A Review on Nano Drug Delivery Systems of Herbal Medicine

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Abstract: Herbal medicines are widely used around the world since history. The advancement of phytochemical and phytopharmacological sciences has enabled elucidation of many medicative plant products' composition and biological activities. The effectiveness of the many species of medicative plants depends on the provision of active compounds. Most of the biologically active constituents of extracts, like flavonoids, tannins, and terpenoids, are extremely soluble in water; however, have low absorption, as a result of their unable to cross the lipoid membranes of the cells, have enormous molecular size, or poorly absorbed, leading to loss of bioavailability and effectiveness. Some extracts are not used clinically due to these obstacles. It has been wide planned to mix seasoner medication with herbal, resulting from nanostructured systems that may be ready to enhance plant extracts' action, reduce the specified dose and facet effects, and raise activity. Nanosystems will deliver the active constituent at a spare concentration throughout the whole treatment amount, directional it to the required web site of action. Typical treatments do not meet these necessities. This study aimed to review nanotechnology-based drug delivery systems and herbal medicines.

Keywords: Natural products, herbal medicines, nanotechnology, drug delivery systems, biological activity

1. Introduction

Knowledge and use of plants as seasoner medicines have occurred in numerous populations throughout human evolution, starting once the man learned to pick out plants for food and alleviate ailments and diseases.[1] However, throughout the last half of the 20th century, seasoner medicines were bit by bit replaced by allopathic medicines, particularly within the Western world. Allopathic treatments square measure presently a lot of wide used than ancient medicines, particularly in developed countries. However, most developing countries still use these natural medicines, presumably that getting a synthetic drug is pricey[2]. in line with the globe Health Organization, eightieth of individuals in developing countries rely upon ancient healthful practices to fulfill and/or supplement their basic health desires[3].

Despite marketing and encouragement from the pharmaceutical trade throughout allopathic medicines, an oversized phase of the population in several countries continues to utilize complementary practices for their health care. Several of those practices are derived from healthy plants. However, thanks to economic, political, and social changes worldwide, the therapeutic use of these natural resources, which are mainly utilized by people who cannot afford different treatments, has dramatically diminished[1,4].

Elucidating the chemical composition of medicative plants and their well-liked uses has become a research focus for all scientific communities. This analysis might result in more and more innovative products with fewer side effects than existing medication[5]. Moreover, the immense diversity of natural product structures and physicochemical and biological properties has impressed researchers. However, except after they are used for native health care needs, the percentage share of plants is tested for medicinal potential. Therefore, there is an absence of data to describe any true potential[6–8].

Several teams of researchers have studied the biological activity of healthy plants from everywhere in the world. These studies are based on the favored uses of various species[9], and on widespread data and scientific studies describing medical plant use, with attention on however these plants may benefit the pharmaceutical industry. Approximately five-hundredths of the medication approved throughout 1981–2006 was directly or indirectly derived from natural products[1]. The chemical complexness of extracts is an essential thought for the success of a formulation. As a result of the formulation should additionally release the active ingredient. Consequently, vehicles should concurrently improve the drug's solubility, minimize the degradation method, reduce any toxicity, and mask any dangerous style while controlling the active absorption and biological response[10-11]. Phytochemical and phytopharmacological sciences have already established the composition and biological activities of many healthful plant products. Most of the biologically active constituents of extracts, such as flavonoids, tannins, and terpenoids, are incredibly soluble. However, they demonstrate a low absorption because they cannot cross lipid membranes, have large molecular sizes, and demonstrate low absorption, resulting in loss of bioavailability and effectiveness. Some studies have shown that herbal medicines have smart activity in assays in vitro, which are not consistent in experiments in vivo. What is more, some essential substances are rarely used, as a result of they are incompatible with alternative components within the formulation or have undesirable properties[12-13]. Several nanotechnological methods, like polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursors systems for liquid crystals (PSLCs), liposomes, and microemulsions, have attempted to interrupt this barrier; they permit substances with totally different properties to be employed in a similar formulation, and should even modification a substance’s properties and behaviour in an exceedingly biological environment. These technological discoveries have drug delivery. The new drug delivery systems have the power to extend the effectiveness of active elements and present alternative components that were discarded as a result of not helpful in the formulation. Moreover, the power to enhance new substances, like increasing property and effectuality, protective against thermal- or photo-degradation, reducing aspect effects, and dominating active constituents' discharge before they are introduced to the market used therapeutically, makes this approach even a lot of engaging[13–16]. Along with advances in recent decades associated with drug development, there is an associate imperative would like for developments in nanoscience and engineering science that relate to the utilization of nanoscale materials, which, to date, have solely been the attention of the cosmetics business. Scientific advances will revolutionize and enhance solutions to problematic aspects of formulation preparation[17]. Additionally to improving the solubility and stability of active constituents, nanostructures may extend a formulation’s action, and with success, combine active sub-stances with different degrees of hydrophilicity/lipophilicity. This technology can also be used to target the distribution of a substance toward

specific tissues or organs[18–21]. Pharmaceutical industries became more and more fascinated by nanotechnological advances. These developments offer benefits, like changed unleash systems, and therefore the potential to develop new formulations that were antecedently unacceptable (due to several aspects related to the active constituents)[22].

Although nanotechnology contributions are advantageous for many therapeutic areas, it is essential to spotlight some disadvantages. Clinical researchers have mentioned some negative factors, like a high price, difficulty of scaling up processes, and the easy inhalability of nanoparticles, which may lead to dangerous respiratory organ diseases, and infrequently cause alternative diseases that will cause changes physiological condition, or maybe death[23-24].

The strategy of applying nanotechnology to plant extracts has been wide cited within the literature. As a result, nanostructured systems may enhance plant extracts' action, promote active constituents' sustained-release, reduce the required dose, decrease side effects, and improve activity[25-26]. Kesarwani and Gupta revealed a review that mentioned many studies that used nanostructured systems to optimize plant extracts' properties[10]. Bhattacharya and Ghosh used lipid-based systems incorporated tea leaf and ginseng (*Panax ginseng CA Meyer*) (Araliaceae) extracts in numerous formulations to extend the absorption of the active components[27]. Su et al. developed nanoparticles exploitation radix herbaceous plant *Miltiorrhiza Bunge* (Lamiaceae) and detected a significant improvement in the extract's bioavailability[28]. Sinico et al. developed liposomes with *Artemisia arborescens L*. (Asteraceae) and noted that these systems helped the active parts from this plant penetrate the cytoplasmic viral barrier[29]. Rajendran et al. obtained nanoparticles employing a methanolic extract of *Ocimum sanctum L*. (Lamiaceae), and according to that, the encapsulated extract demonstrated higher antimicrobial activity than in free-form preparation, once tested against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*[26].

