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Innovative Approaches in Drug Delivery: Exploring Nanosuspension as Phytosome

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ABSTRACT:
Background: Phytosome technology in herbal drug delivery presents a valuable advancement in enhancing the bioavailability and efficacy of phytochemicals. This review explores the structure, biosynthesis, and regulation of polyphenols in plants, along with practical applications. Additionally, it delves into the therapeutic potential of phytoconstituents as immunomodulators and extensively discusses the health.
Body: The review emphasizes the importance of phytosomes as biocompatible nanocarriers for active pharmaceutical ingredients, particularly in improving the solubility and permeability of hydrophilic bioactive chemicals with low bioavailability. Various nanotechnologies, including nanosuspensions and phyto-phospholipid complexes, are discussed as strategies to enhance the active ingredient's absorption and bioavailability. It is shown that photo-phospholipid complexes are formed, significantly increases membrane permeability and the oil-water partition coefficient, leading to improved absorption and bioavailability compared to free active components.
Conclusion: Phytosome technology offers a promising approach to overcoming the challenges associated with poor absorption of active components in medicinal formulations. By utilizing the nanosuspension of phytosomes, researchers can increase the dissolution rate and bioavailability of phytopharmaceuticals. The review underscores the potential of phytosomes and nanosuspensions as innovative delivery systems for improving the therapeutic efficacy of phytochemicals in various applications.
KEYWORDS: Phytosome, Nanosuspension, Nanotechnology, Dissolution rate, Bioavailability.

I. INTRODUCTION:

Phytosomes (herbosomes) are structures formed by the stoichiometric reaction of phospholipids in a non-polar solvent with standardized extract or polyphenolic components(1). Phytosomes have various advantages, including the fact that the active components in crude extracts are protected from being destroyed by guts bacteria and gastrointestinal secretions, and they are very simple to make, requiring little equipment, space, and relatively inexpensive materials. These characteristics make scaling possible(2)(3). They are made of biodegradable lipids that are generally regarded as harmless. Because they are easily permeable and traverse the lipid-rich bio membranes, phytosomes improve the bioavailability of active phytochemical components(1)(3).

The use of nanocrystalline active pharmaceutical ingredients (APIs) has increased the dissolving rate of orally delivered medicinal formulations. Nanosuspension, a new nanotechnology under development, a colloidal solution those are disperses nanocrystalline medicines into medium including stabilizers (such poloxamer, tween, polyvinyl alcohol, and lecithin)(4). Phytosomes are also known biocompatible nanocarriers that could employed to improve phytopharmaceutical solubility and permeability(5). Phytosomes are used specifically for hydrophilic bioactive chemicals with low bioavailability and absorption, either due to bigger molecular sizes or very low solubility, which inhibits their diffusion through lipid biomembranes (6)(7). Phytosomes are self-assembled nanocarriers based on the phospholipid complexation technique, which involves hydrogen bonding complexation between phospholipids and phyto compounds. Hydrogen bonding complexation increases physical stability, which improves phytoconstituent absorption and bioavailability (8)(7).

The creation of emulsions, liposomes, and nanoparticles, are the alteration of chemical structures and administration as prodrugs, are just a few of the options that have been suggested to address the issue of poor absorption. Among the

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potential methods, phyto-phospholipid complexes, also referred to as phytosomes, have shown better promise for increasing the bioavailability of active ingredients (5). Active components are formed complexed with phospholipids at markable molar ratios and under specific circumstances to produce phyto-phospholipid complexes(3). Amphipathic phospholipids serve primarily as "ushers" of active substances, assisting in their passage past the extrinsic membrane of gastrointestinal cells and eventually reaching the blood. The membrane permeability and oil-water partition coefficient of the components are gradually increased after the formation of phospholipid complexes. Compared with free active components, phyto-phospholipid complexes are easily absorbed and produce better bioavailability. Positively, poor bioavailability for several active components has been overcome by the phospholipid complexes approach(9). Nanosuspensions have substantially smaller particle sizes (varying from 50 to 200 nm) than traditional suspensions (0.5 to 10 m), which significantly increase their dissolving rate(4)(10). A new formulation of complex-loaded nanosuspensions was developed. This strategy can be used to enhance the in vivo dissolution and absorption rate of phytosomes. (2)(10).

