Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 15, Issue 2, 2025, 19
https://doi.org/10.33263/BRIAC152.019

Recent Advances in Formulations for Andrographolide Delivery System

Rezky Marwah Kirana [2], Rathapon Asasutjarit [2], Lidya Agriningsih Haruna [2], La Ode Muh Julian Purnama [2], Muhammad Hajrul Malaka [1,2], Ruslin Ruslin [3], Adryan Fristiohady [1,*]

[1] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Haluoleo, Kendari 93132, Indonesia
[2] Thammasat University Research Unit in Drug, Health Product Development and Application (DHP-DA), Department of Pharmaceutical Sciences, Faculty of Pharmacy, Thammasat University, Pathum Thani 12120, Thailand
[3] Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Haluoleo, Kendari 93132, Indonesia
* Correspondence: adryanfristiohady@uho.ac.id (A.F.);

Scopus Author 57194056821
Received: 21.03.2024; Accepted: 7.07.2024; Published: 12.04.2025

Abstract: Andrographolide (AG) is vital in pharmacological activity such as analgesic, antipyretic, anti-inflammation, hepatoprotection, antiviral, antithrombotic, anti-cancer, and hypoglycemic. However, AG has poor drug solubility in water and low bioavailability, which interferes with the performance of andrographolide in treating diseases. Many strategies have been investigated to improve the bioavailability of AG and provide a time-release effect on the absorption process to extend the half-life of AG. The journal review was written using the library study method from 2001-2023, which contained information about the Development of Andrographolide In Drug Delivery Systems. The journal review discussed some approaches to achieving therapeutic goals for AG. The result of this review obtained that some of these approaches, including solid lipid nanoparticles (SLNs), liposomes, microemulsion (ME), nanoemulsion (NE), microsphere (Ms), polymeric nanoparticles, gold nanoparticles (AuNPs), self micro emulsifying drug delivery system (SMEEDS), and niosome, can improve the limitation of conventional formulation of AG by increasing penetration, permeability, and bioavailability of AG.

Keywords: andrographolide; formulation; nanoparticles; liposomes; niosomes.

1. Introduction

Over the past few decades, drug delivery systems have provided tremendous strength in improving the reliability and safety of existing drugs. Nowadays, people use a molecule with multiple therapeutic activities for several disorders. Andrographolide is a major bioactive phytoconstituent present in *Andrographis paniculata* Nees (Acanthaceae family) and is also known as ‘‘King of Bitters’’[1]. *Andrographis paniculata* (Burm.f.) Wall. ex Nees, member of the family *Acanthaceae*, commonly known as Kalmegh, also known in different languages as 'Kirayat' in Hindi, 'Kalamegha' in Sanskrit, 'King of Bitters' and 'Indian Echinacea' in English [2]. The andrographolide content in different parts of the plants found in leaves (4.686 %), which was followed by flower tops (1.955 %), stem (0.533 %), and roots (0.054 %), lowest andrographolide content was found [3].

Andrographis paniculata Nees, a traditional medicine in Southeastern Asian countries, has been widely used in the clinic as an immunostimulant and for the treatment of the common

cold, myocardial ischemia, pharyngotonsillitis, and respiratory tract infections [4]. The major component of *A. paniculata* is andrographolide, which has been used to treat colds, diarrhea, fever, inflammation, and infectious diseases [5]. In addition, the chemopreventive effects against and the inhibitory effects on cancer cell growth of andrographolide have been demonstrated in breast, colon, epidermoid, gastric, liver, leukemia, myeloma, peripheral blood lymphocytes, and prostate cancers. In addition, andrographolide can reduce pulmonary functional damage and prevent pulmonary cancer formation by eliminating VEGF, ERK2, Cyclin A, and Cyclin B proteins [4].

Andrographolide molecules have various pharmacological activities and medicinal properties [1]. Despite the tremendous therapeutic interest, the use of AG is limited due to its low bioavailability and poor solubility [1,6,7]. The low oral bioavailability of AG continues to be highlighted as a significant challenge in developing formulations for clinical efficacy. Low andrographolide solubility (3.29± 0.79 µg/mL) in water and very lipophile character (log P = 2.632 ± 0.135) result in a very low bioavailability (2.67%) [6]. Andrographolide has an α,β-unsaturated γ-lactone ring connected to the decalin ring through unsaturated C2. It affects water solubility, has poor oral absorption, and has low bioavailability because it is not stable under acidic or alkaline conditions in the digestive system. The low bioavailability of andrographolide significantly interferes with the performance of andrographolide to treat diseases. The absorption process of andrographolide will also be disrupted such that the concentration in the blood is insufficient to achieve optimal treatment activity [7]. These barriers can be mitigated by the use of suitable delivery systems to improve AG solubility and encourage drug delivery effectiveness. In a previous study, AG was formulated into an emulsion with particle size in the micrometer range. However, microparticles have relatively low cell uptake and poor tissue penetration. Particles in the nanometer size range (nanoparticles) are more advantageous due to their ability to passively accumulate in tumors via the "Enhanced permeability and retention effect" [8,9]. Moreover, Several studies showed that SNEEDS formulation could enhance the dissolution, bioavailability, and delivery efficacy of AG isolated from *Andrographis paniculata* Nees. Besides that, polymeric nanoformulation of AG enhanced and sustained the inhibition of the proliferation of triple-negative LM2 breast cancer cells when compared to the free drug [8-10]. Considering the potential of nanoparticles for improving molecular pharmaceutical properties of therapeutic agents, the present investigation involved the development of andrographolide in various drug delivery systems to improve its oral bioavailability. The types of drug delivery systems of andrographolide reviewed in this study are summarized in Table 1.

Table 1. Formulation of andrographolide in drug delivery system.

No	Drug delivery system		Formulation	Cells	Target site	Mechanism	Ref.
1	Solid lipid nanoparticles (SLNs)	Lyophilized andrographolide-loaded solid lipid nanoparticles	Parenteral administration	The human immortalized oral epithelial (HIOEC), precancerous leukoplakia (Leuk1), HN6, and HN30 cells	Head and neck squamous cell carcinoma (HNSCC)	ADG-SLN exhibits superior inhibitory activity against head and neck cancer and precancerous cells compared with free ADG due to the higher efficiency of cellular uptake and intracellular absorption by ADG-SLN.	[11]
		Andrographolide-loaded solid lipid nanoparticles (AG-SLNs)	Parenteral administration	The Ehrlich's ascites carcinoma (EAC) cells	Breast	The cellular uptake of SLNs could be accelerated due to non-specifically internalization of SLNs into cells via endocytosis	[12]

