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Review Article

Studies on the Effect of Novel Nanomaterials on Drug Delivery Systems and Targeting for Plant Physiology and Extracts as Well as their Applications: An Overview

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Abstract

Novel medicine delivery and targeting for plant active compounds and extracts are the subjects of substantial ongoing study. Though, research in this area is still at the investigative stage. Many problems in the research, production and application need to be solved. Besides, more attention should be paid to the research on the carrier materials in view of developing more appropriate carriers which can reduce the toxicity of drugs, augment their activity and improve the overall quality of the agents. The enormous therapeutic potential of herbal medications should be investigated using value-added drug delivery methods. Standardized plant extracts or polar phytoconstituents including flavonoids, terpenoids, tannins, and xanthones have a significantly better absorption profile that enables them to pass through the biological barrier and boost bioavailability when administered through a novel drug delivery system. Because of this, a higher amount of the active ingredient is present at the site of action (liver, brain, heart, kidney, etc.) at a similar or lower dosage than with a conventional plant extract or phytomolecule. The outcome is a stronger, more noticeable, and longer-lasting therapeutic effect.

Keywords: *Drug Delivery System; Nanopharmaceuticals; Nanotechnology; Phytomolecule*

Introduction

Nanotechnology is an advanced scientific technique in the 21st century [1]. The word "nano" comes from a Greek word that means "dwarf." In methodical terms, the word "nano" means 10^{-9}, or one billionth of a meter [2]. Over the past decades, nanobiotechnology has expanded quickly on a global scale. Size is the defining feature of this multidisciplinary collection of physical, chemical, biological, engineering, and electronic processes, materials, applications, and concepts. It includes the production, handling, and use of materials with a maximum size of 100 nm [3]. It offers the capacity to develop materials, tools, and systems with essentially novel capabilities and

characteristics [4]. The total function of several active ingredients determines the efficacy of herbal medications since each component works in concert to increase the therapeutic value. Every active ingredient has a significant function and is connected to the others. However, the majority of medications derived from herbal sources are insoluble, which reduces their bioavailability and increases their systemic clearance, necessitating higher doses or repeated administration. As a result, these medications are not good candidates for therapeutic use.The development of nano dosage forms (Polymeric Nanoparticles [Nanospheres and Nanocapsules], Liposomes, Proliposomes, Solid Lipid Nanoparticles, Nanoemulsion, etc.) in phyto-formulation research offers numerous benefits for herbal drugs, such as improved solubility and bioavailability, protection against toxicity, increased pharmacological activity, improved stability, improved distribution of tissue macrophages, sustained delivery, protection against corrosion, etc. Therefore, the use of herbal pharmaceuticals in nanoscale drug delivery systems holds promise for improving their efficacy and resolving issues related to plant medicines. Therefore, it is crucial to incorporate nanocarriers as NDDS into the conventional medical system in order to combat more chronic illnesses as cancer, diabetes, asthma, and others [5].

Types of nanopharmaceuticals [6]

Polymeric system	**Particle size distribution (nm)**
Dendrimers	1-10
Polymer micelles	10-100
Niosomes	10-150
Nanoparticles	50-500
Nanocapsules	100-300
Nanogels	200-800
Polymer-drug nanoconjugates	1-15
Chitosan polymers	100-800
Methacrylate polymers	100-800
Lipid systems	
Solid lipid nanoparticles	50-400
Lipid nanostructured systems	200-800
Cubosomes	50-700
Liposomes	10-1000
Polymerosomes	100-300
Immunoliposomes	100-150
Protein/peptide nanotubes	
Peptide nanotubes	1-100
Fusion proteins and immunotoxins	3-15
Metal nanostructures	
Metal colloids	1-50
Carbon nanotubes	1-10 (diameter) and 1-1000 (length)
Fullerene	1-10
Gold nanoparticles	100-200
Gold nanoshells	10-130
Silicone nanoparticles	25
Magnetic colloids	100-600

Table

Types of nanopharmaceuticals [6]

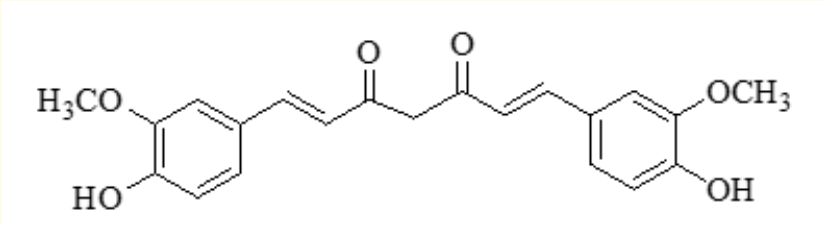
Need for herbal novel drug delivery system