The study of antimicrobial activity is crucial in the search for new ways to combat microbial resistance. Researchers are exploring natural and synthetic sources to discover effective antimicrobial agents. Various testing methods, such as disk diffusion and dilution techniques, are used to evaluate the efficacy of these agents. Understanding antimicrobial properties is essential for developing treatments against resistant pathogens and addressing global health concerns(11).

PHYTO-PHOSPHOLIPID COMPLEX COMPONENTS

1. **Phospholipids-** PC, PE and PS are the main three phospholipids that are utilized to form complexes with the head group of hydrophilic and two hydrocarbon chains. The most popular phospholipid used to create phospholipid complexes is PC. The moderate solubility of PC in both lipid and aqueous environments is among its advantages due to its amphipathic characteristics (12). Moreover, the PC material exhibits excellent biocompatibility and low toxicity because it is a crucial part of cell membranes. Liver illnesses therapy such as hepatitis, fatty liver, and hepatocirrhosis has been reported to be clinically effective due to PC molecules' properties of hepatoprotective (9).

2. **Phyto-active constituents-** Primarily relying on in vivo activities, researchers typically characterize the active ingredients of herbal extracts based on their potent in vitro pharmacological effects. These chemicals primarily consist of polyphenols. Hesperidin is a polyphenolic component of plants that prefers the aqueous part and cannot passing through biological membranes. Curcumin and rutin, have significant lipophilic characteristics and gastrointestinal fluids that are watery cannot dissolve it(13). Hydrophilic polyphenols from the aqueous phase can also penetrate membranes more easily thanks to phyto-phospholipid complexes, which also make lipophilic polyphenols more soluble in water. Additionally, the creation of complexes may shield polyphenols from being destroyed by outside factors such as oxidation, photolysis, and hydrolysis (9)(14).

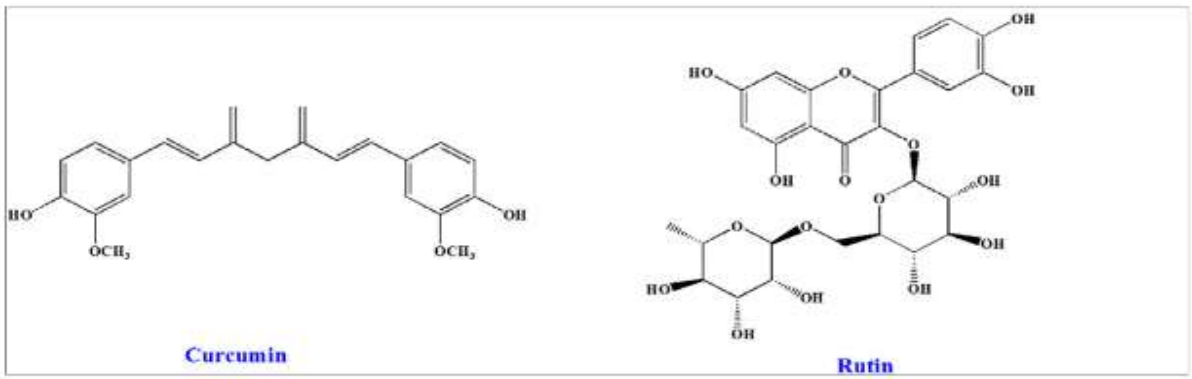

Fig. 1 – Polyphenols structure: (a) Curcumin, and (b) Rutin.

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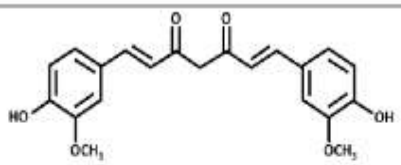
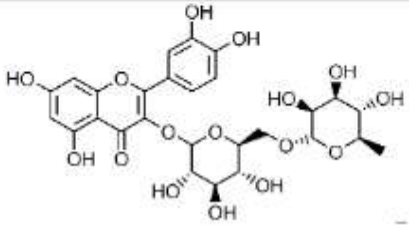
Table 1: Properties of Curcumin and Rutin

