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Herbal Nanosuspensions - A Transformative Approach for Poorly Soluble Drugs

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Abstract:- Herbal formulations have been widely used now a days for their therapeutic effectiveness. Medicinal plants and their active compounds are typically less toxic and have minimal side effects. However, challenges in formulating these compounds often arise due to their poor solubility. Nanosuspensions has emerged as an innovative drug delivery platform designed to overcome this significant challenge. These colloidal dispersions of nanosized drug particles stabilize poorly soluble drugs, enhancing their dissolution rates, bioavailability, and therapeutic efficacy. This review provides a comprehensive overview of nanosuspension technology, with a particular emphasis on herbal nanosuspensions preparation methods and characterization techniques.

Keywords:- *Nanosuspensions, Colloidal Dispersions, Herbal Nanosuspension.*

I. INTRODUCTION

Nanosuspensions have gained considerable attention in pharmaceutical research as a promising solution to the challenges posed by poorly water-soluble drugs. These are colloidal drug particle dispersions, typically in the nanometer range, stabilized by surfactants or polymers. By reducing particle size, nanosuspensions increase the surface area available for dissolution, leading to enhanced solubility, bioavailability, and therapeutic effectiveness of poorly soluble compounds. [1, 2]

Herbal medicines were derived from natural plant sources, essential in global healthcare, especially in traditional medicine. However, many bioactive compounds from plants, such as curcumin, quercetin, resveratrol, and berberine are few examples of many plant-based chemicals that have serious drawbacks, including poor solubility, low absorption, and quick metabolism.[3, 4]

These challenges hinder their therapeutic potential, despite their promising pharmacological properties. Nanosuspension technology presents an innovative solution, offering an effective delivery system that can improve the solubility, stability, and bioavailability of these herbal bioactives.[5,6] In addition to enhancing solubility, nanosuspensions offer several benefits, such as controlled release, targeted delivery and reduced dosing frequency.[7]

The flexibility of this technology allows it to be applied across multiple delivery routes, including oral, parenteral, pulmonary, and ocular systems, thus broadening the possibilities for herbal drug formulations.[8]

This article provides a thorough overview of nanosuspension technology, with a special focus on its applications for herbal medicines. It will explore preparation methods and characterization techniques relevant to herbal nanosuspensions.[9, 10]

II. HERBAL NANOSUSPENSION

The preparation of herbal nanosuspensions involves various techniques that help to enhance the solubility and bioavailability of poorly water-soluble herbal compounds. These techniques include both top-down and bottom-up approaches, each with unique advantages for different types of herbal bioactives. Below are common methods for preparing herbal nanosuspensions.

- *High-Pressure Homogenization (Top-Down)*

It is the most popular technique for creating nanosuspensions of numerous medications that are not very soluble in water.[11] A presuspension prepared by dispersing drug powders in stabilizer solution and homogenized in a high pressure homogenizer at low pressure for pre milling, and finally, it is homogenized at high pressure for 10 to 25 cycles until the required size of nanosuspensions is achieved Several techniques, including Dissocubes, Nanopure, Nanoedge, and Nanojet, have been developed.[12].

- *Media Milling (Top-Down)*

Liversidge was the first to design and report on this strategy in 1992.[13] This process is used, when high shear media mills are used to prepare the nanosuspensions. The milling media, water, medication, and stabilizer were loaded into the milling chamber, which revolved at a very high shear rate for at least two to seven days at a regulated temperature.[14] Highly cross-linked polystyrene resin, glass, or zirconium oxide make up the milling media. Because the drug and milling media impaction causes the drug's micro particles to split into nanoparticles, high energy shear forces are created.

