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A Sylloge on Herbal Solid Lipid Nanoparticles

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Abstract

Herbal medicines have gained global popularity due to their effectiveness and fewer side effects than synthetic drugs; however, the bioavailability and pharmacokinetic profiles of herbal extracts can be improved through the use of novel drug delivery systems (NDDS), including phytosomes, liposomes, nanoparticles, emulsions, microspheres, ethosomes, and solid lipid nanoparticles (SLNs). SLNs can increase solubility and bioavailability, improve stability, enhance tissue macrophage distribution, and provide sustained delivery and protection against physical and chemical deterioration, and thereby reducing toxic side effects by delivering the medication directly to the affected area. Some of the preparation methods of SLNs include hot and cold homogenisation, ultrasonication, and solvent emulsification methods. Examples of herbal drugs used in SLNs include *Hibiscus rosasinensis*, pomegranate etc. The evaluation methods of SLNs include particle size analysis, zeta potential, entrapment efficiency, drug release kinetics, stability studies, toxicity assessment etc.

Keywords: solid lipid nanoparticles , herbal formulations, novel drug delivery system

INTRODUCTION

Herbal medicines have been used for centuries in many Asian countries. The demand for herbal medicines has grown significantly on a global scale in recent years [1]. Herbal medicines are significantly less likely to cause side effects while treating disease than synthetic ones [2]. As the use of herbal medicine grows, it is crucial to inform the medical and scientific fields about it and demonstrate that it possesses some qualities that are specific to phytotherapy and that support both its efficacy and safety. One of them is the synergy theory, which holds that a plant extract is more effective than the combination of its constituent parts. This idea will contribute to the argument that natural medicines have something unique to offer, or it will at the very least provide a logical, scientific defense for the clinical bioequivalence of many plant extracts with synthetic drugs for the same therapeutic indications [3]. It is possible to lessen serious side effects brought on by drug accumulation in areas other than the target, to slow down drug degradation, and to make medication administration simpler for elderly and young patients by combining plant or herbal active ingredients with cutting-edge drug delivery technology. The ideal requirements of novel carriers, such as the capacity to deliver the drug at a rate directed by the body's need and to transmit the active entity of herbal drugs to the site of activity, cannot be met by conventional dosage forms, including prolonged-release dosage forms. For a natural product to have a high bioavailability, it must be hydrophilic (able to dissolve in digestive fluids) and lipophilic (able to cross lipidic biomembranes). Numerous phytoconstituents, such as polyphenolics, have good water solubility but are poorly absorbed due to either their large, multiple-ringed particles that prevent simple diffusion from taking place or their poor miscibility with oil and other lipids, which severely restricts their ability to cross the lipid-rich outer membranes of the enterocytes of the small intestine. Therefore, in the future, the nano-sized NDDSs of herbal drugs may enhance the natural process and address significant problems with plant-based medicines. Novel herbal drug carriers are used to treat particular diseases by delivering the medication only to the affected area of advantage of NDDS is that it minimizes toxic effects while increasing bioavailability by releasing the herbal medication at a controlled rate and delivering it directly to the site of action. To control the drug's social organization, novel drug delivery technology incorporates the drug into a carrier system or modifies the drug's molecular structure. In novel drug delivery technology, the drug's molecular structure is altered to regulate the drug's social organization or the drug is incorporated into a carrier system. Additionally, the addition of herbal medications to the delivery system aids in solubility, stability, toxicity protection, pharmacological activity, tissue macrophage distribution, sustained delivery, and protection from chemical and physical degradation. For example, liposomes serve as possible anticancer drug delivery systems by increasing drug concentration in the tumour and decreasing exposure to or accumulation of drugs in healthy cells and tissues, thereby preventing tissue toxicity effects. [4]

Using herbal plants as a novel drug delivery system has its benefits.

- Acceptance by the general public as a result of their extensive usage history and higher patient tolerance
- A replenishable resource.
- Simpler cultivation and manufacturing processes
- Easy accessibility.
- Enhanced solubility and bioavailability
- Toxicological safety
- Pharmacological effect is improved
- Enhanced stability
- Improved tissue macrophage distribution
- Sustained delivery
- Protection against physical and chemically-induced deterioration [5].

Novel drug delivery system types

Many researchers have focused on creating novel drug delivery systems for herbal medicines, including,

Phytosome

A phytosome is a promising phospholipid-based drug delivery system for herbal medicines that combines polyphenolic phytoconstituents in a molar ratio with

phosphotidyl choline. Phytosome outperformed traditional herbal extracts in terms of results and pharmacokinetic profile [6].