Sl no.	Polyphenol	Structure	Uses	References
1.	Curcumin		1. Used in the management of oxidative and inflammatory conditions, metabolic syndrome, and anxiety. 2. It is used in cosmetics in Thailand. 3. Also used colorant in China.	(15)(16)
2.	Rutin		1. Its potent antioxidant and anti-inflammatory activities. 2. Also Prevent neurodegenerative disorders, cardiovascular diseases, and skin cancer	(17)

3. **Solvents-** Different solvents have been used for the reaction medium in numerous experiments while creating phyto-phospholipid complexes. Protic solvents like ethanol have essentially taken the role of aprotic solvents, which were previously utilized to create phyto-phospholipid complexes. Examples of these solvents include aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, or cyclic ethers. Various types of solvents have undergone successful research(18). Ethanol is a commonly used solvent that is efficient in leaving behind minimal residue and does not cause any harm when the yield of phospholipid complexes is high. In some liposomal drug complexes, phytosomes interact with a solvent that has a lower dielectric constant in the presence of water or buffer solution(9).
4. **Stoichiometric ratio of active constituents and phospholipids-** Phyto-phospholipid complexes are typically formed by reacting a synthetic or natural phospholipid with the active ingredients in a molar ratio ranging from 0.5 to 2.0(9). Whereas the best effective ratio for making phospholipid complexes is pretend to be a stoichiometric ratio of 1:1. Silymarin-phospholipid complexes have been made with various stoichiometric ratios of the active ingredients and phospholipids, including 1:5, 1:10, and 1:15 (9).

ADVANTAGE OF NANOSUSPENDED PHYTOSOME OVER TRADITIONAL PHYTOSOME

A nanosuspension is a liquid medium containing nanoscale particles, usually ranging from 10 to 1000 nano meters in size, that are suspended in it. These tiny particles can consist of drug molecules, active pharmaceutical ingredients (APIs), or other compounds. Nanosuspensions are commonly used in pharmaceuticals to enhance the solubility, bioavailability, stability, and targeted delivery of poorly soluble drugs (19). Different techniques such as high-pressure homogenization, wet milling, or precipitation methods can be used to formulate nanosuspensions. When an active ingredient, usually a plant extract or a medicinal compound, is encapsulated or dispersed within nanosized particles, it is called a nanosuspension of a phytosome (2).

Nano-suspensions and phytosomes are both advanced drug delivery systems, each with its own advantages. Nano-suspensions of phytosomes might be considered better than phytosome complexes:

1. **Enhanced Bioavailability**: Nano-suspensions have smaller particle sizes than traditional phytosome complexes, resulting in increased surface area, better absorption, and enhanced bioavailability of active ingredients (20).

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2. **Improved Stability:** Sometimes phytosome complexes can be prone to degradation or aggregation, especially in certain environmental conditions. Phytosome nano-suspensions offer better stability due to their smaller particle size and uniform dispersion, potentially leading to a longer shelf life and better performance over period of time (21).
3. **Targeted Delivery:** Nano-suspensions enable targeted delivery of active ingredients to desired sites, enhancing therapeutic effects while minimizing side effects (22).
4. **Faster Onset of Action:** The phytosome nano-suspension's smaller particle size allows for faster absorption and onset of action compared to phytosome complexes, making it advantageous for drugs intended for fast relief or acute conditions (23).

FACTORS AFFECTING IN NANOSUSPENSION

1. **Stabilizers-** The primary function of a stabilizer in nanosuspensions is to make sure effective wettings of drug particles, thus preventing Ostwald's ripening and agglomeration (19)(22). Stabilizers such as lecithins, povidones, and polysorbates impede these phenomena, thereby improving physical stability. Lecithin stands out as the favored stabilizer for developing autoclavable nanosuspensions suitable for parenteral administration. This passage is written without plagiarism (24).

2. **Organic Solvents-** When creating nanosuspensions with emulsions or microemulsions, use solvents that are less dangerous and approved by pharmaceuticals, such as isopropanol, methanol, ethanol, or chloroform. For safety and pharmaceutical compliance, choose somewhat water miscible solvents such as benzyl alcohol, ethyl acetate, or ethyl formate over risky alternatives like dichloromethane. These decisions satisfy strict requirements while preserving formulation integrity (25)(26).

