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Review Article

Development And Characterization Of Phytosome As A Novel Carrier By Qbd Approach

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ABSTRACT

In the last few decades, a lot of work has gone into making nanopharmaceuticals that work better with drugs. The term "phytosome" refers to a novel, recently developed method that is frequently used in the production of plant-based pharmaceuticals. As a result, more and more products are being approved by drug regulatory bodies. Although herbal nano medicines follow the same procedures for regulation as traditional pharmaceuticals, the large degree of quality variation is possible due to their nanoscale biological properties. The implementation of systematic quality-by-design (QbD) concepts has led to improvements in medication quality assurance. The QbD approach details the formulation's CQA, CMA, and CPP, which ensure the dosage form's quality. The concept of Quality-by-Design (QbD) was created by the International Conference on Harmonization (ICH) to provide a systematic approach to product development that is grounded in strong science and quality risk management. The production of pharmaceuticals is being enhanced, leading to better drugs in terms of quality, safety, and effectiveness.

INTRODUCTION

Traditional herbal medicine has a long history of usage. As a result of developments in contemporary medicine, herbal remedies are becoming more popular as a result of the increased usage of all-natural ingredients.[1] especially for those dealing with long-term health problems, and that they are both safe and more economical than conventional medicine.[2] With the integration of contemporary science with traditional herbal medicine, a more streamlined approach to discovering novel drugs is anticipated in the near future [3]. the third Eighty percent of people in poor nations still use herbal remedies as their main source of healthcare, says the World Health Organization.[4] The remarkable therapeutic

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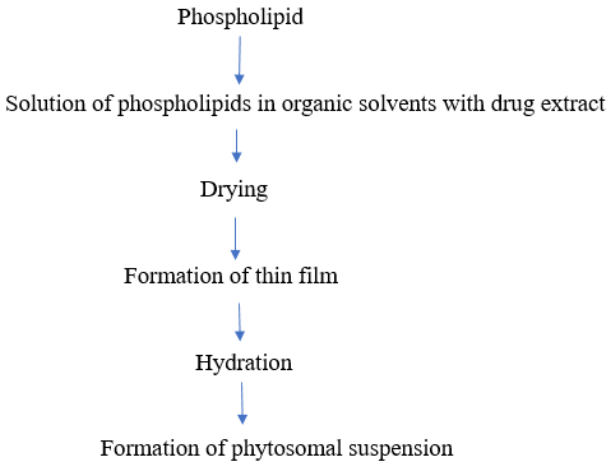
advantages and improved patient compliance of phytomedicines have gained the attention of people and researchers worldwide in recent years.[5] The name "phytosome," often spelled "herbosome" in certain sources, is a combination of the words "phyto" and "some," both of which have a connection to plants and structures that resemble cells. There is a lot of overlap between phytosomes and liposomes. Phytosomes are a novel vesicular drug delivery system that incorporates plant extracts or hydrophilic phytochemicals into phospholipids. This increases their bioavailability and absorption while avoiding the problems and side effects of conventional herbal extracts. These micelles are the result of an interaction between phospholipids and water.[6,7] Plant-derived bioactive compounds including phenolic compounds, lignans, alkaloids, etc. possess a plethora of medicinal properties advantageous for humans. [8] But, the traditional dose forms for herbal medication have certain limitation including inadequate absorption, lower penetration across biological membrane and reduced bioavailability due to large molecular size as well as lipophilicity, which decrease their applications. [9,10] The main goals of medication production are to consistently create products of an acceptable quality and to offer a superior quality product. To verify the authenticity of design, specifications, and system controls, technological proficiency is needed to access data gathered from production and experimental research. Modifications to the production process as well as planning and development are viewed as chances to learn new things or encourage the creation of new system designs. [11-15] The science of creating and producing product lines and formulas that adhere to predetermined standards is known as quality by design, or QbD. [16-18] American engineer J.M. Juran developed idea in early 1970s through his well-known book "Juran on Quality by Design." Joseph M. Juran first proposed the QbD concept in 1992 as a means of handling problems with quality control that arise during the production processes. [19] In the twenty-first century, quality by design (QbD) principles have become more popular for various drug discovery interventions, following in the footsteps of other regulatory guidelines like ICH Q8, Q9, and Q10, as well as current guidance documents, cGMP, and the FDA.[20–27] Avoiding long trials, improving manufacturing alternatives, avoiding problems with governmental compliance, and minimizing sampling errors and investigational variability are just a few of the benefits offered by the QbD approach.pp. [28–30]