No	Drug delivery system		Formulation	Cells	Target site	Mechanism	Ref.
						or phagocytosis. Because of the increased solubility and dissolution rate of drug-loaded SLNs, molecular concentration will be high around the cells.	
		Andrographolide-stealth solid nanoparticles (AG-Stealth-SLNs)	Parenteral administration	PAMPA and hCMEC/D3 cells	The blood-brain barrier (BBB)	The improved blood residence time in brain capillaries creates a higher concentration gradient that enhances penetration across the endothelial cell layer.	[13]
2	Polymeric Nanoparticles (Polymeric NPs)	AG-loaded human serum albumin nanoparticles (AG-HSA NPs)	Parenteral administration	Human cerebral microvascular endothelial (hCMEC/D3) cells	Brain	-	[14]
		AG-loaded PLGA nanoparticles (AG-PLGA-NPs)	Parenteral administration	LM2 breast cancer cells	Breast	Enhanced and sustained inhibition of proliferation of triple-negative LM2 breast cancer cells	[15]
		Fluorescein isothiocyanate labeled AGNP (FITC-AGNP)	Inhalation	IL-4, IL-5, and IL-13	Lungs	AGNP reduced the elevated IL-4, IL-5, and IL-13 levels significantly by pulmonary route. These results altogether denote that AG-released AGNP might have better interfered with cytokines Th2, which is a key mediator in eosinophilic inflammation in asthma.	[16]
3	Gold Nanoparticles (AuNPs)	AG-AuNPs	Parenteral administration	-	Kidney, Liver, Muscle	Inhibition of PLA2 activity, increased receptor targeting, decreased protein availability at target sites, inhibition of pro-oxidant DRRV activity, and increased cellular uptake of AG-AuNPs.	[17]
		AG-AuNPs	Parenteral administration	Human Cervical cancer (HeLa) and MCF7 cells.	Cervix and Breast	AG provided a non-toxic coating on the surface of AuNPs, making them non-toxic to the cell lines.	[18]
		AG-AuNPs	-	*E. coli* and *B. subtilis* bacterial cells	-	Metal nanoparticles are harmful to bacteria, allowing them to adhere to the cell walls of microorganisms, resulting in the destruction and death of the cell.	[19]
4	SMEEDS (Self Micro Emulsifying Drug Delivery System)	AG-loaded SMEEDS	Oral administration	-	Digestive tract	The formed ME enhanced the absorption of the drug because of the close contact between the apical membrane and the ME droplets, creating altered membrane fluidity. Labrasol enhanced tight junction opening that led	[20]

No	Drug delivery system		Formulation	Cells	Target site	Mechanism	Ref.
						to the enhancement of paracellular absorption.	
		Andrographolide-extract (AGPE-SMEEDS)	Oral administration	-	Intestinal membrane	Improving the dissolution of the active ingredient and facilitating the permeation.	[21]
5	Microspheres (Ms)	Andrographolide-loaded Chitosan/Na-Alginate microspheres.	Oral administration	Liver cell	Liver	-	[22]
		Andrographolide-loaded PLGA-microspheres	Parenteral administration	Cancer cells	-	The drug release mechanism was mainly due to the combination of diffusion of the drug through the polymeric matrix and polymer erosion of the PLGA microspheres.	[23]
6	Microemulsion (ME),	AG-loaded ME	Sub-plantar	-	Paws	-	[24]
		AG-loaded biocompatible microemulsion (BMAG)	Oral administration	Epithelial cells of gastrointestinal	Gastrointestinal tract	AG in BMAG can be absorbed by lymphatics after oral administration and contact with the gastrointestinal epithelial cells directly after passing through the hydration layer of the gastrointestinal wall, which makes this ingredient absorbed faster.	[25]
	Nanoemulsion (NE)	AG-loaded NE	Transdermal preparation	The human malignant melanoma-(A375 cells) and non-melanoma cells (A-431 cells)	Skin	Op-AG-NE inhibits the activity of intracellular tyrosinase in the A375 cells.	[26]
		AG/HPCD/PC complex (AHPC)-loaded nanoemulsion (AHPC-NE)	Oral administration	Intestinal membrane	Intestine	The hydrophilic hydroxypropyl groups of HPCD increased the water solubility of AG, and the amphiphilic PC molecule stimulated the outer membrane of intestinal epithelial cells to guide the absorption of AG.	[27]
7	Liposomes (LPs)	Stealth liposomes containing Tween 80 (LPs) and cationic liposomes (CLPs) of andrographolide (AG)	Parenteral administration	PAMPA and hCMEC/D 3 cells	Brain	PAMPA and hCMEC/D3 cells increase the permeation of AG into the cell without alterations in cell viability and monolayer integrity. The presence of a positive charge elevated the cellular internalization of liposomes.	[28]
		Liposomal AG dry powder inhaler	Inhalation	The tumor necrosis factor-α (TNF-α) and interleukin (IL)-1	Respiratory tract	The LDPIs reduced the tumor necrosis factor-α (TNFα) and interleukin (IL)-1 pro-inflammatory cytokines.	[29]
		Mannosylated-chitosan-coated	Oral administration	-	Digestive tract	Produce mannose-grafted nanocarriers with	[30]

No	Drug delivery system		Formulation	Cells	Target site	Mechanism	Ref.
		andrographolide nanoliposomes				improved muco permeability.	
8	Niosome	AG-Niosome	Parenteral administration	HepG2 cell	Liver	-	[31]
		AG-niosomal gel	Topical administration	Human skin fibroblast (HSF) cells	Skin	Promotes re-epithelialization activity on the wounded area of Sprague Dawley rats	[32]

2. Methods

The data used in writing this journal review was collected using the literature study method from primary and secondary literature. Literature searches were conducted using online-based library search instruments such as NCBI-PubMed, Google Scholar, ScienceDirect, and Elsevier from January to February 2024. The keywords and phrases used during the search were then arranged according to the framework. The development of andrographolide in drug delivery system data was compiled in tabular form, and journal review writing was carried out according to the format provided. The journal from 2001-2024 contained information about the formulation of andrographolide In drug delivery systems, shown in (Table 1).

3. Discussion

Andrographolide (AG), with a chemical formula C20H30O5 (Figure 1.), has low oral bioavailability (2.67%), leading to poor therapeutic applicability. The factor attributed to the poor bioavailability of andrographolide includes site-specific absorption from the upper part of the GI tract, pH-dependent hydrolysis in the neutral or weak alkaline environment of the intestine, extensive hepatic metabolism with 90% excretion through urine and feces, sulfonated phase I metabolism in the small intestinal, glucuronide conjugated phase II metabolism. It has high lipophilicity (log *P* value = 2.632 ± 0.135) and low aqueous solubility (3.29 ± 0.73 µg/ml) [33]. Considering these limitations, an efficient drug delivery system is warranted at this stage to enhance its therapeutic efficacy. The primary purpose of using a delivery system is to increase the bioavailability of AG and provide a time-release effect on the absorption process to extend the half-life of AG in the blood [34]. The application of drugs that do not use a carrier yields a short half-life since the body absorbs the drug component according to its ability when it enters the body. Generally, the drug compound that is not absorbed will be excreted through the excretory channel [35]. Therefore, several researchers have modified the use of andrographolide in the delivery system. The types of drug delivery systems of andrographolide reviewed in this study are summarized in Table 1, including solid-lipid nanoparticles (SLNs), polymeric nanoparticles (polymeric NPs), gold nanoparticles (AuNPs), self-micro emulsifying drug delivery system (SMEEDS), microsphere, microemulsion, nanoemulsion, liposome, and niosome, as well as their formulations.

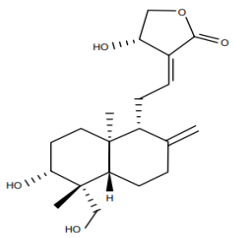

Figure 1. Chemical structure of andrographolide.

3.1. Solid lipid nanoparticle.

Solid lipid nanoparticles (SLNs) are colloidal dispersions with modified properties of other nanoparticles, such as microemulsions, suspensions, liposomes, and polymeric nanoparticles [36]. SLNs are spherical nanoparticles of 50–1000 nm and made up of solid lipids at room temperature, emulsifiers, and API (Figure 2) [37]. The SLN safety profile was based on biocompatible lipids highly tolerable to the lungs and body. SLNs can potentially incorporate hydrophilic, lipophilic drugs in addition to proteins and nucleic acids, which open new frontiers for drug and gene delivery [36]. The phospholipid fatty substances used for SLNs are smaller, flexible, and biologically compatible, allowing them to pass through and penetrate the blood vessels [38]. Drugs with physicochemical incompatibility, lower pharmacokinetic profile, and thermolabile drugs can be delivered to the target site via SLNs. Protein and peptide delivery with higher efficiency and lower toxicity can also be achieved with SLNs [36].