The effectiveness of medicative plant species, or herbal medication, depends on the supply of active compounds. Therefore, new carriers should deliver the active constituent at a comfortable concentration throughout the entire treatment amount and direct it toward the required target because conventional treatments do not entirely obtain these requirements. Partial or total loss of a particular activity can be observed when constituents of an extract are isolated or purified. Moreover, some components are sensitive to the abdomen's acidic pH scale, promoting their destruction and losing the required result after consumption. Some extracts are not used clinically as a result of these obstacles[12]. Using different drug delivery systems based on nanotechnologies, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursor systems for liquid crystals (PSLCs), liposomes, and microemulsions, is an exciting approach to enhance a formulation’s most fascinating properties[10,30]. Furthermore, nanoscale particles might represent a future wherever activity is ensured, and the issues related to using medicinal plants are overcome[12].

2. Nano Drug Delivery Systems of Herbal Medicine

2.1 Polymeric nanoparticles

Currently, nanotechnological processes involving medicinal plants have gained researchers' primary focus, who have developed many innovative delivery systems, together with including nanoparticles. These materials, made from biodegradable and biocompatible polymers, represent a choice for controlled drug delivery. polymeric nanoparticles are a promising formulation used for drug delivery systems; thus, they will be targeted.[31,32] Polymeric nanoparticles are mixture systems that work as vectors to manage drug release, targeting specific locations. Compared to conventional formulations, polymeric nanoparticles will increase constituents' solubility, reduce the therapeutic dose, and improve the active components' absorption. Furthermore, nanoparticles are advantageous once used in blood because they are stable, non-toxic, non-thrombogenic, non-immunogenic, non-inflammatory, do not activate neutrophils, and avoid the reticuloendothelial system. Sometimes, polymeric nanoparticles are used to reach specific tissues or work as a cell surface[12,33–35]. Polymeric nanoparticles can be synthesized using numerous strategies, consistent with their meant application and payload. These particles are made of natural, or artificial, biodegradable polymers. Natural materials are most well-liked because they typically have additional benefits, such as the power to deliver more than one active constituent using a constant carrier, increase residence time within the body, offer a sustained-release system, and reduce side effects[35].

Nanoscale systems are also called sub-micrometers; as a result of the particle, diameters are one μm. they provide varied therapeutic benefits in many areas and routes of administration, site-specificity, and increased therapeutic impact, which makes them desirable to researchers. Oral administration of conventional bound formulations could cause aspect effects, and the degradation of active constituents is promoted by the abdomen's acidic pH. Polymeric nanoparticles can reduce these issues. In ophthalmic administration, nanoparticles control active constituents' discharge, increasing ocular bioavailability and reducing side effects[34]. Polymeric nanoparticles will vary from 10–1,000 nm in diameter while still protective medication with efficiency. They will appear as nanocapsules (NCs) and nanospheres (NSs); these structures differ in their composition and structural organization. Nanocapsules contain an oily core encircled by a polymeric membrane; the active constituent can be adsorbable to the polymeric membrane and dissolved in the oily core. Nanospheres are made only from a polymeric structure, where the active constituent is retained or absorbable. though there is an increasing search for new forms of polymers, many of them have already been used extensively for compound nanoparticles and Poly Lactic Acid (PLA) and copolymers with glycollic acid (PLGA)[12,33,34].

The most necessary strategies used to produce polymeric nanoparticles are broadly classified as follows: the in place polymerization methodology, with distributed monomers (alkyl cyanoacrylate), or a method of precipitation of preformed polymers, like poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), methacrylic acid copolymers, and acrylic or methacrylic esters. Regardless of the chosen methodology, the product is obtained as liquid mixture suspensions. However, some issues will

obstruct industrial relevance; for example, nanoparticle precipitation and physicochemical stability issues will be reduced through drying processes, like sublimation (freeze-drying), that permits dehydration whereas preventing particle aggregation[34]. Some characteristics of colloidal nanoparticles cause technical difficulties throughout physicochemical characterization; this includes morphological analysis, particle size, mass distribution, zeta potential, pH determination, drug concentration within the nanostructures, drug release kinetics, and stability over an extended period[35]. Das et al. tested the basis extract of *Phytolacca decandra* (PD) (*Phytolaccaceae)* in free form (PD) and PLGA-encapsulated forms (NPD) in mice dosed with benzo[a]Pyrene (BaP) (25 mg/kg) and sodium arsenate (SA) (10 mg/kg) in vivo, still as on A549 carcinoma cells in vitro. The nanoencapsulation of PD increased the drug's bioavailability and generated higher chemopreventive action against carcinoma in vivo and on A549 cells *in vitro* than free form PD[36].

Rajendran et al. evaluated the antimicrobial activity of ethanolic, methanolic, oil ether, and aqueous extracts of leaves of the genus *Ocimum sanctum* (Lamiaceae) (OS). They used an agar diffusion and microdilution technique to determine the minimum inhibitory concentration (MIC) against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *Aspergillus niger*, and genus *Penicillium spp.*; the best result was a gift to the methanolic extract, following by alcohol, petroleum ether, and aqueous extracts. After this screening, methanolic extracts demonstrated the most effective antimicrobial activity and were loaded into sodium alginate chitosan nanoparticles (OSN) through a cation-induced, controlled gelation technique. The particles were deposited on cotton fabric using a pad dry cure technique[26]. Compared to OS and nanoparticles only, OSN demonstrated higher and longer-lasting antimicrobial activity than the unloaded formulation, manufacturing cotton materials with excellent antimicrobial activity.[26] One of the most essential difficulties in therapy is the inability to deliver the active constituent, inapplicable doses, to specific sites affected by the disorder. Many of the antineoplastic therapeutics found in polymeric nanoparticle formulations are evaluated in diagnosing and clinical studies. Polymeric nanoparticles address problems found in therapy by reducing toxicity, thanks to the protecting barrier that forestalls interaction between the active constituents and healthy cells[37]. Curcumin maybe a yellow polyphenol extracted from rhizomes of *Curcuma longa* (Zingiberaceae); it has demonstrated potent antineoplastic properties in many studies involving human neoplasm cells and animal models of carcinogenesis. This active constituent is very potent and nontoxic. The bioactive agent, found in turmeric, is employed as another drug for treating many disorders. However, its clinical applications are limited because of its low aqueous solubility and bioavailability.