3. **Co-Surfactants-** In nanosuspension development using microemulsions, the choice of co-surfactant significantly impacts internal phase uptake and drug loading, affecting phase behavior (27). While bile salts and dipotassium glycyrrhizinate are frequently mentioned, other solubilizers like transcutol, glycofurol, ethanol, and isopropanol are also suitable for microemulsion formulation without introducing undue risks (27)(26).

APPLICATIONS OF NANOSUSPENSIONS

1. **Ocular application -** Topical ocular medication delivery is extensively utilized for treating in both external and internal ocular conditions. The appeal chosen depends on whether drugs need to be reserve at the cornea and/or conjunctiva (e.g., for conjunctivitis, blepharitis, or keratitis sicca) or if they must penetrate these barriers to reach inner side of eye tissues (e.g., for glaucoma or uveitis), tailored to the specific target site for different ocular diseases. Drug bioavailability in the eyes is restricted to around 5% because to a number of variables, including blink reflex, fluid drainage, and enzymatic breakdown in the eye (19)(28). Following application, drug molecules are momentarily retained in the precorneal area. Drugs have to pass through tissues like the cornea and conjunctiva in order to enter the inner eye. The qualities of the medication, the desired release profile, and safety considerations all have a role in the choice of a technique for ocular drug administration. Therefore, choosing an approach that balances better delivery with potential side effects requires careful thought (20).
2. **Topical application**- Inhalers and nebulizers are used to deliver aerosols directly into the lungs, providing local and systemic therapeutic options for lung diseases. Higher medication concentrations and selectivity are two benefits of local application. On the other hand, the pulmonary route is being investigated more and more for systemic distribution because it avoids first-pass metabolism and has a large alveolar surface area (19). Effective delivery is contingent upon various parameters, including aerosol characteristics and respiratory system clearance. Aerodynamic parameter optimization is critical, taking into account the needs of the patient and the medication properties. Each strategy has advantages and disadvantages, necessitating customized delivery systems (29)(30).

3. **Dermal application-** Nanosuspensions are employed in topical dermal applications to enhance drug delivery and boost the active ingredient's bioavailability with moderate

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solubility. The smaller particle size in nanosuspensions increases the drug contact surface area with the skin, aiding improved absorption. Nanocrystals in these suspensions not only enhance solubility saturation and dissolution rates but also enhance adhesiveness to the skin, improving cutaneous distribution (23).

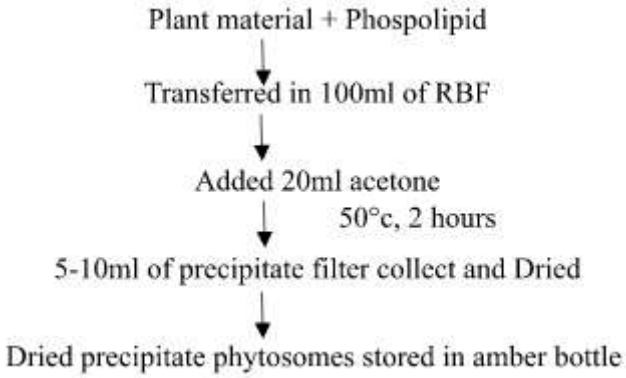
Examples of nanosuspension formulations of topical use include cyclosporin A, diclofenac sodium, and nitrofurazone, which demonstrate enhanced skin penetration, drug accumulation, improved dissolution rates, and increased drug permeability through the skin (31)(19).

Researchers are exploring nanocrystals in topical dermal applications for anti-inflammatory drugs, cosmetic products, and pharmaceuticals skin preparations such as anti-inflammatory creams, gels, sunscreen, and anti-aging treatments. Overall, nanosuspensions present a promising approaches for topical dermal application, enhancing drug absorption, bioavailability, and skin distribution (19).

