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Review Article

NOVEL FORMULATION STRATEGIES FOR PHYTOPHARMACEUTICALS

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ABSTRACT

Phytopharmaceuticals are herbal medicinal products of plant origin. They are multi-component mixtures containing many phytocompounds present in different ratios. It is explained here on formulation strategies. The novel formulation strategies for phytopharmaceuticals discussed here covers; Solid dispersion (SD), Liposomes, Phytosomes (Phyto-phospholipid complex), Niosomes, Ethosome, Transferosome and transgelosome, microspheres, polymeric nanoparticles (PNPs), Microemulsion, Nanoemulsions and Self-Emulsifying Drug Delivery Systems (SEDDS), Solid Lipid Nanoparticles (SLNPs), Nanostructured lipid carriers (NLC), carbon dots etc. The chemical complexity of phytopharmaceuticals possess various pharmaceutical challenges for formulation and delivery. Rational choice of formulation strategies may overcome these challenges.

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Introduction

Phytopharmaceuticals are herbal medicinal products of plant origin. They are multi-component mixtures containing many phytocompounds present in different ratios. Phytopharmaceuticals are rich in secondary metabolites and may be broadly considered under natural products. In the context of modern understanding, they are standardized plant preparations used for therapeutic, nutraceutical, cosmeceutical, and excipient purposes. The concept of a novel formulation of phytopharmaceuticals is mainly related to the loading of standardized multi-constituent plant extract or enriched fraction of extract into a suitable dosage form.

Novel formulation strategies

Need of novel drug delivery systems (NDDS)

- Most of the biologically active components of extracts are highly water-soluble but possess a low absorption because they have little tendency to cross the biological lipid barrier.
- Some of the constituents show poor water solubility.
- Phytoconstituents have high molecular sizes and low lipophilicity; hence, permeation is a rate-limiting step in absorption.
- Phytoconstituents possess poor bioavailability.
- Some of the plant extracts possess unpleasant taste and odor
- Some essential constituents are incompatible with excipients.
- Degradation in gastric medium subsequently decreases their stability and efficacy.

Over the past several years, novel drug delivery systems (NDDS) with the incorporation of standardized phytopharmaceuticals have extensively been exploited to avoid the above-mentioned problems. These novel formulations are reported to possess some advantages, such as enhancement of solubility, absorption, bioavailability, protection from degradation, enhancement of physical and chemical stability, improved tissue distribution, targeted delivery, reduce the required dose, reduction of side effects, control the release and enhancement of therapeutic activity over conventional herbal preparations. The following are some of the novel formulation strategies for phytopharmaceuticals:

Solid dispersion (SD)

Solid dispersion is the dispersion of one or more active pharmaceutical ingredients in an inert matrix at a solid state formulated by the fusion (melting), solvent, or melting-

solvent procedure. SD causes a reduction of particle size, improvement of wetting, solubility, dissolution, absorption, and ultimately the efficacy (1). The drug inside the SD exists as suspended form in the carrier, as phase-separated partially dissolved crystalline form or amorphous form, or as a completely dissolved homogeneous molecular dispersion. Standardized *Piper longum* ethanolic extract was formulated into SD to improve the dissolution and bioavailability of piperine as a representative marker (2).

Liposomes

These are spherical nanovesicles consisting of one or several lipid bilayers surrounding an aqueous core made up of amphiphilic phospholipids. Vesicular sizes of liposomes range from 30 nm to several micrometers (3). It can entrap both hydrophilic and lipophilic material. They improve solubility and bioavailability, protect the encapsulated drug from degradation, enhance intracellular uptake, better biodistribution, in vivo stability, and prolong the action (4). The bilayer of liposomes is comprised of phospholipids (e.g., phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine) and cholesterol. The cholesterol improves the bilayer stability while exposed to biological fluids. The nanovesicles can be decorated by charged phospholipids or polyethylene glycol to enhance their stability as well as prolong their in-vivo circulation. Many of the lipolosomal formulations of white Hibiscus extract, Aloe vera extract, Guarana extract, and *Camellia sinensis* extract are in the market for various pharmaceutical uses (4).

Phytosomes (Phyto-phospholipid complex)

Phytosome is a patented technology developed by Italian pharmaceutical and nutraceutical company (Indena), to load standardized water-soluble plant extracts into phospholipids to improve their absorption, bioavailability, and therapeutic effectiveness (4). In liposomes, the water-soluble materials are physically entrapped inside the aqueous core of the phospholipid bilayer, whereas in phytosomes the molecular complexation between phospholipid and hydrophilic constituents occurs by chemical bond. The higher absorption and bioavailability of constituents loaded into phytosome are attributed to the improvement of membrane permeability and oil-water partition coefficient. Phytosome of *Centella asiatica* extract was developed to improve their pharmacological activity (5).