Various polymeric nanoparticles have solved some formulation problems, like some constituents' hydrophobic properties, like curcumin. Bisht et al. synthesized a mixture containing curcumin-loaded compound nanoparticles, using aggregated structures containing randomly crosslinked copolymers of N-isopropyl acrylamide, N-vinyl-2-pyrrolidone, and poly (ethylene glycol) mono acrylate. Physicochemical characterization, via dynamic light-weight scattering and transmission electron microscopy (TEM) measurements, confirmed that these polymeric nanoparticles had a favorable size distribution of fifty nm. The curcumin-loaded polymeric nanoparticles were referred to as "nano curcumin" (as opposition "free curcumin") and were distributed in liquid media. Nanocurcumin revealed therapeutic efficacy in vitro

against varied human exocrine gland tumor cells, confirmed by cell viability and clonogenic assays. Nanocurcumin's mechanism of action against carcinoma cells was as follows: free curcumin was discharged, induce apoptosis, block the activation of nuclear factor kappa B (NFkB), and control levels of proinflammatory cytokines, like interleukin 6, interleukin 8, and the tumor necrosis factor. Nanocurcumin provided a chance to increase the clinical use of curcumin via aqueous dispersion[38]. In studies by Mukerjee and Vishwanatha, curcumin was encapsulated in PLGA nanospheres, employing a reliable/oil/water emulsion solvent evaporation methodology, and was evaluated for activity against adenocarcinoma. The encapsulation potency was 90.88%±0.14%, and also the average particle size was forty-five nm. The results of the MTT cell viability assay for the curcumin-loaded PLGA nanoparticles on adenocarcinoma cell lines, LNCaP, PC3, and DU145, and a nontumorigenic cell line, (PWR1E) showed IC50 reduced to 20–22.5 μM, whereas the range without charge curcumin was 32–34 μM – a thirty-fifth reduction was ascertained when curcumin was encapsulated[39].

Bhawana Basniwal et al. developed a new methodology to arrange curcumin-loaded polymeric nanoparticles, which improved curcumin's water solubility[40]. The study also assessed whether or not this formulation would enhance curcumin's antimicrobial activity. Curcumin-loaded polymeric nanoparticles (nano curcumin) were prepared using a method based on the wet-milling technique; nanoparticles were obtained with a narrow size distribution of 2–40 nm. Nanocurcumin's chemical structure was identical to the original molecule (curcumin), proving that no chemical change had occurred throughout encapsulation and showing that the formulation may well be simply distributed in the water while not surfactant. Antimicrobial activity was evaluated employing a microplate dilution technique against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, genus *Penicillium notatum*, and *A. niger*. The water solubility and small size of nano curcumin nanoparticles increased antimicrobial activity relative to free curcumin. The bactericide activity of nano curcumin was more pronounced than its antifungal activity. Among bacteria, gram-positive strains were more sensitive. TEM analysis disclosed that when the nanoparticles were introduced into bacteria, they thoroughly destroyed the cell membrane, leading to bacterial cell death[40].

Honokiol (HN) could be a constituent of the Chinese medicinal plant *Magnolia officinalis* (Magnoliaceae): 3′,5-di(2-propenyl)-1,1′-biphenyl-2,4′-diol. It has many pharmacologic effects, together with anti-inflammatory, antithrombotic, antirheumatic, antioxidant, anxiolytic, central systemic nervous system depressant, and muscle relaxant activities. Additionally, it is potent anticancer activity. Again, this compound's hydrophobic properties represent an obstacle due to high hydrophobicity preventing vascular administration. However, when this active constituent was loaded in polymeric nanoparticles, vascular administration was possible, as shown by Zheng et al. They developed a new formulation containing HN-loaded polymeric nanoparticles for vascular administration, getting higher results relative to free HN[41]. Khuda-Bukhsh et al. developed polymeric nanocapsules containing coumarin (7-hydroxy-6-methoxy) (HMC), that was isolated from an ethanolic extract of *Carolina jasmine J. St.-Hil* (Gelsemiaceae). According to the in vitro evaluations, HMC has a pronounced anti-tumoral activity. However, any studies were discontinued because of their property. A new formulation containing HMC-loaded polymeric nanoparticles demonstrated far better bioavailability than the free active constituent[31]. *Harungana*

madagascariensis Lam. Ex Poir (Hypericaceae) is widely renowned for its antibacterial, antifungal, and antiviral properties.

Moulari et al. evaluated and compared the in vitro and ex vivo antibacterial activity of ethanolic extract of *H. madagascariensis* leaf (HLE), incorporated into poly (D, L-lactide-co-glycolide) (PLG) nanoparticles (PLG-NPs) (HLE-PLG-NP). Two concentrations of HLE (500 µg/mL and 1,000 µg/mL) were evaluated for the in vivo assay; one concentration (500 µg/mL) was tested ex vivo, against two gram-positive microorganism (*S. epidermidis and genus Micrococcus luteus)* and one gram-negative microorganism strain (Moraxella sp.). Ex vivo antibacterial activity was evaluated for *S. epidermidis* CIP 55109 using an artificial contamination methodology. The organism was inoculated for twelve hours on human skin fragment surfaces treated with HLE-PLG-NP, empty PLG-NPs, or HLE answer. In vitro studies revealed that each formulation entirely reduced the microorganism growth of all strains tested at 1,000 µg/mL concentrations. However, the five hundred µg/mL HLE solution did not have a significant medication activity against *S. epidermidis, M. luteus, or Moraxella sp.*, relative to HLE- PLG-NP. During ex vivo evaluation, four hours after artificial contamination, HLE-PLG-NP (500 µg/mL) showed higher antibacterial activity than HLE answer. A thin-layer chromatographic analysis revealed that, of the seven components found within the HLE solution recording, only two were found within the HLE-loaded nanoparticles, together with the flavonoid fraction answerable for the antibacterial properties. Once again, results improved once extracts were loaded into polymeric nanoparticles[42].

In 2006, Moulari et al. investigated the ester extract is in vitro antibacterial activity from *H. madagascariensis* leaves against the prominent oral microorganism strains chargeable for dental caries and periodontitis. To boost antibacterial activity, HLE was loaded among PLG-NPs. Antibacterial activity was assessed via a dilution technique, using microplates, associated polymeric nanoparticles were developed using a surface polymer deposition solvent diffusion methodology. Free HLE displayed good results against most bacterial strains tested, with a five hundred µg/mL MIC. The exception was *lactobacillus casei*. However, HLE-PLG-NP was more practical (MIC: 187.5 µg/mL)[43]. Yen et al. used a nanosuspension methodology to organize *Cuscuta chinensis Lam.* (Convolvulaceae) nanoparticles (CN-CE) and compared the hepatoprotective and antioxidant effects of ethanolic extract from seeds of *Cuscuta Chinensis* (CE) and CN-CE on acute liver injury in rats, induced by acetaminophen and oxidative stress. The degree of aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline enzyme (ALP) were determined to evaluate hepatoprotective effects and examine histopathological sections of the liver, all of that is related to hepatic integrity. The results of the substances on the antioxidant enzymes and lipid peroxidation of the liver were additionally studied by assessing changes in superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and malondialdehyde (MDA) levels, the levels of AST, ALT, and ALP were reduced by similar amounts, with oral doses of ALP at a hundred twenty-five mg/kg and 250 mg/kg, and of CN-CE at twenty-five mg/kg fifty mg/kg, because the hepatoprotective effect causes this reduction. The antioxidant activity of SOD, CAT, and GPx was enhanced with free CE and CN-CE, while that of MDA was reduced. The effects of fifty mg/kg CN-CE were more substantial than a hundred twenty-five mg/kg free CE for each effect; a lower CN-CE dose, relative to free CE, will exert identical effects[44].