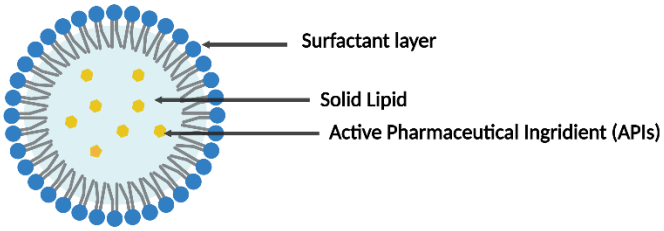

Figure 2. Schematic illustration of solid lipid nanoparticle.

SLNs have many advantages in comparison to other particulate systems, such as the ease of large-scale production, biocompatible and biodegradable nature of the materials, low toxicity potential, possibility of controlled and modified drug release, drug solubility enhancement and the possibility of both hydrophilic and lipophilic drug incorporation. However, because of their perfect crystalline structure, they have low drug loading efficiency and the possibility of drug expulsion due to the crystallization process during the storage conditions. Another drawback is the initial burst release, which usually occurs in these formulations [37-40].

Formulation of andrographolide in solid lipid nanoparticles (AG-SLNs) is superior as a chemopreventive agent. We investigated the anti-cancer activity of AG-containing SLNs in an in-vitro model of stepwise progression of HNSCC by evaluating cell viability, cell cycle arrest, cell apoptosis, and cellular uptake. This study cultured HIOEC, Leuk1, HN6, and HN30 cells as an in vitro head and neck cancer development model. By measuring the anticancer activity in these cell lines, the results found that the IC_{50} value of AG-SLNs was significantly lower than that of free AG, indicating that AG-SLNs are more cytotoxic than free AG. Consequently, AG-SLNs increased AG's bioavailability and anti-proliferative activity in cell lines representing multistage HNSCC development at lower concentrations than free AG [11].

AG, as a solid lipid nanoparticle formulation, can also improve antitumor effectiveness. Treatment of tumor-bearing mice with AD-SLNs returned the hematological parameters to normal levels. The results indicated that the drug and its SLNs have a protective effect on the hemopoietic system. In conclusion, it was found that AD-SLNs inhibited the growth of tumors and were more active than AD [12]. A study of the pharmacokinetics of AG-SLNs was also obtained. The SLNs resulted in increased bioavailability of AD by oral administration. The AD plasma concentrations were significantly higher for rats treated with AD-SLNs than those treated with AD [12].

Novel nanoformulations based on drug delivery systems offer significant promise in overcoming AG's limitations. The present study established that stealth-SLN successfully enhanced AG permeation in vitro BBB models, PAMPA, and hCMEC/D3 cells. Furthermore, the ability of nanoparticles to cross the BBB and reach brain tissues was confirmed by in vivo tests in healthy rats. SLNs have physical characteristics for systemic administration regarding particle size, polydispersity, encapsulation efficacy, and -potential. In vitro drug release studies have revealed that SLN releases AG in a sustained and controlled manner. SLN shows excellent chemical and physical stability as both suspension and lyophilized products. In vitro transport studies performed with PAMPA and hCMEC/D3 cells revealed that SLN successfully enhanced AG's permeation, while in vivo studies confirmed that nanoparticles could cross the BBB and reach the brain tissues [13].

3.2. Polymeric nanoparticles (Polymeric NPs).

Polymeric Nanoparticles (NPs) are spherical solid colloidal particles composed of biocompatible and biodegradable polymers ranging from 10 nm to 1000 nm [41]. Their small size allows the particles to penetrate capillaries and be absorbed by cells, increasing drug accumulation at the target site of action [42]. The term "nanoparticle" comprises nanocapsules and nanospheres, which differ in their morphology. Nanocapsules are composed of an oily core in which the drug is usually dissolved, surrounded by a polymeric shell that controls the release profile of the drug from the core. Nanospheres are based on a continuous polymeric network in which the drug can be retained inside or adsorbed onto its surface. These two polymeric NPs are recognized as reservoir systems (nanocapsules) and matrix systems (nanospheres), as shown in Figure 3. Various biodegradable polymers commonly used in making polymer NPs include poly(lactide) (PLA), poly(lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL) copolymers, and poly(amino acids) as well as several natural polymers such as alginate, chitosan, gelatin, and albumin [43-44]. Encapsulation in nanoparticles can overcome the problem of poor water solubility because appropriately formulated nanoparticles exhibit excellent suspension stability in biological fluids [15]. Advantages of NPs are drug release in controlled and sustained manner, incorporation of hydrophilic and hydrophobic drugs, tunable chemical and physical properties, use of a lot of biodegradable materials when desired, potential use for controlled release of drug, existence of pH, enzymatic, hydrolysis, etc., sensitive properties when preferred proper polymers, reproducible data when used synthetic polymers, higher stability than lipid-based ones, being many methods to prepare polymeric NPs. Polymeric NPs' disadvantages are difficulty scaling [44,46].

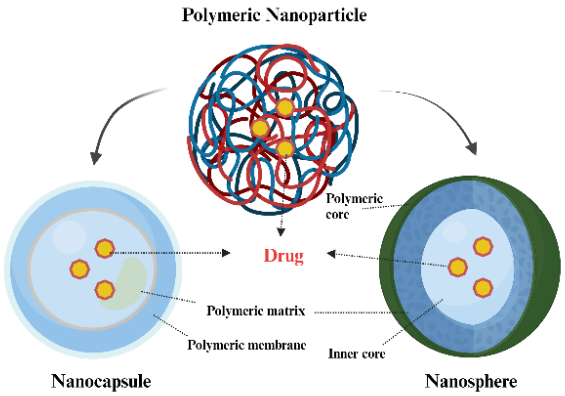

Figure 3. Schematic illustration of the structure of nanocapsule and nanosphere.

The low bioavailability of AG is still a limiting factor in its use. AG was incorporated into human serum albumin-based nanoparticles (HSA NPs) to overcome these limitations. Human Serum Albumin Nanoparticles (HAS NPs) are made by thermal (HSAT AG NPs) and chemical cross-linking (HSAC AG NPs). The NPs were characterized by size, zeta potential, polydispersity, and AG release studies. Additionally, the ability of free AG and AG loaded in HSAT NPs to cross the blood-brain barrier (BBB) was assessed using an in vitro BBB model based on the human brain microvascular endothelial cell line (hCMEC/D3). The result was that free AG did not penetrate the BBB model, as also predicted by in silico studies. Meanwhile, HSAT NPs slightly increased the permeability of AG across the cell monolayer. HSAT NPs are considered a better drug delivery system [14]. AG was also encapsulated in nanoparticles using PLGA polymer. This formulation demonstrated enhanced and sustained inhibition of triple-negative LM2 breast cancer cell proliferation compared to the free drug. This formulation can serve as a template for further developing andrographolide as a potential anticancer agent for clinical use [15]. AG has an antiasthmatic potential. However, its poor bioavailability and short plasma half-life constrain its efficacy. To overcome them, AG was encapsulated in nanoparticles (AGNPs), and AGNPs were evaluated for antiasthmatic efficacy on the murine asthma model by oral/pulmonary delivery. Plasma and lung pharmacokinetic data showed predominantly improved AG bioavailability upon AGNPs administered orally/by pulmonary route. Cell numbers, IL-4, IL-5, and IL-13 levels in broncho-alveolar lavage fluid and serum IgE content were reduced significantly after administration of AGNPs compared to free-AG treatment [16].