Niosomes

These are nonionic surfactant-based vesicular drug delivery systems in aqueous media, having structures similar to liposomes. They are considered to be the better alternative to liposomes due to the use of nonionic surfactant, low cost, greater

stability, low toxicity, biocompatible, biodegradable, non-immunogenic, and ease of storage (6, 7). The niosomal chemistry is influenced by the choice of surfactant, hydration temperature, nature of the drug, the addition of kinetic energy, nature of membrane additives, and size reduction techniques (6). Niosomes can be formulated by the conventional film hydration method, reverse phase evaporation, and ethanol injection (7). *Nerium oleander* extract was formulated as a noisome and evaluated for its antioxidant activity (8).

Ethosome

These are soft vesicular drug delivery systems containing phospholipid, ethanol in relatively high amounts (20-45%), and water. Ethanol interacts with the polar head group of phospholipid, thereby increasing the membrane fluidity permeability, making it soft and flexible. During topical administration, liposomes mostly remain confined to the skin due to their less penetration ability (9). However, due to the presence of ethanol in ethosomes, they act as permeation enhancers. The high penetration is also attributed to the synergistic action of both ethanol and phospholipid on the stratum corneum of the skin (10). The hydrophobic, hydrophilic, and amphiphilic substances can be effectively loaded into ethosomal formulation. Ethosomal gel was prepared with *Camellia sinensis* leaves extract for improved penetration of phytoconstituents through the skin (11).

Transferosome and transgelosome

These are ultradeformable self-optimizable nanovesicles, primarily composed of phospholipids, surfactant or edge activators (EAs), and water (12); used for improving the transdermal permeation of drugs. TFs are a patented product of the company IDEA AG (Munich, Germany). They have the advantages of noninvasiveness, ultradeformability, self-administration ability, excellent skin tolerability (due to the presence of phospholipids), and offer sustained release and accommodation for both hydrophilic and hydrophobic drugs. The stratum carenum of skin is composed of protein and lipid layers, which are structurally arranged as ‘bricks and mortar’ that obstruct the entry of drugs during transdermal delivery. EAs of transferosome make the membrane ultradeformable and improve skin permeation by acting as penetration enhancers and fluidizing skin lipids. The transferosomes penetrate the skin utilizing the principles of elasto-mechanics and the transdermal osmotic gradient (12). Due to their self-optimizing deformability behavior, they penetrate rapidly across the tight junctions of the intact skin by varying their size and shape. The maintenance of a transdermal osmotic gradient across the skin (dehydrated surface

of the skin: ~15% water and relatively hydrated aqueous epidermis: ~75% water) also acts as a driving force. Due to the low viscosity of the transferosome, suitable gelling agents may be incorporated to produce transgelosome for better patient compliance and to improve its retention at the application site. Transgelosome of standardized *Piper longum* ethanolic extract was successfully prepared and evaluated for ex-vivo skin permeability and in-vivo anticancer activity against syngeneic transplantable tumor model in C57BL/6 mice (13).

Polymeric nanoparticles (PNPs)

These nanoparticles consist of natural, or artificial and biodegradable or non-biodegradable polymers (14). Biodegradable polymeric nanoparticles are highly accepted due to their biocompatibility with tissue and cells. Most commonly used polymers for the synthesis of biodegradable nanoparticles include poly-d,l-lactide-co-glycolide (PLGA), Polylactic acid (PLA), Poly-Ɛ-caprolactone (PCL), gelatin, chitosan, poly-alkyl-cyano-acrylates (PAC) Poly(ethyl) cyanoacrylate, etc. The diameter of the polymeric nanoparticles ranges from 10–1000 nm. PNPs are classified as nanospheres (NSs) and nanocapsules (NCs). In NSs the drug molecule is dispersed in the polymeric matrix, whereas in NCs the drug is confined in the core surrounded by polymeric membrane (4). The enhanced anticancer potential of *Polygala senega* NPs was observed compared to extract (15).

Microsphere

Microspheres or microparticles are spherical particles with diameters ranging from 1 μm to 1000 μm. Based on the distribution of drugs in the microsphere, they are classified as microcapsules and micromatrices. Different types of microspheres include bioadhesive microspheres, magnetic microspheres (therapeutic magnetic microspheres and diagnostic magnetic microspheres), floating microspheres, and polymeric microspheres (biodegradable, synthetic polymeric microspheres) (16). Techniques, such as single emulsion technique, double emulsion technique, polymerization method, spray drying technique, solvent evaporation, and phase separation co-acervation technique, are used for the preparation of the microsphere (17). Yesil et al. incorporated *Rosmarinus officinalis* extract into polycaprolactone microsphere (18).