Preparation of Phytosomes:

Phytosomes are fabricated by treatment of plant extract into phospholipids mostly phosphatidylcholine.[31] Solvent evaporation, freeze drying, and anti-solvent precipitation are the three primary methods for producing phyto-phospholipid complexes. Stoichiometric interactions between standardized plant extracts and either natural or synthetic phospholipids are necessary for the creation of phytosomes complexes.[32] An evaporation method, a thin layer hydration method, an anti-solvent precipitation method, a co-solvent lyophilization method, [33] and a salting-out process. [34]



A. Solvent evaporation method:

Solvent evaporation is a conventional and commonly employed approach for the fabrication

of phytosomes. Briefly, active phytoconstituents and phosphatidylcholine in a designed stoichiometric ratio are placed in a flask and dispersed in a suitable solvent by the process of heating at an optimum constant temperature for a specific duration. Solvent is evaporated under vacuum to obtain fabricated phytosomes.[35] The solvent evaporation method was applied to form evodiamine-phospholipid complexes.[36]

B. Anti-solvent precipitation:

Preparation of phytosomes using this approach is the second most common.[37] The anti-solvent precipitation approach involves refluxing the phospholipid and medication in an optimal solvent. After concentrating the mixture formed, another solvent is added with continuous stirring for precipitation. Then, formed precipitates are filtered, collected and then kept in desiccators overnight.[38]

C. Co-solvent lyophilization approach:

In co-solvent lyophilization approach of phytosomes preparation, both phospholipid and drug are refluxed in an appropriate solvent separately. Both are then mixed by gentle stirring until a clear solution is formed. Then the resulted homogeneous mixture is freeze-dried and kept in an air tight bottle for its further utilization. [38,39]

D. Thin layer hydration method:

In this method, phytochemicals and phospholipid are mixed in methanol and cholesterol is mixed in the dichloromethane. Then, evaporation of mixture is conducted using a rotary evaporator till production of dry thin film. Generally, nitrogen gas is moved over thin film formed to get rid of organic solvents completely. Next, organic solvents are completely evaporated by vacuum drying. Then the film is hydrated using distilled water.[38]

E. Supercritical fluid-based techniques:

For the manufacturing of particles ranging in size from 5 to 2000 nm, supercritical fluid is an efficient technique. To make drugs that aren't very soluble more soluble, scientists have turned to a variety of supercritical fluid-based techniques, including the gas anti-solvent technique, the rapid expansion of supercritical solutions, the supercritical anti-solvent method, the compressed anti-solvent approach, and solution enhanced dispersion by supercritical fluids.[40]

Sr. no	Formulation	Method of preparation	Material	DOE	Stability	QBD Parameters				REF
						CQA		QTPP		
						Particle size	Entrapment efficiency	Therapeutic	In vitro release	
1	phytosomal tablets	Solvent evaporation method. direct compression technique	Terminalia arjuna bark water soluble extract, Soya phosphatidyl choline	Box–Behnken	For 3 months Temp. 45°C	4nm	-	cardiovascular disease, for antioxidant	96.29 ±0.31	41
2	phytosomal tablet	thin-film hydration technique	Extract of Andrographis paniculata, soy lecithin and cholesterol	Box–Behnken	3 months	255 ± 9 nm	-	Anti hypertensive, anticancer, antidiabetic,	-	42
3	Phytosomal tablet	solvent evaporation method.	Cuscuta reflexa extract, soya lecithin, n-hexane	three-level Box-Behnken design	three months 4±0.5℃	173.5 ±6.17 nm to 215.9 ±6.53 nm,	52.9±1.65 to 77.2±1.1%.	Anti spasmodic anti emetic, Antiviral	96.3± 3.7%	43