3.3. Gold nanoparticles (AuNPs).

Gold nanoparticles (AuNPs) can be used as a delivery method for various therapeutic agents. Molecules with different functional groups can bind with high affinity to the surface of AuNPs. Other functional thiols or adsorbed ligands can replace the capping agent surrounding AuNPs via ligand exchange reactions [47]. AuNPs can bind covalently or noncovalently with other materials through surface modification. Covalent conjugation stabilizes the conjugates for imaging. Different interactions (such as specific binding affinity, electrostatic, and hydrophobic interactions) can attach molecules to AuNPs noncovalently. These interactions produce modified AuNPs that are suitable for drug delivery because they require easy release of the drug for targeting purposes. Figure 4 shows a simple route of conjugating AuNPs with drugs for targeting cancer cells [48].

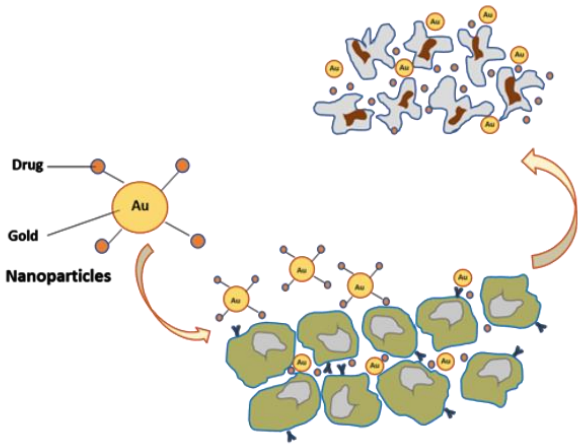

Figure 4. Schematic illustration showing the killing of cancer cells by gold nanoparticles.

AuNPs can be functionalized into different compounds that bring healing effects. Coating molecules (e.g., PEG and BSA) are attached to provide a binding surface to specific cells, thereby minimizing non-specific targeting to other tissues. For example, PEGylation of AuNPs can minimize macrophage and monocyte uptake, protecting and prolonging their availability and concentration in tumor tissue. Not only small molecular drugs but also large biomolecules (such as DNA, RNA, peptides, and proteins) are produced by AuNPs [49]. Gold nanoparticles have unique optical, physical, and chemical properties due to their size and shape and high surface area, which provide dense drug loading. Particles are biocompatible and are readily available for conjugation with small biomolecules such as proteins, enzymes, carboxylic acid, DNA, and amino acids. Gold nanoparticles have controlled dispersity. Due to their small size and unique dispersion, they can easily reach the targeted site with blood flow, are non-cytotoxic to normal cells, and are easily synthesized by various methods. Disadvantages of gold NPs include the utilization of rigorous synthesis procedures, harsh chemicals, high energy and operating costs, and lower productivity [50-51].

Andrographolide, a diterpenoid compound found in the Andrographis paniculata plant (a well-known anti-snake venom plant), was s conjugated with gold nanoparticles (AG-AuNPs), and its efficacy against Daboia russelii russelii venom (DRRV) induces local damage, organ toxicity, and inflammatory response. Envenomation of DRRV followed by treatment with AG-AuNPs protected against edema, hemorrhage, defibrination, organ toxicity, and inflammation caused by toxins in animal models. Neutralization of toxins by AG-AuNPs > andrographolide confirmed the increased efficacy of andrographolide after conjugation with gold nanoparticles [17].

AG-AuNPs protected rattlesnake venom-induced phospholipase A2 activity and minimum plasma coagulation dose. In animal models, Daboia russelii russelii (DRRV) venom causes nephrotoxicity, hepatotoxicity, and myotoxicity. Elevated levels of urea, creatinine, calcium, phosphate (for nephrotoxicity), AST, ALT, λGT, ACP and ALP (for hepatotoxicity) and LDH (for myotoxicity) were seen in control viper venom animals, which decreased significantly after treatment with AG- AuNPs demonstrated that AG-AuNPs inhibited toxin-induced organ damage (kidney, liver, muscle) in animal models [17]. AG-AuNPs can work through (a) inhibition of venomous snake venom PLA2 activity, (b) increased DRRV receptor targeting by AG-AuNPs, (c) decreased availability of DRRV protein at the target site, (d) inhibition of the pro-oxidant activity of DRRV, and Neutralizing damage caused by toxins to the vascular bed, (e) disruption of cellular and molecular markers (pro-inflammatory markers, antioxidants, etc.), and (f) increased cellular uptake of AG-AuNPs. Treatment with AG-AuNPs reduced the level of oxidative stress caused by poisonous snake venom in animal models [17]. In another study, The synthesized AG-AuNPs were tested for their effect on HeLa (human cervical cancer) and MCF7 (human breast cancer) cell lines and found to be non-toxic and biocompatible, which are potential carriers for hydrophobic drugs [18]. Furthermore, the antimicrobial potential of AG-conjugated AuNPs was assessed. The obtained results indicate the better antimicrobial potential of herbal extract conjugated AuNPs than the herbal extract alone, and a larger zone of inhibition is probably due to the better dispersion of the compound in an aqueous solution. Metal nanoparticles are harmful to bacteria, and this characteristic allows them to adhere to the cell wall of microorganisms, resulting in the destruction and death of the cell [19].

3.4. SMEEDS (self-micro emulsifying drug delivery system).

Much attention has recently been focused on lipid-based systems, particularly self-emulsifying drug delivery systems (SEDDS), to improve the oral bioavailability of poorly water-soluble compounds. SEDDS/SMEEDS are isotropic mixtures of oil, surfactants, cosolvents or cosurfactants, and drug substances (Figure 5) [52]. This system forms oil-in-water (o/w) emulsions when diluted in a liquid medium such as GI fluids with light agitation produced by gastrointestinal movement. This is necessary for self-emulsification in vivo. The droplets formed are between 100 and 300 nm, while the self-microemulsifying drug delivery system (SMEDDS) forms transparent microemulsions with droplet sizes of less than 50 nm [52]. SEDDS/SMEDDS are physically stable, easy to manufacture, and can be filled in soft gelatin capsules. The dissolved form of the drug in the SMEDDS formulation helps increase drug absorption [53].

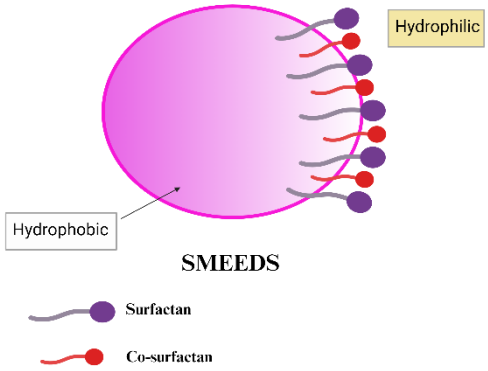

Figure 5. Diagrammatic representation of SMEDDS (self-micro-emulsifying drug delivery).

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, cosolvent or cosurfactant, and drug substance. This system forms oil-in-water (o/w) emulsions when diluted in an aqueous medium such as GI fluids with light agitation produced by gastrointestinal movement. This is necessary for self-emulsification in vivo. The size of the droplets formed is between 100 and 300 nm, while Self-microemulsifying drug delivery systems (SMEDDS) form transparent microemulsions with droplet sizes of less than 50 nm. SEDDS/SMEDDS is physically stable, easy to manufacture, and can be filled in soft gelatin capsules [20].