Microemulsion, Nanoemulsions and Self-Emulsifying Drug Delivery Systems (SEDDS)

Based upon the size of the dispersed phase, emulsion is classified as macroemulsions (size >400 nm), nanoemulsions (100-400 nm), and microemulsions (10-100 nm). Microemulsions are transparent,

thermodynamically stable colloidal dispersion systems of oil and water stabilized by emulsifying agents (19). Nanoemulsion is called mini-emulsions or ultrafine emulsions. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, and sometimes co-solvent that are capable of self-emulsifying during mild agitation (motility and mild agitation in the gastrointestinal tract). Some of the essential oil and plant extracts were studied by being loaded into such emulsion systems for enhancing solubility and therapeutic effects. *Thymus daenensis* essential oil was developed as a nanoemulsion for amplifying antibacterial activity (20).

Solid lipid nanoparticles (SLNs)

These are colloidal drug delivery systems composed of highly purified triglycerides, mainly containing lipids that are solid at room temperature or mixtures thereof stabilized by surfactants (21, 22). The particle size ranges from 50 to 1,000 nm. Their nano size and lipid solubility enhance the diffusion of drugs through biological barriers (liver, spleen, corneal barrier, and the blood-brain barrier). There are various methods to formulate SLNs, such as emulsification-sonication, high-pressure homogenization, microemulsion, and solvent emulsification-evaporation method (22). SLN loaded with aqueous extract of *Salvia officinalis* and *Sature jamontana* showed higher antioxidant activity (23).

Nanostructured lipid carriers (NLC)

NLC type of vesicular lipid carriers developed to overcome the problems associated with SLN, such as limited drug loading capacity and expulsion of drugs during storage (24). They contain a mixture of liquid lipid and solid lipid phases that form a disorganized liquid lipid matrix (22). During the storage of SLN, the lipid is modified to its more perfect crystalline form (ß-modification), leading to the increased perfection of the lipid crystal structure, leaving less space to accommodate drug substances and ultimately leading to the expulsion of the drug to the external aqueous medium. The incorporation of chemically different liquid lipid in the SLN, produce imperfections in the crystal structure, which possess a higher drug-loading ability called as NLC. Based on the architecture, they are classified as imperfect type, structureless type, and multiple oil-in-solid fat-in-water (O/F/W) type (24). Lipids uses in the solid phase include glyceryl dilaurate, glyceryl monostearate, stearic acid, hydrine, and cetyl alcohol, and liquid lipid include glyceryl monodicaprylate, oleic acid, and caprylic or capric acid. The methods utilized for the formulation of SLNs can be used for the preparation of NLCs (22). *Ocimum sanctum* leaf extract prepared as

NLC showed improved permeability and excellent antiarthritic activity (25).

Carbon dots

Carbon dots (CDs) are fluorescent carbon nanomaterials with size ranging between 1 and 10 nm, which shows adjustable fluorescence. Apart from cancer theranostics application of carbon dots have applications in the detection of ions and other important biomolecules, bacterial imaging and detection, gene delivery, ion sensing, radicals scavenging, targeted drug delivery, determination of adulterations, etc. Some of the synthetic methods that are used for preparing different types of CDs are laser ablation, solvothermal, electrochemical synthesis, microwave-assisted, arc discharge, acidic oxidation, etc.(26-30). One of the crucial characteristics of CDs is their photoluminescent ability which is primarily exploited in biomedical and pharmaceutical fields. The CDs facilitate early diagnosis, which in turn caters to efficient management of metastatic cancers. They are inert, less toxic to normal host cells, biocompatible, in vivo stable, and economical in terms of low cost of production. Carbon dots of many plants have already been reported for their theranostic properties, such as *Andrographis paniculata*, *Curcuma longa*, *Tinospora cordifolia*, *Piper longum*, and many more.

Conclusion

The current content has tried to watch from back - a time zone where there has been a progressive transition from documented formularies to novel formulations. The chemical complexity of phytopharmaceuticals possess various pharmaceutical challenges for formulation and delivery. Rational choice of formulation strategies may overcome these challenges. Beyond this, for safety considerations, there is an urgency to keep our eyes on the toxicity profile & adverse drug reaction monitoring of various formulated phytopharmaceuticals.

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