In order to address the shortcomings of the conventional drug delivery systems, a new drug delivery system was developed. The most recent development in the pharmaceutical drug delivery sector is the use of tailored drug delivery nanoparticles to treat chronic diseases like cancer [7]. Many of the herbal medications' ingredients will be broken down in the stomach's extremely acidic pH before they can enter the bloodstream, and the liver may also metabolize additional ingredients.As a result, the blood may not receive the ideal amount of the herbal medications. There won't be any way to demonstrate the medication's therapeutic impact if it doesn't get to the affected area in the ideal quantity at the "minimum effective level." When used in herbal treatments, nanocarriers will deliver the maximum amount of the medication to the site of action while avoiding all obstacles, including the stomach's acidic pH and liver processing. Because of their small size, they will also prolong the drug's circulation into the blood. The following characteristics of herbal treatments led to their selection as a viable drug candidate for distribution via a nano delivery system:

1. Effective chloroform, petroleum, acetone, and methanolic extracts are available which may not be suitable for delivery as such.
2. These are the bulk drugs so dose reduction is intended.
3. Target specificity for a number of chronic disorders is lacking in currently marketed formulations.
4. Some other side effects are related with presently marketed formulations.
5. Patient non-compliance as a result of high dosages and ineffective formulations.

The creation of innovative drug delivery methods for herbal medications has received a lot of attention in the last several decades. The novel herbal medication method has the benefit of administering the herbal drug at a controlled pace and at the site of action, which reduces adverse effects and increases the drugs' bioavailability. By integrating the drug into a carrier system or altering the drug's molecular structure, innovative drug delivery technologies can govern the drug's distribution. This summary highlights recent developments in nanotechnology for improving the bioavailability of chemical constituents derived from herbs [7].

Curcumin nanoparticle: The rhizomes of *Curcuma longa* Linn. (Zingiberaceae) are the source of curcumin, a bioactive ingredient in turmeric, a popular spice and dietary supplement [8]. Inflammatory illnesses, cardiovascular disease, cancer, Alzheimer's disease, and neurological disorders have all been linked to curcumin's possible pharmacological activities in recent years. However, curcumin's primary disadvantages-instability, low solubility, poor bioavailability, and rapid metabolism-severely restrict its therapeutic use [8]. In order to improve curcumin's bioavailability and therapeutic potential, these drawbacks have prompted numerous studies to create innovative drug-delivery strategies, such as microemulsions, nanoemulsions, liposomes, solid lipid NPs, microspheres, polymeric nanoparticles, and



Figure

self-microemulsifying drug-delivery systems [8].

Antioxidant and anticancer properties of curcumin have been reported. However, due to its limited water solubility, the chemical has poor absorption after high oral dosages. A new curcumin nanoparticle system was created in order to increase the solubility of curcumin, and its physicochemical characteristics and improved dissolution mechanism were examined. The findings showed that curcumin nanoparticles had enhanced physicochemical characteristics, such as a decrease in particle size and the development of an amorphous state through hydrogen bonding, both of which enhanced the compound's drug release. Furthermore, curcumin nanoparticles dramatically increased curcumin's antioxidant and antihepatoma properties, according to *in vitro* research ($P < 0.05$) [9].

Curcumin solid lipid nanoparticle: Solid lipid nanoparticles are made of natural or synthetic lipid or lipoid, such as lecithin and triglycerides, which are solid at human physiological temperature [10]. SLNs present many potential advantages. For example, they protect labile compounds from chemical degradation, provide sustained release to improve the availability of the drug, and target the effect to improve the efficiency of the drugs [11].

Curcumin-loaded solid lipid nanoparticles with an average particle size of 134.6 nm and a total drug content of 92.33 ± 1.63% was also produced by Kakkar., *et al*. using a microemulsification technique to enhance bioavailability to establish its therapeutic usefulness especially for neurodegenerative and cancerous disorders in humans [10].

Curcumin-containing nanoparticles were also made utilizing a combination of random and crosslinked copolymers of polyethylene glycol monoacrylate (PEG-A) and nisopropylacrylamide (NIPAAM) with N-vinyl-2-pyrrolidone (VP). According to *in vitro* release experiments, 40% of curcumin was released in 24 hours in phosphate buffer at physiological pH, and even at a 20-fold void range of nanoparticles, no tissue-related toxicity was detected. When compared to free medication, the dispersion of nanocurcumin in aqueous medium demonstrated their potential as a cancer treatment carrier [11].