SMEEDS have spontaneous formation, thermodynamic stability, improved bioavailability, and enhanced solubility, such as improvement in oral bioavailability by increasing solubility and efficient drug transport, ease of manufacture and scale-up as compared to other lipid dosage forms, reduction in inter- and intra-subject variability and food effects, ability to deliver peptides that are prone to enzymatic hydrolysis in GIT, no influence of lipid digestion process unlike the other lipid-based drug delivery systems, when polymer is incorporated in the composition of SMEDDS, it gives prolonged release of medicament. Disadvantages of SMEDDS such as lack of good predictive in vitro models for assessment of the formulations, in vitro model needs further development and validation before its strength can be evaluated, chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT, volatile cosolvents in the conventional self micro emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs, the precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent [55-56].

Andrographolide formulation in the optimized self-contained liquid microemulsifying drug delivery system (SMEDDS) consists of A. paniculata extract (11.1%), Capryol 90 (40%), Cremophor RH 40 (40%) and Labrasol (8.9%) %). This liquid SMEDDS is then absorbed into colloidal silicon dioxide and microcrystalline cellulose and converted into pelleted SMEDDS by extrusion/spheronization techniques. After dilution with water, liquid, and pellet formulation, microemulsion droplet sizes are 23.4 and 30.3 nm [20]. The in vitro drug release results showed that the SMEDDS formulation produced a faster and greater AG release rate and indicated that this drug delivery system could increase the dissolution of A. paniculata extract. Pharmacokinetic studies in rabbits showed that liquid and pellet preparations of SMEDDS administered at a dose of 17.5 mg/kg showed 15- and 13-fold greater absorption of andrographolide, respectively, compared with a dose of 35 mg/kg of the unformulated extract. Therefore, using SMEDDS in liquid and pellet dosage forms can increase oral bioavailability, which allows for reducing the dose of Andrographis paniculata extract [20]. The SMEDDS formulation was also optimized using an experimental design in which the optimal condition was acquired, which was to be loaded with Andrographolide extract (AGPE) and filled into soft capsules. The AGPE-loaded SMEDDS increased drug dissolution and membrane permeation while maintaining physical and chemical stability throughout the storage period under accelerated conditions. This study proposed developing and optimizing an AGPE-loaded SMEDDS formulation with the dissolution of a permeation enhancement. Also, the ease of scale-up for industrial manufacturing was illustrated. The developed SMEDDS could be proven to increase drug absorption and bioavailability in further vivo studies [21].

3.5. Microspheres.

Microsphere is a spherical microparticle with sizes ranging from 1–1000 μm. Microscale particles are widely used as adsorbents because of their high surface area and surface-to-volume ratio. Based on its ability as an adsorbent, the microsphere can absorb drug compounds and be used as a drug carrier [57-59]. The microsphere structure includes the multicore shell and the matrix type in which the core material is dispersed like small droplets inside the shell material (Figure 6) [60]. The main advantage of applying microspheres as a drug delivery system is the controlled release of the drug content. Microspheres provide a constant and prolonged therapeutic effect, reduce the dosing frequency, and thereby improve patient compliance, could be injected into the body due to the spherical shape and smaller size, improve the bioavailability, and reduce the incidence or intensity of adverse effects. Microencapsulation is used for retarding the drug release from dosage forms and reducing the adverse effects, increasing patient compliance. Besides that, efficient absorption and enhanced bioavailability of the drugs due to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of the drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions, and antibodies. Some of the disadvantages were found the costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations, the fate of polymer matrix and its effect on the environment, the fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers, reproducibility is less, process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated [61,62].

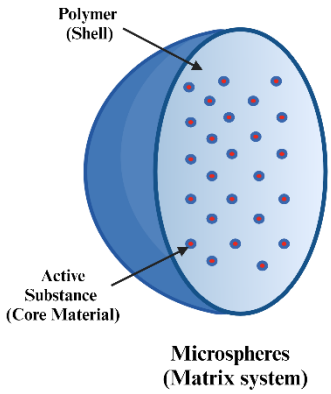

Figure 6. Schematic structure of microsphere.

Microspheres developed from chitosan/Naalginate have been established as potential formulations in treating various diseases with drugs such as Metformin HCL, diclofenac sodium, etc. Alginates have been widely used in designing drug delivery systems as rate-limiting excipients that provide superior matrices for the entrapment of drug molecules. This has been explored effectively by researchers in developing microspheres for pharmaceuticals. Chitosan is a linear polysaccharide containing N-acetyl glucosamine and glucosamine units and is biocompatible, biodegradable, and non-toxic in oral administration [22].

Two polymers of Na-alginate and chitosan as AG carriers proposed a unique approach to formulating optimal AG-encapsulated microspheres that indicate steady-state plasma drug concentrations. In vivo hepatoprotective studies were carried out on the CCl_4-poisoned Wistar Rat model to test the hepatoprotective activity of the optimized formulation. The result was that AG microspheres were formulated to be a successful oral regimen for liver disorders. It showed remarkable effects on increasing liver enzyme levels and hepatocellular necrosis in CCl4-poisoned Wistar Rats. The findings of this study suggest that andrographolide microspheres may be a potential delivery system with high oral bioavailability and a sustained drug release profile against liver necrosis [22]. A sustained-release injectable formulation containing AG-loaded poly (D, L-lactide-co-glycolide acid) (PLGA) microsphere was prepared by solid-in-oil-in-water (s/o/w) emulsion solvent evaporation method. The encapsulation of AG into PLGA helped drug loading overcome the defects of conventional oral dosage forms of AG (tablets and dripping pills), which included low bioavailability and frequent administration. After a single intramuscular injection in rats, microspheres maintained a relatively high sustained plasma concentration of AG over one week with a 40-fold improved mean retention time compared to pure AG solution. Therefore, these results suggest that the PLGA microspheres might be a promising formulation for AG for cancer therapy [23].

3.6. Microemulsion (ME) dan nanoemulsion (NE).

Microemulsions (ME) and Nanoemulsions (NE) are nanoscale emulsions with high stability and transparency. However, the terms "ME" and "NE" are not interchangeable; ME is an isotropic liquid mixture that forms spontaneously and is thermodynamically stable. NE is a nanoscale dispersion obtained through mechanical forces and is only kinetically stable. The two phases, NE and ME, are water or oil continuous. Additionally, ME can feature bicontinuous (sponge-like systems) [63].

Microemulsion is an oil, water, and surfactant dispersion that forms an isotropic and thermodynamically stable system. Microemulsions have domain diameters ranging from 10–100 nm [64]. The microemulsion method can increase the bioavailability of oral drugs because it combines oil, water, and surfactant systems (Figure 7). The solubility of the drug compound increases because it can dissolve in two fused systems: water (polar) and oil (non-polar). This solubility in two fused systems is necessary to overcome the low bioavailability of andrographolide when administered orally [65]. The microemulsion is very easy to prepare and scale up due to spontaneous formation ability, good system to raise the rate of absorption as well as bioavailability by eliminating interfering variations, able to improve the solubility of lipophilic drug, thermodynamically more stable system as compared to a conventional system and hence suitable for long term use, can be preferred to develop sustained and controlled releases drug system, the best system to minimize first-pass metabolism. Some disadvantages include the additional use of excess surfactant and co-surfactant, increased cost, and excess concentration of surfactants, which can lead to mucosal toxicity [66].

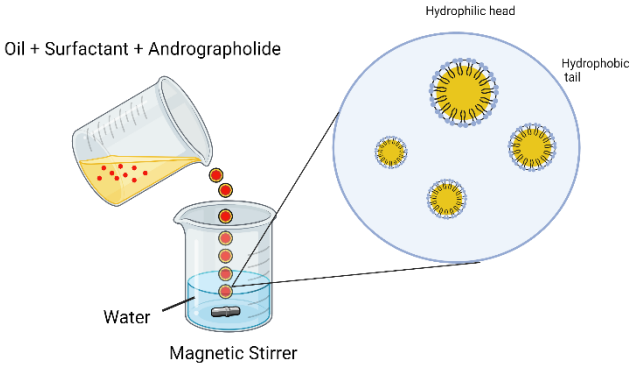

Figure 7. The preparation process to create an AG-loaded microemulsion.