4	Phytosomal phospholipid complex	solvent evaporation technique	Diosmin and Phosphatidylcholine were dissolved in Dimethylsulphoxide	three-level Box-Behnken design	-	233.4 ±20.0 nm	89.52±1.3%	vascular-protecting agent, anti-inflammatory, antidiabetic	89%	44
5	Phy toso mal gran ules	thin-layer hydration technique	leaves of A. vasica Nees cold maceration with methanol , ethyl acetate, chloroform	Box–Behnken	Good Stability	231.0 - 701.4nm	20.02-95.88%	Bronchodilator, asthma	68.80%	45
6	Phytosomal granuales	solvent evaporation technique	Tamarind and phospotidyl-choline,	central composite design	Good stability	233.4 ±20.0 nm	-	Anti inflammation, stomach pain, Rheumtism.	49% in 12hr	46
7	Phytosomal complex	Nano precipitation method	Berberine chloride Sodium lauryl sulphate	Box Behnken design.	180 days at 25±2	339 - 1259 nm	32.8% to 64.54%	Antimicrobial	0.89%	47
8	Nasal Vaccine	solvent evaporation technique.	Diammonium glycyrrhizin, tetrahydrofuran.	Plackett-Burman design	-	20-30 nm	-	respiratory diseases, induce nasal immune responses	45.19% to 56.82%	48
9	Phytosomal complex	solvent evaporation technique.	salicin and PHOSPHOLIPON 90H, Ethanol.	Central composite design	three months at 30±2 0C at 65% ± 5%	50 nm to 100 nm average	-	anti-inflammatory, analgesic and antipyretic activity	93.43%	49
10	Phytosomal particles	Antisolvent Precipitation Technique	Extract of M. koenigii	Factorial design	Good stability at 2-8°C	236 nm	75.1%	Antidiabetic and Hypolidemic Activity	50%	50
11	Phytosomal powder	solvent evaporation technique.	Nigella sativa Seed Powder,	Box-Behnken Design	Good stability	50nm to 100 nm average	-	Anticancer, antimicrobial, analgesic	-	51
12	Phytosomal gel	thin-layer hydration method.	Aloe-vera extract, ethanol, lecithin, Carbopol 934	central composite design	4 ± 0.5°C3 months	123.1 ± 1.44 nm	95.67 ± 0.27 %	anticancer, antioxidant, antidiabetic, and	56.91 ± 4.1% in 24hrs	52
13	Phytosomal gel	solvent evaporation method	Annona squamosa (AS) and Cinnamomum tamala (CT) leaves, Carbopol 934	Central composite design	-	122.15 ± 3.73 nm	-	Antioxidant, anticancer, Anti-inflammatory	84.2 ± 4 1%	53
14	Phytosomal gel	solvent evaporation method	Annona squamosa (AS) and Cinnamomum tamala (CT) leaves, Carbopol 934	central composite design	-	215.5 ± 0.45 nm	-	Anti-inflammatory, Anti-fungal,	84.22 ± 5.62%.	54

15	Phytosomal gel	thin-film hydration	Carvacrol, Carbopol 934	Molecular docking design	(25 ± 1°C) for 6 months.	263.2 ± 13.6 nm	92.87 ± 1.21%	Anti-inflammatory, Antioxidant, Anti-bacterial	-	55
16	Phytosomal cream	thin-film hydration	Trigonella foenum graecum extract, ether	central composite design	-	264 nm	72.18%	Anti-arthritic, Anti-inflammatory	-	56