Quercetin (QU) is a natural flavonoid with pharmacological properties, like anti-inflammatory, antitumor, antiviral, restrictive cataracts in diabetics, antihistamine (anti-allergic), cardiovascular, antioxidant, and hepatoprotective effects. QU is present in fruits, vegetables, herbs, and related products, e.g., Apples, Onions, Ginkgo biloba (Ginkgoaceae), and wine. To evaluate the antioxidant effects of pure Quercetin and QU incorporated in nanoparticles, WU et al. developed a nanoprecipitation technique using Eudragit® E (Evonik Industries, Essen, Germany) (EE) and polyvinyl alcohol (PVA), alongside the flavonoid quercetin (QUEN). The system was prepared using a 1:10:10 weight ratio of QU to EE to PVA because the yield was better, and the encapsulation efficiency was larger than the ninety-nine. Relative to di(phenyl)-(2,4,6-trinitrophenol) iminoa zanium (DPPH) scavenging, anti-superoxide formation, superoxide anion scavenging, and anti-lipid peroxidation activities, QUEN was more effective than QU[45]. *Camptothecin* (CPT) is a natural plant alkaloid extracted from *Camptotheca acuminata* Decne. (Cornaceae), Furthermore, it has been incontestible to be a potent malignant neoplasm drug, targeting intracellular topoisomerase. However, because of its low water solubility and unstable lactone ring, clinical use is not viable. Min et al. developed nanoparticles based on hydrophobically changed glycol chitosan (HGC) as a delivery system. A dialysis technique was wont to prepare Camptothecin-Encapsulated nanoparticles (CPT-HGC); the loading potency exceeded eightieth. The hydrophobic core of the HGC nanoparticle protected the crucial lactone ring from hydrolysis under physiological conditions. To verify the nanoparticles' antitumoral activity, a subcutaneous tumor was established by inoculating MDA-MB-231 human carcinoma cells in the back of a mouse. Once intravenous (iv) injection of CPT-HGC, at ten mg/kg and thirty mg/kg, tumor growth was significantly inhibited, relative to free CPT (30 mg/kg). The vigorous antitumoral activity of CPT-HGC was most likely related to prolonged blood circulation and high accumulation in tumors, as confirmed by close to infrared study[46]. Yen et al. developed a naringenin- (NAR) loaded nanoparticles system (NARN), using a nanoprecipitation technique, to enhance limited bioavailability and increase hepatoprotective effects vivo after oral administration of NAR. The nanoparticle delivery system was successfully developed exploitation Eudragit (E) and PVA as carriers. Tetrachloromethane was wont to induce hepatotoxicity in male Wistar anomaly rats of weight 180–220 g, haphazardly divided into four groups of 5 rats each. For the oral administration of medication, one group of rats was treated with a NAR suspension in distilled water with Tween® twenty (1% ratio, by volume [v/v]), at a hundred mg/kg per day; another group was treated with NARN at a hundred mg/kg per day. Each treatment was administered, by gavage, for three consecutive days. Examining hepatoprotective effects, NARN protected more of the liver; the NAR group displayed a considerable reduction in liver performance index and lipid peroxidation. Additionally, there was a substantial increase in antioxidant levels enzymes. Moreover, NARN significantly reserved the activation of caspase-3, caspase-8, and caspase-9 signaling, whereas NAR solely noticeably inhibited caspase-3 and caspase-9[47].

The ethanolic extract of *Polygala senega* (Polygalaceae) (EEPS) is employed as an expectorant to treat cough, sore throat, bronchitis, and asthma antihyperglycemic agent. *Polygala senega* has low water solubility, preventing aqueous dispersion and limiting its potential. *Polygala senega* its diminished bioavailability[48]. EEPS was encapsulated by using biodegradable PLGA. Subsequently, the anticancer

effects of EEPS, and therefore the nano encapsulated form (NEEPS), were evaluated against carcinoma cell line A549. EEPS and NEEPS induced cell death of A549 cells, which was associated with decreased expression of surviving and proliferating cell nuclear antigen (PCNA) mRNA, and increased expression of caspase-3 and p53 mRNAs in A549 cells. The anticancer potential of the NEEPS formulation surpassed that of EEPS alone[49].

2.2 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) are colloidal carrier systems, developed within the early Nineteen Nineties (1990), that mix the benefits of alternative colloidal systems (such as emulsions, liposomes, and polymeric nanoparticles) for drug delivery while avoiding, or minimizing, some of their drawbacks[50]. SLNs have higher physicochemical stability and provide higher protection against labile drug degradation; they can also be simply created on a large scale[30,51,52]. SLNs are colloidal particles containing too pure triglycerides, composed mainly of solid lipids at temperature. These structures are produced from solid lipids or mixtures thereof and stable by surfactants[53]. The matrix of the lipid particle is solid; it will protect drug molecules against chemical degradation. However, crystallization happens when the system is created, resulting in low encapsulation efficiency and drug release[30]. Adding a liquid lipid (oil) to an oil/water emulsion containing a solid lipid, or a mixture of solid lipids, promotes the formation of SLNs[51]. thanks to their small size (50–1,000 nm) and biocompatibility, SLNs may be utilized in the pharmaceutical field for varied routes of administration, such as oral, parenteral, and transdermal[52]. Nanostructured lipid carriers (NLCs) improve encapsulation efficiency and minimize active particles' expulsion throughout encapsulation[54]. NLCs are second-generation systems and are attracting attention as various vehicles for colloidal drugs. These systems contain a mixture of lipid and solid phases that forms a disorganized liquid lipid matrix that accommodates active substances[30].

Some samples of lipids utilized in the concrete section are saturated fatty acid, glyceryl dilaurate, hydrine, glyceryl monostearate, and cetyl alcohol. Samples of the liquid section include monounsaturated fatty acid, glyceryl mono-di-caprylate, and caprylic/capric acid. In most cases, around five-hitter of the drug (by weight) is incorporated within the initial precursor mixture for NLCs, leading to drug loading potency {of around|of roughly} 3-dimensional to four-dimensional (whereas typical encapsulation potency is approximately 70%)[55]. Many routes are also used to administer these formulations: oral, pulmonary, intravenous, and dermal. The latter is advantageous; as a result of the films forms occlusions, there is a controlled release profile, and therefore the formulation is perishable and comparatively nontoxic. Moreover, the two particles' small size ensures contact with the corneum, facilitating increased drug penetration into the skin[30].