A microemulsion system consisting of isopropyl myristate oil phase (2.5% w/w), Tween 80 surfactant phase (25% w/w), and alcohol co-surfactant (50% w/w) can be prepared easily. The microemulsion prepared according to this formulation is of the O/W type, with an average droplet size of 15.9 nm. This microemulsion showed high andrographolide solubilization capacity. The andrographolide-containing microemulsion was stable, as evidenced by monitoring its changes in different removal time intervals, temperatures, and gravity states—the study of the anti-inflammatory effects of albumin-induced rat paw edema. The results showed that microemulsions containing andrographolide had much better anti-inflammatory effects and higher bioavailability than conventional andrographolide. In addition, microemulsions containing andrographolide also show very low acute oral toxicity, which was proven through animal experiments. The results show that microemulsions containing andrographolide are a promising dosage form of andrographolide and have broad clinical application prospects [24].

The biocompatible microemulsion (BM), containing lecithin and bile salts, was optimized in the present study, showing good physical stability. The pharmacokinetic results of BMAG showed that the AUC0-7 and AUC0→∞ values of BMAG were 2.267 and 27.156 μg·mL−1 ·h–1, respectively, and were about 1.41-fold and 6.30-fold more significant than that of ethanol extraction, respectively. These results demonstrated that the bioavailability of rographolide extracted by BMAG was significantly higher than that of ethanol in rabbits. In

our experiment, andrographolide in BMAG can be absorbed by lymphatics after oral administration and contact the gastrointestinal epithelial cells directly after passing through the hydration layer of the gastrointestinal wall, which makes this ingredient absorbed faster. In conclusion, the BMAG preparation displayed an improved dose form for future clinical applications [25].

Nanoemulsion is a soft material that results from the dispersion of solid substances, droplets, and polymers, forming a viscous liquid. This liquid is a thermodynamically stable and isentropic system. The discontinuous and dispersed phase is termed the internal phase. In contrast, the continuous outer phase is known as the dispersion medium, where the emulsifying agent is referred to as the intermediate phase (Figure 8). Oil in water and water in oil are the most common types of nanoemulsions [67]. Nanoeulsion enhances drug absorption, higher loading capacity, drug protection from degradation during the process, controlled drug release, greater stability, efficient carrier for hydrophobic drugs, and low production cost. Disadvantages include less stability as compared to other dosage forms, less permeability and bioavailability of the drug, a short shelf-life, low viscosity and spreadability, non-compatibility and skin irritability, creaming, cracking (breaking), flocculation and phase inversion are common problems observed during storage of emulsions [66,68].

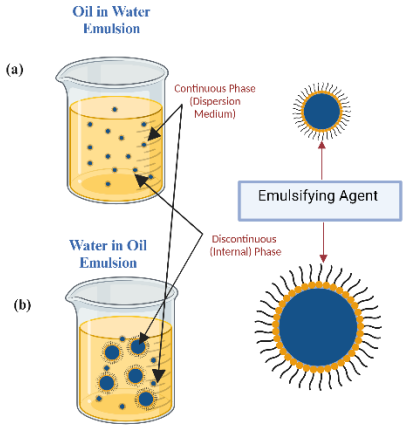

Figure 8. Schematic illustration of nanoemulsions with **(a)** oil-in-water emulsions; **(b)** water-in-oil emulsions, with surfactants emulsifying agents.

Nanoemulsion (NE) containing AG was formulated to improve low water solubility, poor AG bioavailability, and protective action against skin damage. AG-loaded nanoemulsion (AG-NE) was formulated and prepared using a microfluidization technique. This study aimed to determine the effect of AG-NE on skin cancer cells and UVB irradiation-induced skin disorders in rats. The Optimized AG-NE (Op-AG-NE) showed promising cytotoxicity effects on the human malignant melanoma- (A375 cells) and non-melanoma cells (A-431 cells) via apoptosis induction with a high selectivity index and also inhibited intracellular tyrosinase activity in the A375 cells. Op-AG-NE could properly reduce UVB irradiation-induced skin pigmentation and damage in rats. It reduced the melanin index values of the rats exposed to UVB radiation and healed their skin after exposure to UVB radiation. Thus, Op-AG-NE had the potential to treat skin cancers and skin disorders from exposure to UVB radiation [26]. Pharmacokinetic studies revealed that AHPC-NE significantly improved AG's oral bioavailability. The hydrophilic hydroxypropyl groups of HPCD increased the water solubility of AG, which was aided significantly in drug absorption. Further, the amphiphilic PC molecule might stimulate intestinal epithelial cells' outer membrane to guide AG's absorption. In addition, the oil phase molecules in the prescription of AHPC-NE may penetrate biological

membranes and interact with phospholipid polar groups to change the fluidity of the membranes, and the formation of nano-sized droplets loaded with AHPC could further increase the transport of AG and intestinal absorption. Moreover, the nano-sized droplets were evenly dispersed in the continuous phase, and this wrapping effect of the oil phase forms a natural barrier to reduce the metabolism of AG by gastric acid or other enzymes, thereby increasing the absorption of AG in the intestine [27].

3.7. Liposomes.

Liposomes (LPs) are non-toxic, biocompatible, and biodegradable drug carrier systems. Their structure, composed of phospholipids with an aqueous reservoir, allows the encapsulation of various hydrophilic and hydrophobic agents (Figure 9) [28]. Liposomes exhibit outstanding properties as drug vehicles, such as protecting the encapsulated substances from physiological degradation, extending the drug's half-life, controlling the release of drug molecules, and excellent biocompatibility and safety. Furthermore, liposomes can selectively deliver their payload to the diseased site through passive and/or active targeting, thus decreasing the systemic side-effect, elevating the maximum-tolerated dose, and improving therapeutic benefits [69].

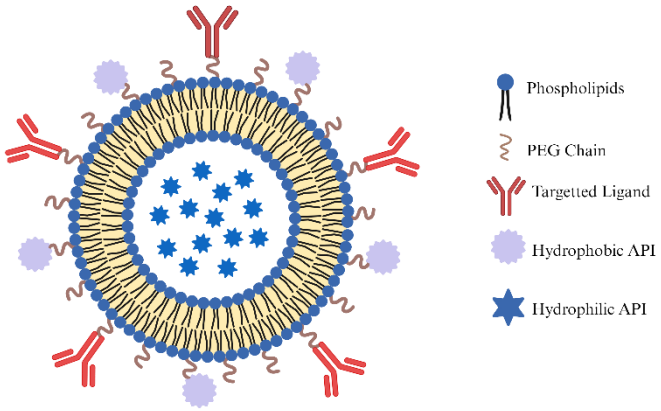

Figure 9. Structure of liposome drug delivery system.

Liposomes increase the efficacy and therapeutic index of a drug (actinomycin-D), increase stability via encapsulation, non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations, reduce the toxicity of the encapsulated agent, help reduce the exposure of sensitive tissues to toxic drugs, site avoidance effect, flexibility to couple with site-specific ligands to achieve active targeting. Disadvantages of liposomes include low solubility, short half-life, sometimes phospholipid undergoes oxidation and hydrolysis-like reactions, leakage and fusion of encapsulated drug/molecules, high production cost, and fewer stables [70,71].