Liposome

Liposomes are amphipathic molecules with a hydrophobic tail and a hydrophilic polar head. The aqueous volume of the concentrated bilayered vesicles known as liposomes is completely encircled by a membranous lipid bilayer composed of phospholipids, which may be either natural or synthetic [7].

Nanoparticles

Due to their nano-sized and distinctive structure of synthetic or semi-synthetic polymers, nanoparticles are a drug delivery system that not only increases the absorbance of herbal formulations but also their solubility. Colloidal systems containing particles between 10 and 1000 nm in size are known as nanoparticles. It either has the drug surface-adsorbed or matrix-embedded [8].

Microemulsions

A clear, isotopic, and thermodynamically stable Micro-emulsion is created by combining oil, water, surfactant, and co-surfactant. A biphasic system can be created by intimately dispersing one phase in the other phase to produce micro-emulsions with diameters between 0.1 and 100 nm. In order to lessen the surface tension between the two liquid layers, these droplets are coated with a surfactant [9].

Microspheres

Microspheres range in size from 1 mm to 1000 mm and can be made from a variety of natural or artificial materials [10].

Ethosomes

Medication can now penetrate the deepest layers of the skin thanks to ethosomes, a modern drug delivery technology. Ethanol is reportedly added to the vesicular system to create elastic nanovesicles, acting as a dependable permeation enhancer. To enhance the delivery of various drugs, ethanolsomes, a novel class of lipid carriers made of ethanol, phospholipids, and water, was developed [11].

Niosomes

Niosomes are amphipathic vesicles made up of non-ionic surfactants. These non-ionic surfactants are inexpensive and safe for use in biomedicine. Niosomes are non-ionic surfactant-containing vesicles, whereas liposomes are phospholipid-containing vesicles.

Proniosomes

Niosome is inferior to the Proniosomes gel system, which has a variety of uses for delivering activities to the desired site. Proniosomal gels are the compositions that transform into niosomes when in situ hydrated with skin water. Proniosomes are water-soluble carrier particles coated with surfactants that, upon brief agitation in hot aqueous media, can be hydrated to create niosomal dispersion just before use. [12]

There are only a few novel drug delivery systems that will possess their superiority over others, one of which is solid lipid nanoparticles. Each novel drug delivery system will have its own advantages and disadvantages based on a variety of factors.

Solid lipid nanoparticles

Solid lipid nanoparticles, or SLNs, are an improved alternative to traditional colloidal carriers such as emulsions, liposomes, and polymeric micro- and nanoparticles. They were first developed in 1991 [13]. Smaller than 1000 nm, SLNs are submicron-sized [14]. The drugs used in SLNs are from BCS Classes II and IV, and the SLNs are colloidal carrier systems made of a high melting point lipid core that is solid and then covered in an aqueous surfactant [15]. The lipid used in SLNs is solid, as opposed to the liquid lipid used in other colloidal carriers. For the oral drug delivery method known as lipid pellets, the solid lipid is frequently used as the matrix material [16]. Triglycerides, partial glycerides, fatty acids, hard fats, and waxes are all considered to be lipids in a broad sense. The lipid matrix of the SLN is made up of physiological lipids, so there is less likelihood of both acute and long-term toxicity. There is no doubt, this is advantageous [17]. The first generation of lipid-based nanocarriers is made from lipids, which are solid at body temperature and stabilized by emulsifiers and are known as solid lipid nanoparticles (SLNs) [18].

It has been demonstrated that using solid lipid rather than lipid-lipid improves the stability of included chemically-sensitive lipophilic components and increases control over the release kinetics of encapsulated chemicals. Numerous physicochemical traits connected to the lipid phase's physical state are the root of these potentially advantageous effects. To begin with, chemical degradation reactions may proceed more slowly in a solid matrix because reactive chemicals are less mobile than in a liquid matrix. Controlling the microphase separations of the active components and carrier lipid within individual liquid particles can prevent a buildup of active chemicals at the surface of lipid particles, where chemical decomposition events frequently occur. Third, it has been demonstrated that incorporating poorly absorbed bioactive substances into solid lipid nanoparticles improves absorption. Numerous studies have shown that using a solid matrix rather than a liquid matrix slows lipid digestion and allows for more continuous release of the encapsulated substance. Aqueous-type surfactants are also important excipients in SLNs. The administration route significantly affects their decision. In order to create o/w type emulsions, they primarily serve as stabilizers for SLNs dispersion and emulsifiers. The medication is typically dissolved or distributed inside of a solid hydrophobic core in these materials [19]. The primary techniques used to prepare SLNs are high pressure homogenization or microemulsification. Lyophilization is a process that can be used to produce solid, dry,

reconstitutable powders from any method of SLN preparation, which can be used to improve their stability. The spray drying method is a quick and affordable substitute for lyophilization [20].