- *Solvent-Evaporating Emulsification Method (Bottom- Up)*

Drug molecules in solution can be converted into herbal drug nanoparticles using the bottom-up emulsification-solvent evaporation approach. In this process the herbal bioactive ingredient is converted into nanoparticles by evaporating the organic solvent after emulsification.[15]

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➢ *Solvent-Antisolvent Precipitation (Bottom Up)*

Precipitation has been used in the past ten years to create submicron particles, particularly for medications that are poorly soluble[16]. After dissolving the medication in a solvent, a miscible antisolvent is added to the mixture while surfactants are present. When a drug solution is quickly added to the antisolvent, the drug becomes suddenly super-saturated and forms ultrafine crystalline or amorphous drug solids. [17]

➢ *Supercritical Fluid (SCF) Process*

The solubilization and nanosizing technologies using the super critical fluid process were able to reduce the particle size considerably. Drug- particles can be micronized to the submicron level by this method. Recent developments in the SCF technique produce nanoparticulate suspensions with diameters ranging from 5 to 2000 nm. [18]

➢ *Lipid based Nanoparticles (Solid Lipid Nanoparticles – SLNs)*

Solid Lipid Nanoparticles (SLNs) are occasionally employed to enhance the delivery of herbal bioactives, particularly for lipophilic substances, even though they are not exactly a nanosuspension technique. This method produces stable nanoparticles by combining herbal components with solid lipid matrix. In this process, the herbal extract is emulsified after being dissolved in melted lipids. These lipid matrices improve the bioavailability of the active components .[19]

➢ *Melt Emulsification Method*

This approach creates an emulsion by dispersing the drug in the stabilizer's aqueous solution, heating it over the drug's melting point, and homogenizing it. In order to keep the emulsion's temperature above the drug's melting point, the sample holder was wrapped in a heating tape that had a temperature controller attached. Next, the emulsion was chilled on an ice bath or gradually to room temperature.

➢ *Ultrasound Assisted Sono-Crystallization Method*

Stable nanosuspension is prepared using this innovative method. The size distribution of active ingredients is controlled and particle size reduction is improved by using ultrasound at frequencies between 20 and 100 kHz. It is also regarded as a successful method for reducing the process of nucleation and crystallization. [20]

III. CHARACTERIZATION OF HERBAL NANOSUSPENSIONS

Characterization of herbal nanosuspensions is crucial to ensure their quality, stability, and performance in enhancing the solubility and bioavailability of poorly soluble herbal compounds. The characterization methods assess various physical, chemical, and functional properties of the nanosuspensions, such as particle size, morphology, zeta potential, and drug content.[21]

➢ *Particle Size Distribution*

One of the most important factors of a nanosuspension is the particle size because they impact the physical stability, rate of dissolution, and biological performance of nanosuspensions. Particle size analyzer was used to measure the particle size, Studies have shown that altering the size of medication particles significantly alters both dissolving and saturation solubility.[22]

➢ *Zeta Potential*

Zeta potential measures the surface charge of nanoparticles and serves as a key indicator of stability of nanosuspension. A high zeta potential (above ±30 mV) generally suggests stable dispersion, while a low zeta potential may indicate potential particle aggregation. Zeta potential is usually assessed using instruments like a Zetasizer or other electrophoretic light scattering techniques.[23]

➢ *Drug Content and Encapsulation efficiency*

Drug content refers to the amount of herbal active compound present in the nanosuspension, while encapsulation efficiency measures how much of the drug is successfully incorporated into the nanoparticles. These factors are usually determined using techniques like high-performance liquid chromatography (HPLC) or UV-visible spectrophotometry.[24]

➢ *Rate of Dissolution of the drug*

The Noyes-Whitney equation states that as surface area particles increase in size—from micron to nm—the dissolving velocity increases as well. [25] This type of heterogeneous process can be understood as one in which solid surface deposition and solute molecule escape lead to mass transfer.[26] *In vitro* drug release is the quantity of drug ingredient that enters the solution per unit of time was measured by using dissolution apparatus.