Liposomes (LPs) were prepared using P90G, CHOL, and Tween 80. This compound was selected as a coating agent to increase the formulation's stability, produce "stealth" nanovesicles, and promote endocytosis of the carrier at the level of cerebral endothelial cells. LPs-AG were physically and chemically characterized. The ability of liposomes to increase the permeability of AG was evaluated by artificial membranes (PAMPA) and hCMEC/D3 cells. Based on the obtained results regarding size, homogeneity, ζ-potential, and EE%, LPs-AG optimized liposomal formulations of AG are suitable for parenteral administration. The systems showed excellent chemical and physical stability during a month of storage as suspensions or freeze-dried products. The optimized liposomes enhanced AG's solubility and

cellular permeability, as in vitro tests with PAMPA and hCMEC/D3 cells demonstrated. Both carriers increase the permeation of AG into the cell without alterations in cell viability and monolayer integrity. Positive charge elevated the cellular internalization of liposomes [28].

MCS coating on the liposomal surface was successfully formulated. The in vivo pharmacokinetics study and ex vivo permeation study proved the enhanced permeation of AG through MCS-AGL, thereby enhancing oral bioavailability. The mannosylated chitosan coating (MCS) on nanocarriers is a potential alternative to improve the permeation of lipophilic drugs and facilitate the absorption of liposomes through the intestine, thus improving its bioavailability. The hydroxyl groups on mannose contribute hydrophilicity to the molecule, which may have stealth characteristics when grafted onto nanocarriers to produce mannose-grafted nanocarriers with improved muco permeability. The results suggest the presence of mannose receptors in the intestinal membrane and liver, which attracted the positively charged mannosylated chitosan and increased its absorption [30].

The AG-loaded liposomes were freeze-dried to formulate LDPIs and were suitable for pulmonary delivery in treating pneumonia induced by *Staphylococcus (S.) aureus*. A stronger in vivo anti-S.aureus pneumonic effect of the formulation was found at a tenfold dose, compared with unformulated AG or penicillin. The LDPIs significantly reduced the tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 pro-inflammatory cytokines. Phosphorylation of IjB-a in the nuclear factor-jB pathway was also inhibited to an extraordinary degree [29].

3.8. Niosome.

Niosomes provide a relatively new method that is used as the drug delivery system. The purpose of using niosomes to encapsulate drug compounds is to increase drug bioavailability and improve tissue distribution [72]. Niosomes are formed from the assembly of nonionic amphiphiles in an aqueous medium, resulting in a closed bilayer structure. Niosomes have been prepared from various classes of nonionic surfactants [73]. Cholesterol is generally added to nonionic surfactants, which provide rigidity and orientational order to the niosome bilayer. Niosomes have many advantages, such as better patient compliance and better therapeutic effects than conventional oily formulations, a high ability to entrap hydrophilic, lipophilic, and amphiphilic drugs, and much more stable than liposomes. It can also protect drugs from biological enzymes and deliver targeted drugs to specific organs. Therefore, niosomes are highly effective drug-delivery tools for combining and targeting various therapeutically active agents [74]. Limitation of niosomes may exhibit fusion, leaching, or hydrolysis of the entrapped drug, which limits the shelf life, insufficient drug loading capacity, specialized equipment required for manufacture, leakage of the entrapped drug, physically unstable, time-consuming techniques required for formulation, aggregation, and expensive [75].

Andrographolide niosomes (AG Niosomes) were made using span-60 and cholesterol using film hydration (Figure 10). The prepared liposomes showed drug entrapment efficiency, drug loading, and average particle size of 72.36%, 5.90%, and 206 nm, respectively. Biological activity and tissue distribution studies revealed that niosomes reduced AG elimination and caused more accumulation in the liver compared with free AG, indicating their potential to target the liver. Additionally, niosomes maintained AG's anti-hepatocellular carcinoma (HCC) activity in HepG2 cells. Thus, the current study suggests that AG niosomes may have significant potential in targeting the liver, which makes a major contribution to HCC chemotherapy [31]. Niosomal gel containing AG ethanol extracts exhibited an excellent healing process promoting re-epithelialization activity on Sprague Dawley rats' wounded area.

AG ethanol remained cytocompatible, resulting in a high percentage of wound closure when tested with human skin fibroblast (HSF) cells. Therefore, niosomal gel containing AG ethanol extracts can aid topical application with better drug penetration into the skin layer for effective drug delivery [32].

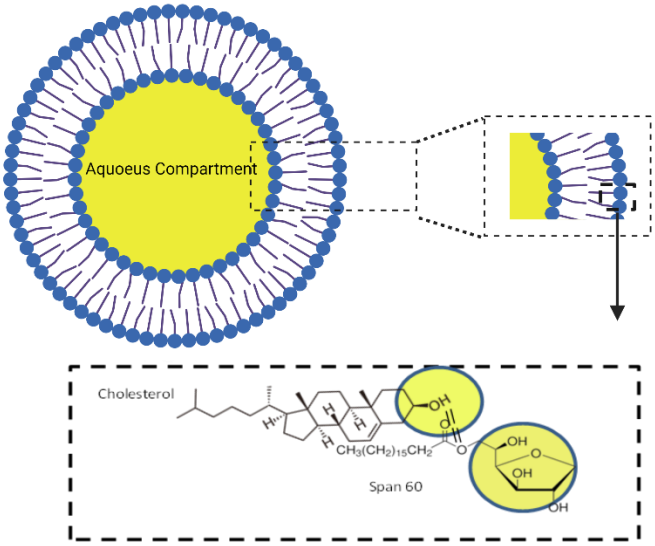

Figure 10. Structure of niosome.

4. Conclusion

Andrographolide (AG) is used as a drug that has many pharmacological activities. However, AG as a natural substance has several outcomes, including poor drug solubility in water and low bioavailability that interferes with the performance of andrographolide in achieving optimal therapeutic activity. Several strategies are carried out by formulating AG in various drug delivery systems, such as solid lipid nanoparticles (SLNs), liposomes, microemulsion (ME), nanoemulsion (NE), microsphere (Ms), polymeric nanoparticles, gold nanoparticles (AuNPs), self micro emulsifying drug delivery system (SMEEDS), and niosome, which can increase the limitations of conventional AG formulation.

Funding

This research received no external funding.

Acknowledgments

The authors would like to thank all parties who have participated in preparing the review of this article.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Chellampillai, B.; Pawar, A.P. Improved bioavailability of orally administered andrographolide from pH-sensitive nanoparticles. *Eur J Drug Metab Pharmacokinet*, **2011**, *35*, 123-9, https://doi.org/10.1007/s13318-010-0016-7.
2. Raina, A.P.; Kumar A.; Pareek, S.K.; Sharma, S.K. Evaluation studies on Kalmegh (*Andrographis paniculata* Nees). *Acta Hort*, **2013**, *972*, 117-120, https://doi.org/10.17660/ActaHortic.2013.972.15.