List of excipients used in solid lipid nanoparticles preparation

Lipids

Triglycerides, Tricaprin, Trilaurin, Trimyristin (Dynasan 114), Tripalmitin (Dynasan 116), Tristearin (Dynasan 118), Hydrogenated coco-glycerides (Softisan Ò 142), Hard fat types, Witepsol ÒW 35, Witepsol ÒH 35, Witepsol ÒH 45, Witepsol ÒE 85, Acyl glycerols, Glyceryl monostearate (Imwitor Ò900), Glyceryl distearate(Precirol), Glyceryl monooleate(Peceol), Glyceryl behenate (CompritolÒ 888 ATO), Glyceryl palmitostearate (PrecirolÒ ATO 5), Waxes Cetyl palmitate, Fatty Acids, Stearic acid, Palmitic acid, Decanoic acid, Behenic acid, Acidan N12, Cyclic complexes, Cyclodextrin para-acyl-calix-arenes.

Surfactants

Phospholipids

Soy lecithin (LipoidÒ S 75, LipoidÒ S 100), Egg lecithin (LipoidE 80)

Phosphatidylcholine (Epikuron170, Epikuron 200)

Ethylene oxide/propylene oxide copolymers

Poloxamer 188, Poloxamer 182, Poloxamer 407, Poloxamine 908

Sorbitan ethylene oxide/propylene oxide copolymers

Polysorbate 20, Polysorbate 60, Polysorbate 80

Alkylaryl polyether alcohol polymers

Tyloxapol

Bile salts

Sodium cholate, Sodium glycocholate, Sodium taurocholate, Sodium taurodeoxycholate

Alcohols

Ethanol, Butanol, Butyric acid, Dioctyl sodium sulfosuccinate, Monooctyl Phosphoric Acid, Sodium [19].

Proposed advantages include:

- The possibility of controlled drug release and targeted drug delivery
- improved drug stability; significant drug payload
- Drugs that are both lipophilic and hydrophilic can be included.
- There is no biotoxicity in the carrier.
- Organic solvent usage restrictions
- There have never been any problems with mass production or sterilization.
- improved biopharmaceutical characteristics
- Sustained drug release
- achieving high local concentration
- Enhancing bioavailability
- extending the time that drugs stay in the lung
- Possibility of treating lung cancer by encapsulating chemotherapy drugs in lipid nanoparticles. Cationic SLNs have the potential to deliver genes, preventing negative side effects from medications.
- excellent storage stability
- Low toxicity
- Increasing patient compliance
- Bypassing hepatic first-pass metabolism
- Mucoadhesiveness
- Long dosing intervals
- Prevention of peptide and protein premature degradation for pulmonary systemic drug delivery
- The rapid and straightforward large-scale drug production capabilities of the high-pressure homogenization method, as well as the drugs' biocompatibility and biodegradability [20][21].

SLNs also have a few drawbacks:

- There is no information on human safety. Lipase degradation in some lipid matrix compositions causes a change in the drug release profile.
- Toxic effects could be brought on by these nanocarriers' burst drug release.
- Rapid clearance of drugs by macrophages. They should be encapsulated in lipid microparticles because their small particle size makes them unsuitable for deep lung delivery.
- Lipid nanoparticle aggregation, clotting, and fragmentation during nebulization
- Loss of a loaded drug during nebulization
- Due to their flawless crystalline structure and the possibility of drug expulsion caused by the crystallization process during storage conditions, they have a low drug loading efficiency. Another disadvantage of these formulations is the frequent occurrence of the initial burst of release.

These are the goals of solid lipid nanoparticles. SLN is said to combine the advantages of other colloidal carriers while avoiding their drawbacks.

METHODS OF LIPID NANOPARTICLES PREPARATION

Various techniques could be used to create lipid nanoparticles, including

- Hot and cold high pressure homogenization
- Solvent emulsification/evaporation
- Microemulsion formation technique
- Ultrasonic solvent emulsification.
- Double emulsion method
- Spray drying method and high pressure homogenization techniques are primarily used to produce lipid nanoparticles on a large scale [22][23].