Curcumin hydrogel nanoparticle: In another study, hydrogel nanoparticles were prepared using a combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone. Due to potential reticulo-endothelial system evasion, the aim of this work was to take advantage of the size and hydrophilic character of the prepared nanocarriers to improve absorption and extend the quick clearance of curcumin [12]. Reproducible nanoparticles of size around 100 nm and encapsulation efficiency of 72% were produced by the solvent emulsion-evaporation technique. This optimized system was further subjected to freeze-drying. *In vivo* anti-malarial studies revealed significant superior action of nanoparticles over curcumin control suggesting the possibility of the formulation being employed as an adjunct anti-malarial therapy along with the standard therapy. Acute and subacute toxicity studies confirmed the oral safety of the formulation. A battery of genotoxicity studies was conducted to evaluate the nongenotoxic potential of the developed formulation thus indicating the possibility of the formulation being employed for prolonged duration [12].

Curcumin-loaded lipid cubic liquid crystalline nanoparticles: Hot and high-pressure homogenization was used to create lipid cubic liquid crystalline nanoparticles loaded with curcumin. The resulting lipid cubic liquid crystalline nanoparticles loaded with curcumin exhibit strong sustain-release properties and great entrapment efficiency [13].

Curcumin micropellets: Pectin-HPMC coated curcumin pellets are reported for delivery of curcumin to colon for the treatment of inflammatory disease [14].

Curcumin as microemulsion: Curcumin has a relatively low oral bioavailability and is not very water soluble. Curcumin's oral absorption has been reported to be enhanced by a self-micro-emulsifying drug delivery system. Ethyl oleate, cosurfactant, and surfactant

were used to create the microemulsion. When compared to the simple emulsion, the self micro-emulsifying drug delivery system showed an increase in the oral absorption of curcumin [15].

Curcumin as micelles: Using a modified dialysis and nano-precipitation approach, curcumin was encapsulated within a methoxy poly (ethylene glycol) (MePEG)/poly-ε-caprolactone (PCL) diblock copolymeric micelle to address its poor solubility, stability, and bioavailability issues. The t1/2 and AUC of curcumin *in vivo* were enhanced by encapsulation in MPEG-PCL micelles. In terms of cellular uptake, cell cytotoxicity, and apoptosis of pancreatic cell lines MIA PaCa-2 and PANC-1, the anticancer efficacy of the curcumin-encapsulated micelle formulation was compared with unmodified curcumin. It was discovered that curcumin-encapsulated micelles increased the bioavailability of curcumin due to enhanced uptake (2.95 times more than with unmodified) and comparative cytotoxic activity (by inducing apoptosis) when compared to unmodified curcumin at equimolar concentrations [16,17].

Curcumin as nanospheres: Curcumin is one of the powerful anticancer drugs that has been shown to be highly effective against a wide variety of cancer cell types. However, curcumin's limited water solubility results in a low systemic bioavailability when taken orally, which is its main drawback. Curcumin was encapsulated utilizing the solid/oil/water emulsion solvent evaporation process in poly (lactic-coglycolic acid) (PLGA) nanospheres to improve its bioavailability. Studies on cell viability showed that, in comparison to free curcumin, the curcumin-loaded nanospheres were able to have a more noticeable impact on the cancer cells [18].

Curcumin as liposomal delivery vehicles: Liposomal nanoparticle delivery of curcumin, a broad-spectrum anticancer medication, has been investigated for the treatment of osteosarcoma (OS). Since curcumin is insoluble in water, cyclodextrin encapsulation and subsequent liposome encapsulation provide an efficient delivery method. The resultant 2-hydroxypropyl-γ-cyclodextrin/curcumin-liposome complex exhibits encouraging anticancer potential against the MCF-7 breast cancer cell line and the KHOS OS cell line both *in vitro* and *in vivo*. γ-cyclodextrin liposomes loaded with curcumin show great promise as delivery systems for the treatment of malignancies of various tissue origins [19].

Curcumin as phytosome: 25 diabetic patients were given two tablets (1g Meriva/day) of curcumin phytosome (Meriva) for four weeks in order to assess the potential use of curcumin for the treatment of diabetic microangiopathy. There were no dropouts during the follow-up period; every participant in the treatment and control groups finished. At four weeks, microcirculatory and clinical assessments of the therapy group showed a decrease in skin flux ($P < 0.05$) at the foot's surface, which is a sign of improved microangiopathy. Typically, patients with diabetic microangiopathy had higher skin flux. Additionally, there was a noteworthy improvement in the venoarteriolar response ($P < 0.05$) and a considerable decrease in the edema score ($P < 0.05$) [20].