➢ *Stability Studies*

To improve suspension stability and lessen the possibility of the Ostwald ripening effect, stabilizers are used. These stabilizers create ionic or steric barriers. In nanosuspension applications, stabilizers such as poloxin, lecithin, polyoleate, polysorbates, cellulosic acid and povidones are frequently used. [27]

IV. APPLICATIONS OF NANOSUSPENSIONS: ORAL DRUG DELIVERY

The recommended method of administration for many medications is oral. However, poor solubility and limited absorption often reduce the bioavailability and effectiveness of some drugs. Nanosuspensions can enhance drug absorption and dissolution rates by increasing the surface area and improving adhesiveness, particularly in such cases. Additionally, nanosuspensions can extend the time the drug remains in the gastrointestinal tract, further boosting bioavailability. Key features contributing to this improvement include enhanced adhesiveness, higher saturation solubility, and a greater surface area. Furthermore, nanosuspensions can effectively mask the flavor of particulate matter.[28]

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➢ *Parenteral Drug Delivery*

Low-solubility medications that can't be injected directly need to be turned into formulations suitable for intravenous delivery using nanosuspensions. Modern manufacturing methods for nanosuspensions allow for the production of uniform particles with better control over particle size. Many studies highlight the benefits of using nanosuspensions for parenteral drug delivery. [29]

➢ *Pulmonary Drug Delivery*

Medications with low solubility for lung delivery can be effectively given using nanosuspensions. Current methods, like dry powder inhalers and aerosols, face challenges such as limited diffusion to the target area and a short time the drug stays in the lungs. Nanosuspensions can help overcome these issues. Successful examples include budesonide and fluticasone, which have been formulated as nanosuspensions for pulmonary delivery. [30]

➢ *Ocular Drug Delivery*

Drugs that have limited solubility in tear fluid can be effectively administered using nanosuspensions. These systems enhance the saturation solubility of hydrophobic medications, making them an ideal method for eye drug delivery.

➢ *Dermal Application*

Nanocrystals have increased membrane penetration, enhanced permeability, and higher adhesiveness, making them ideal for cutaneous applications.[31]

➢ *Targeted Delivery*

The degree of absorption is influenced by the size of the drug nanoparticles. Modifying the in vivo behaviour of nanoparticles by modifying their properties, like their surface, enables targeted distribution. The successful application of atovaquone nanocrystals coated with tween 80 for effective parasite removal in the brain during toxoplasmosis treatment demonstrates the potential of tween 80-coated nanocrystals for brain targeting. [32]

➢ *Sublingual Delivery*

Herbal nanosuspensions can also be formulated for sublingual administration (under the tongue), allowing for rapid absorption into the bloodstream, bypassing the digestive system, which can be beneficial for quick relief of conditions like anxiety or pain.

➢ *Oral Delivery*

Herbal nanosuspensions can be taken by mouth, improving the absorption of poorly soluble herbal compounds in the gastrointestinal tract. This makes them more effective in treating conditions such as digestive disorders, inflammation, or metabolic diseases.

➢ *Rectal Delivery*

Herbal nanosuspensions can be formulated into suppositories for rectal administration, which can be particularly beneficial for patients who cannot take oral medications. This route is useful for delivering herbal compounds directly to the gastrointestinal tract, offering relief for conditions like constipation, hemorrhoids, or inflammatory bowel diseases.