There are many ways to manufacture SLNs and NLCs, including aggressive homogenization, emulsification-sonication, microemulsion, and solvent emulsification-evaporation techniques. For hot, high-pressure homogenization (HPH), the lipid is melted, and the drug is dissolved homogeneously within the molten lipid. A hot solution of surfactant is then dissolved into the liquified drug-lipid mixture and

homogeneously distributed (pre-emulsion) employing a high shear combination device. Afterward, the new pre-emulsion is subjected to high-pressure homogenization; this method is repeated till the required average particle size is obtained. Then, the nanoemulsion is cooled to temperature. Throughout cooling, lipid droplets within the nanoemulsion recrystallize, forming lipid nanoparticles within the concrete matrix. The cold HPH is similar to hot HPH: the lipid is melted, and therefore the drug is homogeneously dissolved within the melted lipid. Then, the drug-lipid melt is quickly cooled, exploitation liquid nitrogen or dry ice, and subsequently processed to create microparticles.

The microparticles are suspended in a cold aqueous surfactant solution and homogenized at low temperatures to create lipid nanoparticles. This technique is employed for hydrophilic or thermolabile drugs to prevent drug degradation. The emulsification–sonification methodology is similar to the primary portion of HPH. After the drug is dissolved in a melted solid lipid, a hot aqueous surfactant solution is extra to soften and homogeneously distributed using a high shear combination device. In the course, the hot oil-in-water emulsion is ultrasonicated using a probe sonicator till a nanoemulsion of the desired size forms. Finally, lipid nanoparticles are obtained by permitting the hot nanoemulsion to cool down to room temperature. The microemulsion methodology utilizes a drug dissolved during a liquified solid lipid. The aqueous surfactant/cosurfactant solution is added to the lipid with gentle agitation to get a clear microemulsion. Afterward, the microemulsion is distributed in cold water (2°C–10°C) with gentle agitation, wherever it breaks into ultrafine nanoemulsion droplets, that instantly crystallize to form SLNs. Within the solvent emulsification-evaporation methodology, the lipid is dissolved during a water-immiscible organic solvent (e.g., cyclohexane and chloroform) and emulsified, in an aqueous part containing surfactants, with continuous stirring. The organic solvent evaporates throughout emulsification, precipitating the lipids.[56]

Quercetin could be a natural flavonoid that becomes a lot useful when incorporated into lipid carriers. Li et al. incorporated QU, which is poorly soluble in aqueous media, in SLNs (QU-SLN) using the emulsification-solidification methodology at low temperatures. The specified amounts of QU, glyceryl monostearate, and soy lecithin were mixed with the solvent (chloroform and acetone in 1:1 ratio v/v). The SLNs were spherical, with an average size of one hundred fifty-five.3±22.1 nm, falling into the nanoscale range (20–500 nm). QU-SLN exhibited a controlled release in vitro. Within the in vivo experiments, the bioavailability of QU-SLN was more than five times greater. It demonstrated increased absorption within the intestine (rather than the stomach), compared to free QU[57]. In another study, Guo et al. incorporated QU into NLCs (QU-NLCs) to evaluate the formulation's potential as a topical delivery system. The formulation contained QU, glyceryl monostearate, octadecanoic acid, and soy lecithin and was using mistreatment the emulsion evaporation-solidification methodology at low temperatures. The nanoparticles were spherically shaped, had an average particle size of 215.2 nm, and an average entrapment potency of 89.95%±0.16%. Therefore, the incorporation was efficient; it might promote QU, increase the number of QU retained in stratum and derma, and enhance the flavonoid's antioxidant and anti-inflammatory effects. Studies of the effects of QU-NLCs on the skin's surface confirmed that they might weaken the stratum corneum's barrier operation and facilitate

drug permeation through the skin. In vivo anti-inflammatory assays indicated that QU-NLCs stopped ear dropsy, elicited in rats by xylene.

In vitro studies searching into superoxide anion, radical scavenging activity confirmed that QU's complete functional architecture was maintained after nanoencapsulation. This study provided extra proof that NLCs have a targeting capability, a prolonged-release, and excellent dermal delivery potential[58]. Bose and Michniak-Kohn evaluated whether or not nanoscale lipids might deliver QU topically. The systems were prepared by replacement of some of the solid lipid (glyceryl dibehenate) (Compritol® 888 ATO) within the SLN formulation with a liquid macromolecule (oleic acid) to supply QU-NLCs using the probe ultrasonication methodology. This study evaluated the stability of those nanosystems for fourteen weeks, at 2°C–8°C. The typical size of the NLCs was 282 nm, indicating that the structures had excellent stability. TEM measurements discovered spherical particles. The NLC system showed the most considerable improvement throughout topical delivery of QU, which was expressed mistreatment the number of flavonoids maintained in full-thickness human skin, compared against a control formulation with a similar composition and a particle size within the micrometer range.

This study illustrated that the NLCs area unit viable for improved topical deliveries of QU[59]. A study performed by Kakkar et al. sought to enhance the oral bioavailability of curcumin by incorporating it into SLNs composed of soy lecithin. The small emulsification methodology was used to prepare this formulation. The SLN particles were spherical and medium-sized (134.6±15.4 nm); drug entrapment potency was 92.33%±1.63%. Studies of stability discovered that SLNs loaded with curcumin (C-SLN) showed only a decrease of roughly 9-11 in the potency of incorporation, after twelve months of storage at 5°C±3°C, indicating that the C-SLNs were stable.

Moreover, C-SLN exhibited prolonged drug release in vitro. In vivo pharmacokinetic studies revealed that after orally administered C-SLN (50 mg/kg, 25 mg/kg, 12.5 mg/kg, and 1 mg/kg), a significant improvement in oral bioavailability was achieved, compared to free cu (by [32, 39, 59], and one hundred fifty-five times at fifty mg/kg, 25 mg/kg, 12.5 mg/kg, and 1 mg/kg doses, respectively)[60]. Mei et al. incorporated triptolide (TP) into SLNs (TP-SLN) consisting of glyceryl ester and octadecanoic acid to enhance solubility and absorption into the skin. TP is a pure compound that validated a conventional Chinese medicine isolated from the shrublike vascular plant, Tripterygium wilfordii Hook. F (Celastraceae). Studies have shown that vascular plant extracts are useful for treating certain diseases and inflammatory and reaction diseases, like rheumatoid arthritis. The results revealed that TP-SLN increased the acute anti-inflammatory activity because TP penetrated further into the skin[61]. Martins et al. developed and validated a simple, high-performance liquid, a significant methodology to determine Camptothecin (CP) content in various organs in rats, once administration of CP via SLN. Their formulations utilized cetyl palmitate as the lipid and polysorbate eighty because the surfactant, at a five-hitter ratio by weight (w/w) and 2 (w/w). A Prominence UFLC system (Shimadzu Scientific, Kyoto, Japan), equipped with two pumps (LC-20AD; Shimadzu), an autosampler (SIL-20AC; Shimadzu), and a column oven (CTO-20AC; Shimadzu), was used for every chromatographic analysis. The optimized methodology used a binary gradient mobile phase with one

chronicle (v/v) triethylamine buffer at pH five. The flow rate was one.2 mL/min, and therefore the injection volume was 10 .10. The eluted peaks were monitored at the excitation and emission wavelengths of 360 nm and 440 nm. This methodology was reliable, precise, and accurate for deciding the amount of CP in samples from organs of rats treated with CP in suspension, or CP incorporated in SLNs[62].