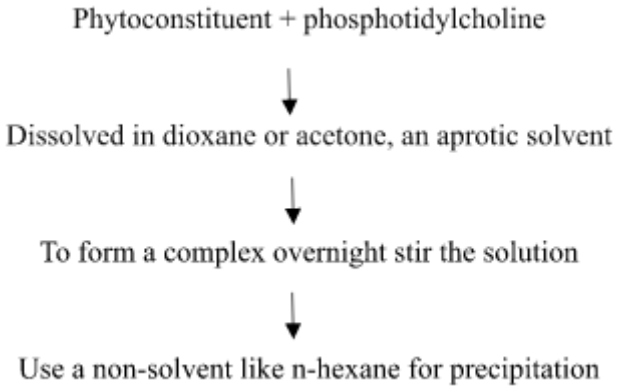
PREPARATION OF PHYTOSOMES

There are several techniques used to prepare phytosomes, including:

1. Solvent evaporation method (32) (33)



2. Salting out method (32)



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3. Lyophilization technique (32)

Phytoconstituent and phospholipid, whether synthetic or natural, are dissolved in various solvents

↓

Phytoconstituent solution added to the phospholipid solution

↓

Stirring continues until complex formation occurs

↓

Isolate the formed complex by lyophilization

4. Mechanical Dispersion method (34)

Aqueous phase with medication is introduced to lipids dissolved in an organic solvent

↓

The outcome of removing the organic solvent by applying reduced pressure.

↓

Supercritical fluids (SCF), such as gas anti-solvent technique (GAS), compressed anti solvent procedure (PCA), and supercritical anti solvent method (SAS), are applied in the fabrication of phospholipid involutes

↓

It involves the formation of complexes with compounds

5. Anti-solvent precipitation process (34) (33) (35)

Plant material + phospholipid

↓

100 ml RBF

↓

20 ml di-chloromethane 60°c,2 hrs

↓ 60°c,2 hrs

Added n-hexane

↓

Filter dried & crush

↓

100 # sieved

↓

Powder complex in amber bottle

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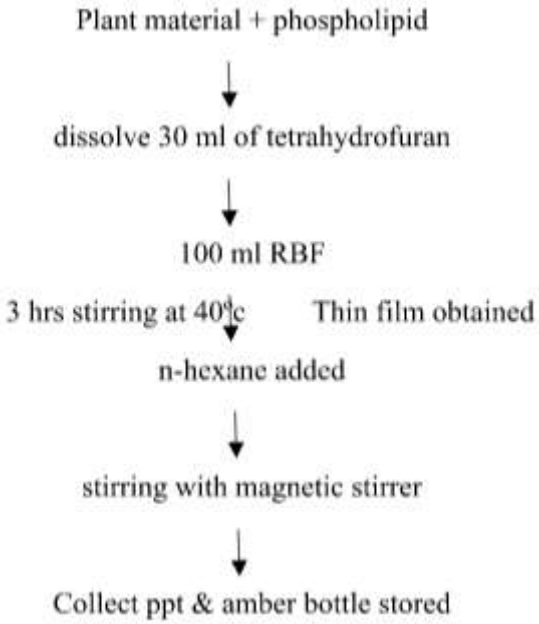
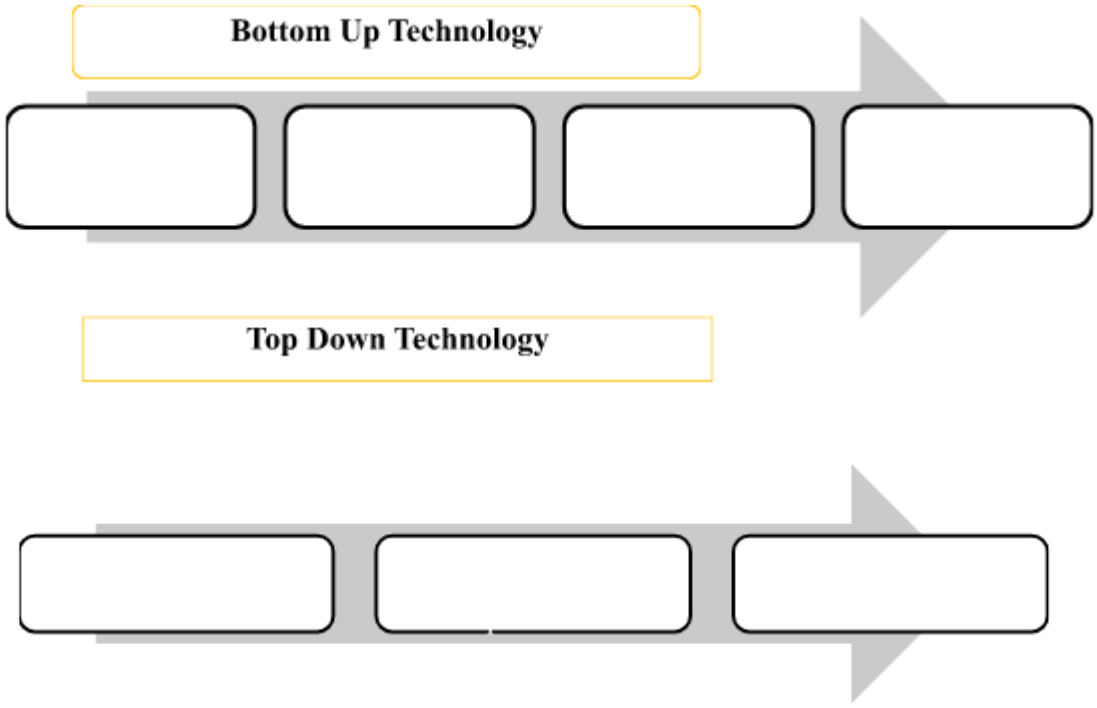
6. Rotary evaporation process (34)