Table.2: Phytosomal formulation

Sr No	Formulation	Material	Method	Particle Size	Entrapment Efficiency	Therapeutic Uses	Drug Release	Ref.
1	Tablet	Cucumis Sativus Were Washed With 80% Ethanol, Methanol, Dichloromethane, Soya Lecithin, Cholesterol, Hexane	Antisolvent Precipitation Technique	452.88 ± 0.5nm	91.5 ± 0.63%	Anti-Oxidant, Anti-Diabetic, Anti-Helmenthic, Anti-Microbial.	-	56
2	Tablet	Mangifera Indica Extract, Dichloromethane, Soya Lecithin, Formic Acid And Orthophosphoric Acid.	Solvent Evaporation Method	763± 0.23nm	76.89 ± 0.11%	Antiseptic, Anti-Inflammatory, Diuretic, Anti-Diabetic	-	57
3	Tablet	Silymarin Extract, Phospholipid Complexes, Ethanol,	Thin Layer Method	133.534 ± 8.76 Nm	97.169 ± 2.412 %	Anti-Diabetic, Antioxidant, Liver Diseases	-	58
4	Tablet	Phyllanthus Amarus And Phospholipon 85 G, Dichloromethane, N-Hexane	Solvent Precipitation Technique	226.26±31. 97nm Average	-	Treat Jaundice, Malaria, Anti-Diabetic	112.28% In 12hrs	59
5	Tablet	Green Tea Extract	Antisolvent Precipitation Technique	100–150 Nm	-	Obesity	-	60
6	Oral Phytosome	Citrullus Colocynthis (L.) Momordica Balsamina And Momordica Dioica	Solvent Evaporation	254±20.0 Nm	72% And 92.1 ± 5.1%	Anti-Diabetic	-	61
7	Phytosomal Capsule	Boswellia Serrata Extract, Ethano	Solvent Evaporation Method	179-514.8nm	39% To 74%	Treat Osteoarthritis	-	62
8	Phytosomal Capsule	Morinda Citrifolia Extract	-	279 Nm	89.87%	Gastric Ulcer, Anti-Cancer	92.57% Over 12hrs	63
9	Phytosomal Capsule	Beutea Monospora Extract, Soya Lecithin	Solvent Evaporation Method	263.2 ± 13.6 Nm	94.55%	Anti-Diabetic, Hepato-Protective	80.36 % 6hrs	64
10	Phytosomal Capsule	Mucuna Prureins Hydroalcoholic, Soya Lecithin, Acetone	Solvent Evaporation Method	216.3±14n m	99.76±1.24%	Treat Cancer, AIDS, And CNS-Related Disorders	90 %	65
11	Phytosomal Capsule	Physalis Minima Linn Extract, Petroleum Ether, Trichloromethane, Ethyl Acetate, Ethanol	Solvent Evaporation Method	254nm	51%	Antioxidant, Anti-Cancerous, Anti-Diabetic, Analgesic, Antipyretic And Ant-iinflammatory Potentials.	93%	66