High pressure homogenization technique

- **Hot high pressure homogenization**

During this process, the lipid phase is heated to 90 °C before being combined with an equally heated aqueous phase that contains surfactants. In a high pressure homogenizer, the pre-emulsion is homogenized at 90 °C for three cycles. Finally, SLNs are solidified by bringing the produced oil in the water emulsion to room temperature [24].

- **Cold high pressure homogenization**

In this method, the melted lipid phase is cooled until it solidifies, and then it is ground to produce lipid microparticles. After being obtained, lipid microparticles

are dispersed in a cool, surfactant-containing aqueous phase to create a presuspension. The pre-suspension is then homogenized in a high pressure homogenizer for five cycles at room temperature [25].

- **Solvent emulsification and evaporation**

This procedure involves lipid phase dissolution in an organic phase, usually acetone. At 70 to 80 °C, the organic phase is then combined with the aqueous phase (surfactant solution in water), while being continuously stirred. The stirring is carried on until the organic phase has evaporated completely. The lipid nanoparticles are then solidified by cooling the nanoemulsion to below 5 °C [26].

- **Microemulsion formation technique**

In this procedure, the right temperature is used to melt the lipids, and the same temperature is also applied to the aqueous phase that contains the surfactants. The melted lipids will then be mixed with the hot aqueous phase while still being at the same temperature. By dispersing hot oil in a water microemulsion at a ratio of 1:50 in cold water, lipid nanoparticles are solidified [27].

- **Ultrasonic solvent emulsification technique**

This technique involves dissolving the lipid phase in an organic solvent and heating it to 50 °C. Then, while still containing surfactants and emulsifiers, the aqueous phase is heated to the same temperature. The aqueous phase is added to the organic phase and stirred at 50 °C after the organic solvent has partially evaporated. To solidify the lipid nanoparticles, the resulting emulsion is cooled in an ice bath after being sonicated for the appropriate length of time. [28][22]

- **Double emulsion method**

The production of hydrophilic drug-loaded SLN involved a novel technique based on solvent emulsification evaporation. To prevent drug partitioning to the external water phase during solvent evaporation in the external water phase of the w/o/w double emulsion, the drug is here encapsulated with a stabilizer [29].

- **Solvent injection method**

In this method, the lipids are first dissolved in a water-miscible solvent before being injected through an injection needle into a stirring aqueous solution, either with or without a surfactant. The parameters of the process for the synthesis of nanoparticles include the type of injected solvent, the concentration of the injected lipids, the volume of injected lipid solution, the viscosity, and the diffusion of the injected lipid solvent phase into the aqueous phase[30].

Few Examples of solid lipid nanoparticles

Herbal drug	Lipid polymer	SLN's type	Treatment	Reference
Hibiscus rosa sinensis	Glyceryl monostearate	Emulsifcation-hot melt homogenization method	Antidepressant activity	[31]
Pomegranate	Stearic acid, precirol ATO5	Hot homogenization followed by the ultra-sonication method	Anti-oxidant activity	[32]
Triptolide	Tristearin glyceride, stearic acid	Probe sonication	Anti-inflammatory activity	[33]
Calendula officinalis	Stearic acid, palmitic acid, arachidic acid	warm microemulsion technique	Re-epithelialization activity	[34]
Frankincense and myrrh	Glyceryl dibehenate	high-pressure homogenization	Antitumor activity	[35]
Neem oil	Cholesterol	Double emulsification method	Anti-Toxoplasma activity	[36]
Annona muricata	Stearic acid	High-pressure homogenization followed by ultrasonication method.	Anti cancer activity	[37]
Yuxingcao	Glyceryl behenate	High-shear homogenization method	Respiratory tract infection	[38]
Andrographolide	Stearic acid, glyceryl monostearate	modified solvent injection technique	Anti-cancer activity	[39]

Evaluation of solid lipid nanoparticles

- Electron microscopy
- Zeta potential
- Particle size and polydispersity index
- Encapsulation efficiency
- Viscosity
- Invitro release study

Electron microscopy

Electron microscopy is a type of microscopy that uses a beam of electrons to create images of tiny structures or specimens. Unlike traditional light microscopy, which uses visible light to magnify images, electron microscopy uses a focused beam of electrons that can achieve much higher magnifications and resolutions. There are two main types of electron microscopy: transmission electron microscopy (TEM) and scanning electron microscopy (SEM) [40,41].