Table 1 List of various Herbs used as Nanosuspensions

S.no	Herb	Scientific Name	Constituents	Method of Preparation	Applications	References
1	Common wormwood	Artemisia absinthium	Flavonoids such as quercetin, myrecetin, hesperidin, rutin , and artemisnin and phenolic acids such as salicylic, coumaric, syringic, vanillic, and chlorogenic acids,	Antisolvent precipitation technique	Antimalarial, Antimicrobial, Antioxidant, Anti-inflammatory and nephroprotective activities,	33-39
2	Milk thistle	Silybum marianum	Silymarin, silybin, isosilybin, silychristin, isosilychristin, silydianin, and silimonin	Nanoprecipitation method	Oral therapy of chronic liver disorder	40-42
3	Cardamom	Elettaria cardamomum	Cellulose, Pigments, steam volatile oil, starch, minerals, fatty oil, pentosans and sugars and cineole, limonene and caffeic acid	Nanoprecipitation method	Treatment of cardiac and gastrointestinal disorders.	43-46
4	Silver cock’s comb	Celosia argentea	Saponins, peptides, phenols, fatty acids, and amino acids, Tlatlancuayin and Betavulgarin, Two flavonoids. Aspartic acid, Threonine,	Nanoprecipitation method	Parasiticide and poultice, astringent, haemostatic, Ophthalmic. Bloody stools, diarrhoea, uterine bleeding, haemorrhoids,	47-49

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			Glutamic Acid, Moroidin, Celogenamide A, and Celogentin A are among the amino acids found in the seed.		Hypertension, cataracts, and bloodshot eyes	
5	Arjuna	Terminalia arjuna	Flavonoids, phenolics, condensed and hydrolysable tannins) Quercetin	Soxhlet extraction	Antioxidant, anti-mutagenic, anti-diabetic and anti-microbial and possessing strong cardioprotective potential	50-52
6	Turmeric	Curcuma longa L.	77% diferuloyl methane, 17% demethoxy-curcumin, and 6% bisdemethoxy curcumin	Precipitation-high speed homogenization (HSH Ultraturrax T-25 IKA) method	Immunomodulatory, chemoprotective, antihyper-lipidemic, antineoplastic, antiulcer, and neuroprotective	53-56
7	Black cumin sedds	Nigella sativa	Thymoquinone (30–48%), thymohydroquinone, dithymoquinone, cymene (7–15%), carvacrol (6–12%), 4-terpineol (2–7%), t-anethol (1–4%), -pinene, and thymol	Nanoprecipitation method	Hypertension, asthma, infections, antitumor, serum-glucose lowering, smooth muscle relaxant, and anti-inflammatory properties.	57-60
8	Onion	Allium cepa	Polyphenols and flavonoids such as quercetin, kaempferol, and their glycosides	Nanoprecipitation method	Defensive effect against coronary heart diseases and cancer	61-,63
9	Sarpagandha	Rauvolfia serpentina	Reserpine, ajamlicine, serpentine, ajmaline deserpidine, and yohimbine alkaloids	Anti solvent precipitation technique	Hypertension, insomnia, epilepsy, psychosis, insanity, and schizophrenia	64-66
10	Cinnamon	Cinnamonnum	Cinnamaldehyde, Cinnamic acid cinnamate, polyphenols antioxidants	Nanoprecipitation technique	Anti-inflammatory, antidiabetic, antibacterial, and anticancer activities	67-69
11	Haima or Chiretta	Swertia chirayita	Swertinin, swerchirin, mangiferin, decussatin and isobellidifolin	Nanoprecipitation technique	Leprosy, cholera, liver problems, and joint discomfort anti-cancer, antimicrobial, and anti-allergic activities	70-73
12	Marigold	Tagetes erecta	Rutin, isoquercitrin, isorhamnetin-3-O rutinosylrhamnoside, isorhamnetin-3-O-glucosylglucoside, and isorhamnetin-3-O-glucoside	High Pressure Homogenization	Wounds and burns, varicose veins, hemorrhoids, duodenal ulcers,	74-77

V. CONCLUSION

Despite the challenges in ensuring the safe use of conventional herbal remedies, nanotechnology-based herbal products hold great potential. Overall, herbal nanomedicines are considered safer, more potent, and offer improved therapeutic outcomes compared to traditional herbal or synthetic drugs.

Techniques like high-pressure homogenization, bead milling, solvent antisolvent precipitation, and supercritical fluid processes are commonly employed, each with its own advantages for specific types of herbal bioactives.

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