Tiya boonchai et al. incorporated curcuminoids into SLNs to characterize factors that may affect the system's processing characteristics and storage stability. The water part consisted of 0.1% (w/w) curcuminoid extract, 5%–15% (w/w) poloxamer 188, 5%–15% (w/w) dioctyl sodium sulfosuccinate, 5%–20% (w/w) ethanol, and deionized water, another to 100 percent (w/w). The oil part contained 5%–12.5% (w/w) octadecanoic acid and four-dimensional (w/w) glyceryl monostearate. Preparation was performed exploitation the microemulsion technique at moderate temperatures. The particles were spherical, of 450 nm average size, and had a 0.4%–70% (w/w) polydispersity index. After being stored within the absence of sunlight for six months, the remaining percentages of curcumin, desmethoxycurcumin, and bisdemethoxycurcumin were 91, 96%, and 88%, respectively. Thus, SLNs improved the stability of curcuminoids within the absence of light[63].

2.3 Liquid crystalline systems

Liquid crystals are a substantial part of condensed structures that rest in an exceedingly|in a very} state intermediate between a crystalline solid and an isotropic liquid; they will be ordered or disordered, as indicated by their easy outflow. States of matter between solids and liquids ar mesophases, which can be cubic or polygonal shape in LCs. LCs are categorized in step with two general provisions: thermotropic liquid crystals (TLCs) and lyotropic liquid crystals (LLCs)[64- 65].

TLCs have temperature-dependent liquid-crystalline phases and a specific temperature at which the liquid crystal becomes an isotropic liquid. Their main constituent is the molecule that forms the mesophase. LLCs possess functional unit micelles that are aggregates composed of amphiphilic molecules. Amphiphiles have a small polar (hydrophilic) large and an outsized (hydrophobic) polar tail. Mesophase formation is dependent on concentration, solvent, and temperature; under certain conditions, micelles will self-organize, generating structures of great complexness[66–68].

Liquid crystalline mesophases are identified using their optical isotropy measurements via polarized light microscopy, microscopy with cryofracture, neutron diffraction, and X-ray scattering at a low angle (SAXS), and neutron scattering at low angles (SANS)[64, 69, 70].

For pharmaceutical applications, LCs have stable and favorable properties for chaperoning biologically active principles that are generally inactive due to unfavorable interactions with lipid membranes at the active site or degradation processes. LCs effectively promote interaction between the drug and a selected target site that was previously not accessible and optimize contact time at the location. LC components promote interactions between the active molecules and cell membranes, facilitating entry into the cell, promoting pharmacologic action[71–73].

The development of a drug delivery system that's reliable, effective, and safe for treatments against diseases could be a goal for various researchers. Furthermore, drug delivery systems should also package drugs that specified their distribution, given a selected administration route, prioritizing the simplest drug-receptor interaction and reducing harmful effects. Therefore, finding a system that meets all of those wants would be extremely valuable. LC-based drug delivery systems are potential candidates[74,75].

Nanotechnology researchers seek to implement new technological approaches to extend the benefits presented by drug delivery systems. Consequently, decreasing harmful effects and/or accumulative effects has met a growing interest in recent years. Additionally, a small increase in the use of natural products has been discovered within nanostructured systems incorporating drugs because medicinal products obtained this way have some advantages over drugs derived from synthetic sources. The natural compounds have fewer side effects (when comparing their toxicological and pharmacological activities) than those obtained from industrial sources[76-77].

One of the foremost helpful forms of plant components for developing LC systems is vegetable oils because they need favorable properties, including low viscosity and low molecular weight. Vegetable oils are used because they manufacture low-occlusion, compared to mineral oils, allowing a more extensive capability for dermal penetration, and allowing increased loading of therapeutic agents[78-79].

Andrade et al. evaluated siloxane as a surface-active agent for forming LC phases in an exceedingly system containing the volatile oil, andiroba (*Carapa guyanensis* Aubl.) (Meliaceae), Cetearyl alcohol, dicetyl phosphate, and a ceteth-10 phosphate-like oily part. To arrange the binary compound part, water and PEG-12 Dimethicone was used. The flavoring compound's victimization did not influence any vital LC parameters, like the formulation's consistency or the good physics stability[80].

Studies have to care about the utilization of products from natural sources throughout the event of nanostructured systems containing LCs. Masson et al. evaluated the influence of peach volatile oil (*Prunus persica)* (Rosaceae) throughout the formation of LCs in oil in water emulsions (o/w) containing a self-emulsifying base. The study incontestable varied advantages of incorporating this volatile oil, together with improved physical stability. The results of those studies are extraordinarily vital as a result adding the volatile oil as a constituent of the oil part did not preclude the formation of LCs[76].

Morais et al. pursued LC systems' development with annatto oil from *Bixa orellana* (Bixaceae) seed, using the hydrophilic/lipophilic balance methodology (HLB). The formulations were composed of annatto oil (oil phase), water (aqueous phase), and oleth-20 (HLB value: 15.3) as the surfactant. The authors observed that was possible to construct LC systems using annatto oil because of the oil phase.[81] Santos et al discovered liquid crystals from marigold oil (*Calendula officinalis*) (Asteraceae), water, and nonionic surfactants. They utilized the HLB methodology to assess the components' influence on the formation of LCs. Different ethoxylated fat alcohols were used, with varying lengths of the carbon chain, and moles of ethylene oxide per molecule of the wetting agent, Ceteth-2 (HLB: 5.3), Ceteth-10 (HLB: 11.0), Steareth-2 (HLB: 4.7),