Zeta potential

Zeta potential is the potential difference that exists between the surface of a particle in a liquid medium and the surrounding liquid. It is a measure of the electrostatic charge that is present at the surface of a particle, which is influenced by the chemical and physical properties of both the particle and the surrounding fluid. Zeta potential is an important property of colloidal systems and is often used to characterize the stability of suspensions or emulsions. It is related to the degree of repulsion or attraction between particles, which can influence the stability of the system. The higher the zeta potential, the greater the repulsion between particles and the more stable the system [42].

Particle size and polydispersity index

Particle size refers to the size of individual particles in a sample, which can range from nanometers to micrometers, depending on the type of particles and the method used to measure them. The particle size can be determined using various techniques such as dynamic light scattering, electron microscopy, or laser diffraction. Polydispersity index (PDI) is a measure of the degree of heterogeneity or variation in the particle size distribution of a sample. It is calculated by dividing the standard deviation of the particle size distribution by the mean particle size. A PDI value of 0 indicates a monodisperse sample, where all particles are of the same size, while a higher PDI value indicates a more polydisperse sample with a wider range of particle sizes. The PDI value is an important parameter for many applications, as it can affect the performance of the particles in various processes, such as drug delivery, surface coating, or catalysis. A lower PDI value generally indicates a more uniform and stable particle size distribution, which can lead to more consistent and predictable performance [43].

Encapsulation efficiency

Encapsulation efficiency (EE) is an important parameter in the development of solid lipid nanoparticles (SLNs), which are a type of nanoparticle used for drug delivery. EE refers to the percentage of drug is successfully encapsulated within the lipid matrix of the SLN.To determine the EE of SLNs, the amount of drug or active ingredient present in the nanoparticles is compared to the total amount added during the formulation process. The EE is calculated as the ratio of the amount of drug or active ingredient encapsulated in the nanoparticles to the total amount added, expressed as a percentage. A high EE is desirable in SLN formulations, as it indicates that a larger amount of the drug or active ingredient is present in the nanoparticles, which can enhance the therapeutic efficacy of the formulation. A low EE may result in lower drug loading, reducing the efficiency of the formulation and leading to potential side effects [44].

Viscosity

Viscosity is an important parameter that affects the stability and behavior of solid lipid nanoparticles (SLNs). Viscosity refers to the resistance of a fluid or material to flow, and it can be influenced by various factors, including the size, shape, and composition of the SLNs, as well as the properties of the surrounding medium. In SLNs, the viscosity of the lipid matrix can affect the physical stability of the nanoparticles, as well as their drug release behavior. A higher viscosity may result in a slower drug release, as it can impede the diffusion of the drug through the lipid matrix. On the other hand, a lower viscosity may lead to faster drug release, but it can also make the SLNs more prone to aggregation and instability. The viscosity of SLNs can be measured using various techniques, such as rheometry, viscometry, or dynamic light scattering. These techniques can provide information on the flow behavior of the nanoparticles and can help in optimizing the SLN formulation for specific applications [45].

***Invitro* drug release study**

These studies involve measuring the rate and extent of drug release from SLNs under controlled laboratory conditions, which can provide valuable information on the drug release behavior and potential applications of the SLN formulation. In general, in vitro drug release studies involve adding a predetermined amount of SLNs to a dissolution medium that mimics the physiological conditions at the target site of drug action. The dissolution medium is typically stirred to ensure uniform mixing and maintained at a constant temperature and pH to simulate *in vivo* conditions.

At specific time intervals, samples of the dissolution medium are collected and analyzed for the amount of drug released from the SLNs using various techniques such as UV spectrophotometry or high-performance liquid chromatography (HPLC). The results of invitro drug release studies can be used to determine the kinetics of drug release from the SLNs, including the release rate and mechanism [46]

CONCLUSION

The incorporation of herbal drugs into solid lipid nanoparticles has shown to be a promising approach in drug delivery. This innovative method offers several advantages over conventional drug delivery systems such as improved pharmacokinetic and pharmacodynamic properties, enhanced drug bioavailability, and targeted drug delivery. The use of solid lipid nanoparticles as carriers for herbal drugs can increase their therapeutics efficacy and reduce toxicity, thus improving patient outcomes. Overall, the incorporation of herbal drugs into solid lipid nanoparticles provides a safe, effective and efficient drug delivery system that can revolutionize the field of medicine. As research in this area continues to advance, we can expect to see more innovative solutions in the development of drug delivery systems that will improve patient care and outcomes.

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