The phospholipids that are utilised to make phytosomes are mostly produced from palmitic, stearic, oleic, and linoleic acids and contain acyl groups that can be the same or different in phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine. Since the active component of phytosomes is affixed to the polar head of phospholipid, it becomes a fundamental component of the membrane (32).

PREPARATION OF NANO-SUSPENSION

Generally, two techniques—"Bottom up technology" and "Top down technology"—are used to manufacture nanosuspensions (4)(10).



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Top-down technology is a technique that involves using high-pressure homogenization and milling methods to reducing larger particles into nanoparticles. Bottom up technology involves assembly ways to make nanoparticles, such as emulsification-solvent evaporation technique, microemulsion, and melt emulsification processes.

High-Pressure Homogenization (4)(10)

Suspension of drug has to pass through a tiny orifice.

(Pressure Reduction Below Boiling point of Water)

↓

Boiling of water leads to the produce gas bubbles within the suspension

↓

Suspension escapes the orifice, the air pressure returns to normal.

↓

Bubbles implode due to the return to normal pressure

↓

The part surrounding the drug particles moves towards the center and forms colloids

↓

Implosion and colloid formation contribute to decrease in particle size

Depending on the drug's hardness, the required homogeneity, and the intended mean particle size, the homogenizer may need to go through several passes or cycles(21).

Milling Techniques (4)(10)

Milling media containing drug, stabilizer, and water or buffer charge the milling chamber.

↓

The rotating chamber at a high speed to create a suspension with a cconsiderable shear rate.

↓

Energy from impaction formed nanosuspension

Microprecipitation – High-pressure homogenization (Nanoedge) (4)(10)

Organic solvent + Drugs + Insoluble drug solvent + stabilizer

↓

Both solutions were added together under high speed agitation

↓

Drug precipitation occours

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Melt emulsification method (4)(36)

Drugs is distributed throughout the stabilizer of aqueous solution

↓ (heated, over the melting point of drug)

Homonized the solution

↓

A heated tape with a temperature controller was used to cover the sample holder

↓

Slowly cool the emulsion at room temperature

Emulsification-solvent evaporation technique (4)(10)

The drug, dissolved in a solution. To solve the problem, the drug needs to dissolved in a suitable solvent.

↓

The solution of drug is emulsified in a non-solvent solution to form tiny droplets

↓

To evaporate the solvent the emulsion is stirred which results the precipitation of the drug

↓

Generate high shear forces to control crystal growth and particle aggregation

Nanojet technology (4,36)

Within a chamber, the suspension stream splits into two or more sections

↓

High pressure colliding between streams produce a colloid that has high shear force

↓

A significant reduction of particle size is caused by high shear forces

↓

utilized micro fluidization for nanosuspension preparation

↓

passing the microfluidizer through several times The final product can have a relatively higher percentage of microparticles

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EVALUATION OF PHYTOSOMES

1. **Percentage yield-**

The percentage yield of the prepared phytosome was determined using the following equation:

Percentage yield (*w/w*) = × 100

Where, The theoretical yield refers to the total weight of ingredients used to create a formulation, while the practical yield is the weight of the actual formulation obtained after the experiment is completed (37)(8).