Steareth-20 (HLB: 15.3), Ceteareth-5 (HLB: 9.2), and Ceteareth-20 (HLB: 15.7). The authors concluded that the proposed formulations were stable because the required HLB value for the formulations was 6.0, making vegetable oil promising for forming LC phases. Below microscopic analysis, no important differences were noted within the structures of the LCs in any of the planned formulations. However, there have been variations in rheological behavior due to variation in the surfactants[82]. Santos and Rocha-Filho developed a formulation for previously-identified lamellar LC phases to ascertain the influence of the length of the carbon chain and, therefore, the number of ethylene oxide units on the stability of a non-ionic emulsion, using marigold oil from seeds and flowers of *C. officinalis*. The system contained marigold oil, water, and several poly-oxy-ethylene alkyl or stearyl ethers (surfactants): poly-oxy-ethylene cetyl ether (Ceteth-2; HLB: 5.1), polyoxyethylene stearyl ether (Steareth-2; HLB: 4.7), poly-oxy-ethylene cetyl ether (Ceteth-10; HLB: 11.0), and poly-oxy-ethylene stearyl ether (Steareth-20; HLB: 15.3). The authors noted that using oil in the formulation is essential for forming the LC phase and identified the carbon chain is responsible for ascertaining stability. The authors complete that the quantity of alkene oxide moieties was not as important as the carbon chain[83]. Following the trend of using natural compounds in systems containing nanostructured LCs, Santos, et al. planned using vegetable oils from plants native to Brazil during evaluations for the formation of lamellar LC crystalline phases. The following vegetable oils were used: andiroba (*Carapa guyanensis*), Aubl (Meliaceae), apricot (*Prunus armeniaca*) (Rosaceae), avocado (*Persea americana* Mill) (Lauraceae), Brazil nut (*Bertholletia excelsa* Bonpl) (Lecythidaceae), Buriti (*Mauritia flexuosa*) (Arecaceae), cupuassu (*Theobroma grandiflorum* Willd. ex Spreng. Schum) (Sterculiaceae), marigold (*C. officinalis*) (Asteraceae), edible fruit (*Passiflora edulis Sims.*) (Passifloraceae), and pequi (*Caryocar brasiliense* Camb.) (Caryocaraceae). Additionally, mineral oil and liquid paraffin were used for comparison. Water was used because of the liquid phase. The surfactants were ethoxylated fatty acids: polyoxyethylene stearyl ether (Steareth-2; HLB: 4.7) and polyoxyethylene cetyl stearyl ether (Ceteareth-5; HLB: 9.2). All the formulations were stable, except for the sample made with mineral oil. The authors demonstrated that mixing {different completely different} surfactants with different HLB masses failed to affect the formation of nanostructured LCs containing a natural oil phase[84]. In recent years, a product from natural sources are utilized in the production of nanostructured systems for drug delivery or within the preparation of high-tech cosmetics. However, there are not any reports of incorporating these compounds in LCs for medicinal purposes, which inspires the scientific community to show to the event of latest LC systems as drug vehicles, to promote vital, indispensable factors, and the bioavailability and therefore the chemical/physical stability of herbal compounds.

2.4 Liposomes and microemulsions

Liposomes are microscopic vesicles composed of one or additional concentric lipid bilayers separated by a liquid medium. Hydrophilic substances are encapsulated within the liquid compartment, whereas adsorbed lipophiles are inserted into the membrane. As an alternative, each kind of substance will be encapsulated. These vesicles consist primarily of phosphor lipids (synthetic or natural), sterols, associated, and antioxidants[85-86]. Liposomes are classified consistent with their size, range of lamellae, and surface charge.

As to surface charge, liposomes are classified as anionic, cationic, or neutral. Regarding the form, size, and range of lamellae, liposomes can be classified as oligo-, uni- or multilamellar, small, large, or giant. Unilamellar liposomes (ULs) contain a single bilayer and are classified in varied size ranges: small unilamellar liposomes (SUVs), with diameters of roughly 25–100 nm; massive unilamellar liposomes, with diameters of a hundred nm to one and big unilamellar liposome, with diameters more significant than one, which reaches sizes in the tens of microns (comparable to being cell size). Multilamellar liposomes (MLVs) include several coaxal lamellae, exhibiting an onion-like structure. ULs are typically found in dilute solutions of surfactants, whereas MLVs are found in more focused systems[85-86]. Andrade et al. developed, characterized, and investigated the antitumoral activity of liposomes containing Cratylia moll is a glycoprotein (Cra) purified from seeds of *Cratylia mollis* mart (Fabaceae) (Camaratu bean) against Sarcoma-180 in Swiss mice. Cra, which has immunostimulatory action, was employed in the supermolecule supplementation of the animals' diet. In vitro, this action assists in producing immunoglobulins in human B lymphocyte cultures and causes antibacterial activity. Systems with charged surfaces were developed using soybean-phosphatidylcholine, cholesterol, and stearyl amine within the molar ratio: 7:2:1 (36 μmol lipids per 10 10 0.2 M phosphate buffer solution; ph 7.4). The animals were treated with Cra-loaded liposomes; histopathological analyses of the tumor, liver, and kidneys were dole out once the treatment. The Cra-loaded liposomes strangled the tumor by seventy-one, whereas Cra resolution strangled the tumor by solely 43%; liposome-encapsulated Cra improved antitumoral activity by twenty-eighth. The liver and kidney were protected from white cell infiltration when Cra was incorporated within the liposomes; reduced death was conjointly observed within the treated tumors. This technique has two advantages: reduced tissue toxicity and increased antitumor activity[87]. Priprem et al. investigated the anxiolytic and cognitive activities of QU in male Wistar rats. The researchers developed liposomes for intranasal administration, composed of a mix of egg phosphatidylcholine, cholesterol, and QU (in 2:1:1 ratio). The mean diameter of the liposomes was two hundred nm; they had a negative surface charge. The vary of encapsulation potency was between 60%–80%. A suspension of QU spread in an exceedingly resolution containing five hundredth polyethylene glycol in water was freshly prepared for oral administration (300 mg of QU per kg body weight) and was compared to orally and intranasally, delivered QU liposomes (0.5 mg QU in 20 μL; dose: 20 μg). QU liposomes were administered orally or directly into the right nasal cavity of every rat. The constant dose was given repeatedly to the same rat at a constant time day after day. To evaluate anxiety and cognitive effects, using the elevated and maze, and therefore the Morris water maze, respectively, the rats had their behavior evaluated after single and perennial daily doses for seven days, 14 days, 21 twenty-eight days. Each QU and oral QU liposomes demonstrated an improvement in cognitive and anxiolytic effects. However, intranasal QU liposomes displayed better results faster and at a lower dose than the other treatments. The most effective cognitive and anxiolytic effects for intranasal QU liposomes could also be attributed to the alteration of varied neurotransmitters, together with gamma-aminobutyric acid and serotonin, respectively[88].