12	Phytosome Loaded Microsphere	Maltodextrin-Gum Arabica, Camellia Sinesis	Thin-Layer Hydration Method	42.58 Nm	50.61±0.93%	Inflammatory Bowel Disease, Anti-Cancer, Anti-Diabetic	85.21% In 4hr	67
13	Phytosomal Eye Drop	L-Carnosine, Lipoid,	Solvent Evaporation Method.	380–450 Nm	55%±3.5% To 90%±6%	Lubricates The Eye	-	68
14	Eye Drop	Triamcinolone Acetonide, Calcium Acetate	Thin-Layer Hydration Method	35.46 ± 4. 49 Nm	90.66 ± 3.21 %	Anti-Inflammatory, Anti-Bacterial	-	69
14	Eye Drop	Triamcinolone Acetonide, Calcium Acetate	Thin-Layer Hydration Method	35.46 ± 4. 49 Nm	90.66 ± 3.21 %	Anti-Inflammatory, Anti-Bacterial	-	69
15	Cream	Phyllanthus Emblica L Extract, Triethanolamine, Propylene Glycol, Stearic Acid.	Antisolvent Precipitation Technique	298.53 Nm± 12.04nm	66.99±0.01%	Lightening Skin, Anti-Aging.	-	70
16	Cream	Cassia Auriculata, Soy Lecithin As A Phospholipid And Aceton	Rotary Evaporation Technique	215 Nm	95 ± 2%.	Anti-Bacterial	-	71
17	Cream	Black Pepper Extracted By 95% Ethanol, Potassium Hydroxide	Rotary Evaporation Technique	30.6 Microns	-	Treat Vitalgo, Anti-Bacterial	-	72
18	Cream	Gotu Kola Leaves And Merbau Wood, 70% Ethano	Thin-Layer Hydration Method	50 To 100 Micrometer	-	Anti-Aging, Skin Lightning	-	73
19	Gel	Tender Coconut Water, Aloe Vera Extract, Grape Seed Extract, Vitamin E, And Jojoba Oil.	Solvent Evaporation Technique	-	-	Anti-Aging	-	74
20	Gel	Tobacco Leaf Extract, Ethanol, Phosphatidylcholine, Cholesterol	Solvent Evaporation Technique	198.17 ± 6.63 Nm To 249.30 ± 1.56nm	49.3 ± 2.5%	Antioxidant, Anti-Aging	-	75
21	Internasal Gel	Geophila Repens Extract	Co-Solvent Lyophilizatio n Technique	444.93 ± 25.24 Nm	51.88 ± 1.025%	Alzheimer's Disease	45.84 ± 5.6%	76
22	Gel	Thymoquinone, Sodium Benzoate, Triethanolamine, Gel Base	Thin Film Method	156± 0.02nm	90.8 ± 0.6%	Antioxidant, Anti-inflammatory, Immunomodulat ory, Anti-Histaminic, Anti-Microbial, Anti-Tumor	94.28 ± 0.39 %	77
23	Face Serum	Ginger Oil Aloe Vera Gel Carica Papaya, Soy Lecithin, Dichloromethan	Anti-Solvent Precipitation Technique	245.21 ± 0.06 Nm	-	Anti-Aging, Moisture Provider	-	78
24	Face Serum	Grape Seed Extract, Phospholipon 90 G, Ethanol 96%	Thin Layer Hydration Method	398.23 Nm	75.01 ± 0.25 %	Anti-Aging	-	79
25	Gel	Bitter Melon Extract And Phosphatidylcholine, Dichloromethane.	Thin Layer Method	282.3 ± 16.4 Nm	90.06 ± 1.07 %	Anti-Diabetic	-	80

26	Gel	Green Tea Extract, Carbopol 934, Methyl Paraben, Triethanol Amine, Aloe Vera Extract Vit E.	Thin-Layer Hydration Method.	249nm Average	-	Anti-Aging	-	81
27	Gel	Quercus Infectoria Extract, Soy Lecithin, Ethyl Acetate	Solvent Evaporation Technique	249nm Average	-	Analgesic, Antidote, Anti-Inflammatory, Antipyretic, Antiseptic, Antistomatitis	-	82
28	Thermogel	Glycine Max (L.) Merrill, Soyabean, Methanol	Solvent Evaporative Technique, Cosolvency	51.66–650.67nm	>99%	Anti-Obesity	77.61–99.78%	83
29	Complex	Rosehip Extract, Ginger Rhizome Extract, Phosphotidyl Choline, Ethanol	Thin-Layer Hydration Method	103.78 ± 6.39nm	91.3 ± 3.0%	Antioxidant, Anti-Inflammatory	-	84
30	Gel	Thuja Occidentalis Extrac	Thin Film Hydration Technique	100nm	78% To 82%	To Treat Warts, Anti-Inflammatory	64%	85
31	Wound Dressing	Moringa Oleifera Extract, Dichloromethane, Soya, Cholesterol	Thin-Film, Solvent Evaporation method	198 ± 21nm	82.8%	Wound Healing Activity	-	86
32	Nasal Gel	Voriconazole, Clove Oil, Soybean Lecithin	Thin-Layer Evaporation Technique	02.96 Nm	71.70%,	Anti-Fungal	82.5%	87
33	Ointment	Nyctanthes Arbor-Tristis Extract Crocetin, Chloroform	Lipid Film Hydration Method	-	71. 4%	Wound Healing, Anti-Inflammatory	-	88