2. **Determination of entrapment efficiency**

The ultracentrifugation method was used for the entrapment efficiency calculation. 100 mg of nanosuspension of phytosomes were diluted with 1 mL of methanol and spun down using a centrifuge on 15 minutes of ultracentrifugation at 15,000 rpm in a room temperature. Centrifugation follows, and the Supernatant and residue were separated, and the Vasicine testing was done on the supernatant. HPLC analysis at 280 nm for entrapment using the approach described above. To determine the area was high in free vaccine concentration altered to replace the linear regression of the calibrating graph (8).

Entrapment efficiency (%) =

3. **Particle size and zeta potential**

With the use of photon correlation spectroscopy , the surface charge and particle size (z-average) of phytosomes were evaluated. The samples were sonicated for five minutes after being diluted in distilled water. Three times the study was run, and the average hydrodynamic particle size was calculated (8).

4. Fourier transform infrared spectroscopy

Using the KBr pellet method, Fourier transform infrared (FTIR) spectra were acquired using an FTIR spectrophotometer. In an agate mortar, dehydrated extracts, phospholipids, and optimised phytosomes were combined with KBr crystals. In a hydraulic press, the powders were compressed into a disc for ten minutes at a pressure of fifteen tonnes. A fixed 400–4000 cm–1 scanning range with a 2 cm–1 resolution was used (8)(38).

5. In vitro drug release studies

In order to imitate intestinal fluids, pH 7.4 phosphate buffer was utilised as the study fluid. The samples were placed into a membrane and incubated at 37°C in a glass 100 mL beaker spinning at 100 rpm. Aliquots from the simulated solutions were taken out at intervals of 0, 10, 15, 30, 45, 60, 120, 180, and 240 minutes in order to calculate the concentration using HPLC techniques. If it was successful in crossing the membrane, the outcome was reported. In order to determine whether phytosomes were present in the sample, a TEM test was also conducted (38).

6. X-ray diffraction analysis

Using an X-ray diffractometer fitted with Cu-Kα radiation sources, the phytosome's powder X-ray diffraction (XRD) pattern was produced. Using a scanning rate of 0.02°/min, the experiment was conducted in Bragg-Brentano geometry at room temperature using 2θ that ranged from 5° to 80°. Utilizing origin software, the phytosome's crystallinity was evaluated (8).

7. 1H-NMR spectroscopy

Phospholipid sample and physical mixture were analysed by 1H-NMR, respectively. DMSO-d was used to dissolve silybin and the physical combination, and CDCl3 was used to dissolve phospholipid and SPCs. At an experimental temperature of 303 K, these samples were examined using a nuclear magnetic resonance spectrometer equipped with a Varian (Chemagnetics) QR T3 HFXY 2.0 mm probe. The outcomes of the tests were then compared (2).

II. CONCLUSION:

The integration of nanosuspension technology with phytosome delivery systems represents a significant advancement in drug delivery. By encapsulating active ingredients within nanoscale particles, nano-suspended phytosomes offer enhanced solubility, bioavailability, stability, and targeted delivery of poorly soluble drugs. This innovative approach provides numerous advantages over traditional phytosome complexes, including increased surface area for better absorption, improved stability, targeted delivery to specific sites, and faster onset of action. The synergistic combination of nanotechnology and phytosome technology holds great promise in revolutionizing drug delivery systems, ultimately leading to improved therapeutic efficacy and patient outcomes.

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Sodepur, Kolkata-700 114, West Bengal, India, and the guide Sumana Roy are also acknowledged by the author.

Authors' contributions

To gather relevant information, Anindya Modak has conducted plenty of review on nanosuspension of phytosome technology, herbal medicine, and other associated subjects. Anindya Modak and Sumana Roy worked together to write the title and abstract, with each author contributing to a distinct portion and ensuring unity and clarity throughout the work. Every author took part in evaluating and improving the abstract, adding suggestions, and making sure the data was correct. The abstract was finally approved for submission by all of the authors.

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