Curcumin as transferosome: Curcumin is a common ingredient in strong herbal anti-inflammatory medications. Curcumin's primary issue when taken orally is its poor bioavailability because of decreased GI absorption, even though its activity in treating inflammatory pain is comparable to that of NSAIDs. Using surfactants like Tween 80 and Span 80 in different concentrations, the curcumin transfersomes were created using a modified hand shaking technique. The formation of transfersomes from PC:Span 80 in the ratio 85:15 (in mmol) is a promising method to increase curcumin's permeability over time [21].

Curcumin as nanosuspension: Zhang., *et al.* investigated curcumin albumin nanosuspensions and their releasing properties. Solvent evaporation was used to create curcumin albumin nanosuspensions. The effectiveness of encapsulation was 42.39 +/- 0.91 percent. The 72-hour accumulative release percentage was 96%, according to an *in vitro* release study. The process for creating curcumin albumin nanosuspensions is straightforward. For the delivery of curcumin via nanoparticles, it could be a novel vehicle [22].

Although curcumin liposome formulations are known to increase bioavailability and efficacy while lowering toxicity, the liposomes do not exhibit tissue selectivity. The reticuloendothelial system in the liver and spleen quickly absorbs liposomes after they reach the

body, resulting in a brief circulation period. To improve clinical results, it is therefore crucial to develop efficient liposome modifications, such as polymeric conjugation on the liposome surface. Moreover, despite their simplicity and effectiveness, microemulsions contain several surfactants, which inevitably results in toxicity. Therefore, while creating microemulsions, the selection of surfactants is crucial. Furthermore, the majority of the suggested formulations were made from synthetic polymers; while long-term use of these excipients may result in short-term increases in solubility and bioavailability, there may be risks.

Zedoary turmeric oil as nanocapsule: *Curcuma phaeocaulis* Valeton, *Curcuma kwangsiensis*, and *Curcuma wenyujin* are the sources of zedoary turmeric oil, which has antiviral, anticancer, and antithrombotic properties. The primary biologically active ingredients in zedoary turmeric oil are identified as elemene, curcumol, curdione, germacrone, and pinene. Zedoary turmeric oil nanocapsules have demonstrated enhanced hepatoprotective and anticancer properties of the oil. Furthermore, alginate nanocapsules exhibit strong physical stability when stored for an extended period of time at 4°C, and information on oil loss at critical stages of the process could help refine the method to generate a higher loading capacity [23].

Zedoary turmeric oil as microspheres: The sustained-release microspheres with self-emulsifying capability containing zedoary turmeric oil were prepared by the quasi-emulsion-solvent-diffusion method. The bioavailability of the microspheres was compared with conventional zedoary turmeric oil self-emulsifying formulations for oral administration using 12 healthy rabbits. The plasma concentration-time profiles with improved sustained-release characteristics were achieved after oral administration of the microspheres with a bioavailability of 135.6% with respect to the conventional self-emulsifying formulation; the sustained-release microspheres with self-emulsifying capability containing zedoary turmeric oil have an improved oral bioavailability. Our study offers an alternative method for designing sustained-release preparations of oily drugs [24].

Turmeric oil as a nanocapsule: Turmeric oil's antibacterial, antifungal, antioxidant, and insect-repellent qualities make it a popular choice for pharmaceutical and cosmetic uses. Turmeric oil is volatile, insoluble in water, and unstable in some conditions, which makes it challenging to produce new products and ensure their stability. Chitosan-alginate nanocapsules were created by encapsulating turmeric oil in carriers such as chitosan and alginate in order to address these issues [25].

Conclusion and Future Perspective

There is significant research ongoing in the field of new drug delivery and targeting for plant actives and extracts. Yet research in this field is only at the exploratory phase. Most issues in the research, manufacturing and application must be addressed. Along with this, there is a need to pay greater attention towards the study of the carrier materials so that there can be the creation of more appropriate carriers which can minimize the toxicity of drugs, increase their activity and also the quality of the agents as a whole. Herbal drugs possess a very high therapeutic potential which should be utilized through some value-added drug delivery systems. Lipid solubility and molecular weight are the key inhibitory parameters for drug molecules to cross the biological membrane to get absorbed systemically after oral or topical administration. Standardized plant extracts or predominantly polar phytoconstituents such as flavonoids, terpenoids, tannins, xanthones when given using new drug delivery system have far improved absorption pattern which allows them to cross the biological membrane leading to increased bioavalability. Thus, greater quantity of active ingredient becomes available at the site of action (liver, brain, heart, kidney etc.) at similar or lesser dose compared to the traditional plant extract or phytomolecule. Thus, the therapeutic effect becomes potentiated, more observable and for longer duration. Further research in these directions and goals is underway.

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