Breviscapine (bre) is a flavonoid isolated from the traditional Chinese medicinal herb asteroid dicot genus *Brevis apus* (vant.) Hand. Mazz (Compositae) has proven to effectively protect the brain against ischemic injury via an unknown mechanism. To prolong the duration of your time the drug remains in circulation,

reduces the frequency of injection, and afterward improves patient compliance, multivesicular liposomes (MVLs) (Depo Foam®) were synthesized as a sustained delivery system for bre (bre-MVL). In vitro and in vivo pharmacokinetics were investigated and compared to traditional liposomes containing bre (bre-TLs). Bre-MVLs were ready using a double emulsification process, as represented by Kim et al. [90] and Katre et al. [91], using phosphatidylcholine, phosphatidylglycerol, cholesterol, and triolein or tricaprylin. Both in vitro and in vivo, bre-MVL significantly prolonged sustained delivery relative to bre-TL. The mean residence time obtained from the pharmacokinetic study of bre-MVL was about 16.6 times and 5.04 times longer than that of bre solution and bre-TL, respectively. In vivo, a duration of 4–5 days was achieved by bre-MVL. in conclusion, as a lipid depot delivery system, MVLs may be successfully used for sustained delivery of breviscapine[92].

To overcome insolubility and instability with the active lactone form of camptothecin (CPT), a potent antitumor agent, Watanabe et al. incorporated CPT, isolated from the Chinese plant *Camptotheca acuminata* Decne. (Nyssaceae), into PEGylated liposomes. CPT was incorporated into liposomes by adding three,5-bis (dodecyloxy) benzoic (PO)-polyethylene glycol-containing liposomes and by coating the surface of the liposomes with human serum albumin (HSA-DB-L). The antineoplastic activity was evaluated against mice bearing colon carcinoma [28]. The treatment of female mice with colon adenocarcinoma started two weeks after solid tumor transplantation by iv injection into the lateral tail vein. A CPT as one was used as one injection at 1.5 mg/kg body weight, and HSA-DB-L (e.g., 2.5 mg CPT and twenty-five mg total lipid/mL) was given as one injection at ten mg/kg or fifteen mg/kg, and another at ten mg/kg. The mice's tumor growth was inhibited after a single iv injection of HSA-DB-L at fifteen mg/kg. No vital weight loss; however, a significant increase within the accumulation of CPT in growth tissue was determined (9.6 times greater); the accumulation was a lot of economical than with CPT solution, at twenty-four hours after iv injection. These findings suggest that HSA-DB-L can increase the stability and enhance the CPT.93 Herpes simplex virus's antineoplastic effect is one of the most common viral diseases in humans. H. simplex 1 (HSV-1) and H. simplex 2 (HSV-2) are distinguished by clinical manifestations and biological and serological criteria. Several drugs are used to treat these infections, but the larger problem is, strains that are proof against these drugs. Additionally, there are toxicity cases, particularly in immunocompromised patients. to find less toxic antiviral agents, Sinico et al. investigated in vitro the effect of liposomal inclusion of the anti-herpetically-active volatile oil, *Artemisia arborescens* L. (Asteraceae). Positively charged MLVs and SUVs were prepared to exploit the film methodology with sonication and were obtained from hydrogenated and non-hydrogenated soy phosphatidylcholine, respectively. The antiviral activity of free versus liposomal *A. arborescens* volatile oil (EO) was evaluated against the hsv-1 virus. Both MLV and SUV showed a decent capability to entrap EO (60% and 74, respectively). When EO was entrapped in MLV, a significant increase within the antiviral activity of *A. arborescens* was determined relative to the free oil[29].

Hoar and Schulman initially introduced the term microemulsion (ME) in 1943 to outline a fluid system obtained by volumetric analysis, composed of a simple emulsion with medium-chain alcohol, like hexanol or pentanol; initially semi-transparent, and titrated till transparent[94]. MEs are clear emulsions in which oil is

dispersed in an aqueous medium (or vice-versa) containing a surfactant, with or while not an acceptable cosurfactant. These conditions generate a thermodynamically stable system, with droplets of the internal part measuring nanoscale (nm). Active substances may be carried within the microemulsions when they are solubilized within the oil or the aqueous phases[95-96.] MEs are reservoir systems once the drug is separated from the dissolution medium through a membrane or interface that has to be backward to control the discharge into the atmosphere. These systems provide a dimensionally restricted atmosphere with personal properties and can connect or associate molecules of various teams of medication to improve solubility, standard stability, or bioavailability profile[95]. Another purpose of being highlighted is that the ability of micro emulsified systems to enhance the solubility and stability of the medicine, apart from providing prolonged action; specifically, targeting for specific tissues or organs of the body, and having the ability to convey active substances with differing degrees of hydrophilicity/lipophilicity within a constant formulation[20-21]. Triptolide (TP) is a purified compound from a traditional Chinese medicine isolated from the shrublike vine, *Tripterygium wilfordii* Hook. F (Celastraceae). It exhibits various biologic properties, including anti-inflammatory, immunological disorder, contraceptive and antineoplastic activities. However, its clinical use is restricted because of its low water solubility and a few hepatotoxic effects. to enhance these disadvantages, a microemulsion (ME) system was developed by Mei et al.[61] The researchers developed, characterized, and evaluated in vitro the permeation and anti-inflammatory activity of microemulsions related to TP. The MEs were ready with water (water phase), isopropyl myristate TP (oil phase), and Tween 80:1,2-propylene glycol (surfactant: co-surfactant).

The formulation contained zero.025% TP, 400th isopropyl myristate TP, and five-hundredth Tween 80 in 1,2-propylene glycol (5:1, v/v) discovered the very best permeation profile. Carrageenan-induced rat paw edema was significantly suppressed by the microemulsion incorporating TP. The results show the highest anti-inflammatory effects by TP incorporated in microemulsions.[61] Extracts from the fruit pulp of *Syagrus romanzoffiana* (Cham.) Glassman (Arecaceae) was incorporated into o/w nanoemulsions prepared using the phase inversion methodology, with squalane because of the oil part and a try of oleic alcohol ethoxylated surfactants as non-ionic surfactants (Oleth-3: oleyl alcohol 3OE and oleic alcohol 20OE). Mezadri evaluated those extracts' antioxidant activity using the DPPH chemical agent and noticed an excellent antioxidant activity that was vital for determining the concentration of those extracts to be employed in nanoemulsions. The addition of extracts of *S. romanzoffiana* in formulations did not alter the characteristics obtained. This was the first study involving the development of nanoemulsions that contain these extracts. Further studies should be conducted

to understand higher other pharmacological activities involved when using these materials[97].

3.New approaches and challenges

Nanosized drug delivery systems for herbal medication will potentially enhance biological activity and overcome issues related to plant medicines. However, significant challenges remain for the implementation of clinically viable therapies during this field. Trials of novel methods to control nanomaterials' interactions with biological systems represent a number of the present challenges to translating these technologies into

therapies. New challenges within the development of nanotechnology-based drug delivery systems include the practicableness of scale-up processes that bring innovative therapeutic techniques to the market quickly, and therefore the possibility of getting multifunctional systems to satisfy many biological and therapeutic necessities. Some further new challenges include probing nanoparticles' targeting potency and satisfying international standards for their toxicology and biocompatibility.

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