Characterization:

A. Solubility and partition coefficient:

To describe bioactive components, phytosomes, and physical mixes, it is important to determine the n-octanol/water partition coefficient (P) and solubility in water or organic solvents. Phytosomal complexes outperform bioactive components in terms of hydrophilicity and lipophilicity. [89,90]

B. Vesicle size, polydispersity index and zeta potential:

Vesicles size, polydispersity index (PDI) and zeta potential are very important characteristics of phytosomes which are associated to their stability and reliability. Phytosomes with high zeta potential have great electrostatic repulsion between the particles that indicates the higher stability. Phospholipid complexes typically have an average size between fifty nanometers and one hundred micrometers. Using dynamic light scattering, a particle size analyzer can detect the size of the particles as well as their polydispersity index and zeta potential.[91]

C. Visualization:

If one wants to examine the structure of phytosomes, they can utilize imaging microscopy, atomic force microscopy, or SEM. [92]

D. Entrapment efficiency:

Using ultra-centrifugation, one can determine the phytosome entrapment efficiency. This is accomplished by ultracentrifuging the sample at either higher speed for shorter durations or lower rpm for longer durations. Additionally, the medication or free phytoconstituents can be detected in the supernatant using UV-Visible spectroscopy or, more accurately, high

performance liquid chromatography (HPLC).[89,91]

E. Ultraviolet-Visible spectroscopy:

Specimens that are able to reflect in Ultraviolet and visible light can be utilized to determine their structural characteristics. Most of investigations showed no specific difference in UV light absorption properties of components before and after complex formation.[93]

Advantages: [94,95]

1. One great thing about phytosomes is that they are more bioavailable than regular plant extracts because of their enhanced absorption. A smaller dosage of phytoconstituents is needed to achieve a biological effect due to increased absorption.
2. Phytosomes exhibit better drug entrapment efficiency and stability because of chemical bonds between the bioactive compounds and phospholipid molecules. It makes sure proper drug delivery to the target tissues.
3. Cosmetics make considerable use of phyto-phospholipid complexes because of their superior skin penetration and greater lipid profile, both of which promote the absorption of bioactive phytochemicals across the skin.
4. Phytosomes solubility in an aqueous medium is relatively less that ensures the formulation of stable creams or emulsions.
5. Phytosomes have higher rate drug complexation and also fabrication of phytosomes is not a complex process.

Limitation: [96]

1. Despite of exhibiting a wide range of benefits as a drug delivery system, phytosomal products are not prevalent in market.
2. Its cost of production is high and allergic reactions to the phytosomal components may also be observed sometimes.
3. It exhibits a short half-life.
4. Hydrolysis, leakage, fusion and oxidation is undergone by phospholipid molecules.
5. Phospholipids (soy lecithin) can cause proliferation on MCF-7 cell lines of breast cancer.

CONCLUSION

The term "phytosome" refers to a novel, recently developed method that is frequently used in the production of plant-based pharmaceuticals. These pharmaceuticals contain phytochemicals from plant extract encased in phospholipid, with the majority of the bioactive ingredients in herbal medicine being water soluble flavonoids. Phytosomes have better bioavailability than regular herbal extracts due to their lipid soluble outer layer, which allows for more absorption. Furthermore, the phospholipids utilized offer additional health advantages. The procedures for creating phytosomes are straightforward, unconventional, and repeatable. Innovative phytosome formulations, techniques, and applications have already been approved for many patents and commercial formulations. It is anticipated that additional phytochemicals may benefit from comparable formulations, as several have been successfully encapsulated as phytosomes. Additional research may reveal synergistic benefits when drugs and phytochemicals are combined in nano-vesicles or when phytosomes are coupled with other phytochemicals. Phytosomes combined with other phytoconstituents or nano-vesicles containing both a medicine and a phytochemical can be useful tools for future studies.

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