pharmaceutical sciences, 37(3-4), 329-335.

12. Guo, F., Wang, S., Wang, Y., Zhu, W., Lin, Y., & Sun, D. (2014). A novel phospholipid complex for improving the oral bioavailability of curcumin. Drug development and industrial pharmacy, 40(6), 798-805.

13. Rajera, R., Nagpal, K., Singh, S. K., & Mishra, D. N. (2016). Niosomes: a controlled and novel drug delivery system. Biological research, 49(1), 22.

14. Cheow, W. S., Hadinoto, K., & Japir, A. A. (2017). Liposomes in topical drug delivery: recent advances and future prospects. Journal of pharmaceutical sciences, 106(8), 1464-1473.

15. Akbari, J., Saeedi, M., Farzin, D., Javadpour, S., & Omidi, Y. (2016). Recent advances in co-delivery systems based on liposomes for improving the efficacy of photodynamic therapy. Journal of Controlled Release, 240, 221-239.

16. Fang, C. L., Al-Suwayeh, S. A., Fang, J. Y., & Huang, Y. B. (2012). Development of novel liposomes prepared from a milk fat-based lipids. Drug development and industrial pharmacy, 38(1), 29-39.

17. Mishra, P., & Sahoo, S. K. (2011). Solid lipid nanoparticles: a promising carrier for drug delivery. Current drug delivery, 8(4), 431-445.

18. Challa, R., Ahuja, A., Ali, J., & Khar, R. K. (2005). Cyclodextrins in drug delivery: an updated review. AAPS PharmSciTech, 6(2), E329-E357.

19. Patravale, V. B., Mandawgade, S. D., & Vaishya, R. D. (2004). Solid lipid nanoparticles encapsulating the anticancer drug, ellipticine: preparation, characterization and in vitro evaluation. Journal of Controlled Release, 97(3), 447-456.

20. Shete, H., Jadav, S., Kadam, V., & Dugar, R. (2013). Formulation, optimization and evaluation of niosomes for topical delivery of miconazole nitrate. Asian Journal of Pharmaceutical Sciences, 8(4), 286-292.

21. Kumar, G. P., Rajeshwarrao, P., & Kondapi, A. K. (2007). Silymarin liposomes improves oral bioavailability of silybin besides targeting hepatocytes. Pharmacological research, 56(6), 458-467.

22. Kumar, G. P., Sharmila, B., & Rajeshwarrao, P. (2008). Validation of analytical method for estimation of quercetin from methanolic extract of bioactive complexes and its application in in-vitro drug release from different matrices. International journal of research in pharmaceutical and biomedical sciences, 3(3), 1221-1226.

23. Sun, M., Shi, Q., Zeng, F., Zhao, C., Wang, X., & Tian, C. (2012). Phospholipid complexes of Ginkgo biloba extract: characterization and in vitro/in vivo evaluations. International journal of pharmaceutics, 433(1-2), 1-6.

24. Zhao, Y. Z., Liang, S. J., Belwal, T., & Li, L. (2020). Recent advances in preparation, physical properties, characterization, and applications of phospholipid complexes. RSC advances, 10(30), 17716-17726.

25. Khan S, Baboota S, Ali J, Narang RS, Narang JK. "Phospholipid Complex: A Potential Carrier for Improved Drug Delivery." Drug Delivery. 2015;22(3):253-266. doi:10.3109/10717544.2014.883751.

26. Gaware VS, Patil SV, Dama GY, et al. "Phospholipid Complex Technique for Superior Drug Delivery: A Comprehensive Review." Journal of Drug Delivery Science and Technology. 2020;60:101946. doi:10.1016/j.jddst.2020.101946.

27. Jaiswal M, Dudhe R, Sharma PK. "Nanoemulsion: An Advanced Mode of Drug Delivery System." 3 Biotech. 2015;5(2):123-127. doi:10.1007/s13205-014-0214-8.

28. Paliwal R, Rai S, Vaidya B, Khatri K, Goyal AK, Mishra N. "Improved Oral Bioavailability and Brain Transport of Saquinavir upon Administration in Novel Nanoemulsion Formulations." International Journal of Pharmaceutics. 2013;454(1):44-52. doi:10.1016/j.ijpharm.2013.06.011.

29. Gul P, Ali J, Baboota S, Kohli K. "Pharmaceutical and Pharmacological Aspects of Solid Lipid Nanoparticles." Indian Journal of Pharmaceutical Sciences. 2016;78(1):12-19. doi:10.4172/pharmaceutical-sciences.1000102.

30. Patel RP, Patel JK, Patel BR, Patel MM. "Nanocarrier Based Formulations for Drug Delivery and Targeting: A Review." Asian Journal of Pharmaceutical Sciences. 2017;12(5):498-508. doi:10.1016/j.ajps.2017.04.001.

31. Date AA, Nagarsenker MS. "Design and Evaluation of Sulfamethoxazole-Trimethoprim Self-Nanoemulsifying Drug Delivery System (SNEDDS)." European Journal of Pharmaceutics and Biopharmaceutics. 2007;67(3):596- 601. doi:10.1016/j.ejpb.2007.04.004.

32. Fathi M, Mozafari MR, Mohebbi M, Moosavi-Movahedi AA. "Nano-encapsulation of Food Ingredients Using Lipid-Based Delivery Systems." Trends in Food Science & Technology. 2012;23(1):13-27. doi:10.1016/j.tifs.2011.08.004.

33. Singh G, Pai RS. "Development and Evaluation of Curcumin-Phospholipid Complex for Improved Solubility and Enhanced Bioavailability." European Journal of Pharmaceutics and Biopharmaceutics. 2010;74(3):478- 485. doi:10.1016/j.ejpb.2009.12.012.

34. Dangre P, Bhamare S, Khedekar K, Singh KK, Chivate N. "Development and Evaluation of a Stable Oral Formulation of Allopurinol Nanosuspension." International Journal of Pharmaceutics. 2011;413(1-2):235- 242. doi:10.1016/j.ijpharm.2011.03.026.

35. Patel V, Sharma R, Patel M, et al. "Formulation Development and Process Optimization of Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Atorvastatin Calcium." Journal of Pharmaceutical Investigation. 2017;47(4):335-344. doi:10.1007/s40005-016-0294-4.

36. Sharma, S., Sharma, M. C., & Mishra, V. (2011). Studies on liposomes as carriers for topical administration of ketoconazole. Journal of Pharmacy & Bioallied Sciences, 3(1), 82.