3. Sharma, S.; Sharma, Y.P.; Bhardwaj, C. HPLC quantification of andrographolide in different parts of *Andrographis paniculata* (Burm.f.) Wall. ex Nees. *Journal of Pharmacognosy and Phytochemistry*, **2018**, *7*, 168-171, https://doi.org/10.21276/ap.2018.7.1.15.
4. Tung, Y.T; Chen, H.L.; Tsai, H.C.; Yang, S.H.; Chang, Y.C.; Chen, C.M. Therapeutic Potential of Andrographolide Isolated from the Leaves of *Andrographis paniculata* Nees for Treating Lung Adenocarcinomas. *Hindawi Publishing Corporation* **2013**, *305898*, 1-8, https://doi.org/10.1155/2013/305898.
5. Shen, Y.C.; C.F. Chen, C.F.; Chiou, W.F. "Andrographolide prevents oxygen radical production by human neutrophils: possible mechanism(s) involved in its anti-inflammatory effect," *British Journal of Pharmacology*, **2002**, *135*, 399–406, https://doi.org/10.1038/sj.bjp.0704493.
6. Ye, L.; Wang, T.; Tang, L.; Liu, W.; Yang, Z.; Zhou, J.; Zheng, Z.; Cai, Z.; Hu, M.; Liu, Z. Poor oral bioavailability of a promising anticancer agent andrographolide is due to extensive metabolism and efflux by P-glycoprotein. *J Pharm Sci*, **2011**, *100*, 7-17, https://doi.org/10.1002/jps.22693.
7. Adiguna, S.P.; Panggabean, J.A.; Atikana, A.; Untari, F., Izzati, F.; Bayu, A.; Rosyidah, A.; Rahmawati, S.I.; Putra, M.Y. Antiviral Activities of Andrographolide and Its Derivatives: Mechanism of Action and Delivery System. *Pharmaceuticals* **2021**, *14*, 1102, https://doi.org/10.3390/ph14111102.
8. Oseni, B.A.; Azubuike, C.P.; Okubanjo, O.O.; Igwilo, C.I.; Panyam, J. Encapsulation of Andrographolide in Poly(lactide-co-glycolide) Nanoparticles: Formulation Optimization and in Vitro Efficacy Studies. *Frontiers in Bioengineering and Biotechnology* **2021**, *9*, https://doi.org/10.3389/fbioe.2021.639409.
9. Pornpitchanarong, C.; Akkaramongkolporn, P.; Nattapulwat, N.; Opanasopit, P.; Patrojanasophon, P. Development and Optimization of *Andrographis paniculata* Extract-Loaded Self-Microemulsifying Drug Delivery System Using Experimental Design Model. *Pharmaceutics* **2024**, *16*, 166, https://doi.org/10.3390/pharmaceutics16020166.
10. Syukri, Y.; Martien, R.; Lukitaningsih, E.; Nugroho, A.E. Novel Self-Nano Emulsifying Drug Delivery System (SNEEDS) of Andrographolide isolated from *Andrographis paniculata* Nees: Characterization, in-vitro and in-vivo assesment. *Journal of Drug Delivery Science and Technology* **2018**, *47*, 514-520, https://doi.org/10.1016/j.jddst.2018.06.014.
11. Li, H.; Qu, X.; Qian, W.; Song, Y.; Wang, C.; Liu, W. Andrographolide-loaded solid lipid nanoparticles enhance anticancer activity against head and neck cancer and precancerous cells. *Oral Diseases*, **2020**, *28*, 142-149, https://doi.org/10.1111/odi.13751.
12. Li, H.; Qu, X.; Qian, W.; Song, Y.; Wang, C.; Liu, W. Andrographolide-loaded solid lipid nanoparticles enhance anticancer activity against head and neck cancer and precancerous cells. *Oral Diseases*, **2020**, *28*, 142-149, https://doi.org/10.1111/odi.13751.
13. Li, H.; Qu, X.; Qian, W.; Song, Y.; Wang, C.; Liu, W. Andrographolide-loaded solid lipid nanoparticles enhance anticancer activity against head and neck cancer and precancerous cells. *Oral Diseases*, **2020**, *28*, 142-149, https://doi.org/10.1111/odi.13751.
14. Badwaik, H.R.; Kumari, L.; Nakhate, K.; Verma, V.S.; Sakure, K. Phytoconstituent plumbagin: Chemical, biotechnological and pharmaceutical aspects. *Studies in natural products chemistry* **2019**, *63*, 415-460, https://doi.org/10.1016/B978-0-12-817901-7.00013-7.
15. Graverini, G.; Piazzini, V.; Landucci, E.; Pantano, D.; et al. Solid lipid nanoparticles for delivery of andrographolide across the blood-brain barrier: in vitro and in vivo evaluation. *Elsevier*, **2018**, *161*, 302-313, https://doi.org/10.1016/j.colsurfb.2017.10.062.
16. Chakraborty, S.; Ehsan, I.; Mukherjee, B.; Mondal, L.; Roy, S.; Saha, K.D.; Paul, B.; Debnath, M.C.; Bera, T. Therapeutic potential of andrographolide-loaded nanoparticles on a murine asthma model. *Nanomedicine* **2019**, *20*, 102006, https://doi.org/10.1016/j.nano.2019.04.009.
17. Ghosh, S.; Dasgupta, S.C.; Dasgupta, A.K.; Gomes, A.; Gomes A. Gold Nanoparticles (AuNPs) Conjugated with Andrographolide Ameliorated Viper (*Daboia russellii* russellii) Venom-Induced Toxicities in Animal Model. *Journal of Nanoscience and Nanotechnology* **2020**, *20*, 3404-3414, https://doi.org/10.1166/jnn.2020.17421.
18. Babu, P.J.; Saranya, S.; Sharma, S.; Tamuli, R.; & Bora, U.. Gold nanoparticles: sonocatalytic synthesis using ethanolic extract of *Andrographis paniculata* and functionalization with polycaprolactone–gelatin composites. *Front. Mater. Sci.* **2012**, *6*, 236–249, https://doi.org/10.1007/s11706-012-0175-3.
19. Razalli, N.; Gopinath, S.C.; Kasim, F.H.; Yaakub, A.R.W.; Anbu, P. Antimicrobial Potential of *Andrographis paniculata* Conjugated Gold Nanoparticles. *INNOSC Theranostics and Pharmacological Sciences* **2019**, *2*, 19-24, https://doi.org/10.26689/itps.v2i1.744.

20. Sermkaew, N.; Ketjinda, W.; Boonme, P.; Padoongsombat, N.; Wiwattanapatapee, R. Liquid and solid self-microemulsifying drug delivery systems for improving the oral bioavailability of andrographolide from a crude extract of *Andrographis paniculata*, *European Journal of Pharmaceutical Sciences* **2013**, *50*, 459, https://doi.org/10.1016/j.ejps.2013.08.006.
21. Pornpitchanarong, C.; Akkaramongkolporn, P.; Nattapulwat, N.; Opanasopit, P.; Patrojanasophon, P. Development and Optimization of *Andrographis paniculata* Extract-Loaded Self-Microemulsifying Drug Delivery System Using Experimental Design Model. *Pharmaceutics* **2024**, *16*, 166, https://doi.org/10.3390/pharmaceutics16020166.
22. Hazra, M.; Mandal, D.D.; Mandal, T.; Rao, B.P.; Samaddar. Optimization and characterization of hepatoprotective andrographolide microspheres in the necrotic rat model. *Journal of Drug Delivery Science and Technology* **2021**, *65*, https://doi.org/10.1016/j.jddst.2021.102679.
23. Jiang, Y.; Wang, F.; Xu, H.; Liu, H.; Meng, Q.; Liu, W. Development of andrographolide loaded PLGA microspheres: Optimization, characterization and *in vitro–in vivo* correlation. *International Journal of Pharmaceutics* **2014**, *475*, 475-484, https://doi.org/10.1016/j.ijpharm.2014.09.016.
24. Du, H.; Yang, X.; Li, H.; Han, L.; Li, X.; et.al. Preparation and Evaluation of Andrographolide-loaded Emulsion. *Journal Microencapsul*, **2012**, *29*, 657-665, https://doi.org/10.3109/02652048.2012.680508.
25. Yan, L.X.; Xin, N.; Jin, F.Q.; Zhi, Y.X.; Wei, W.D.; Tong, Z.; Lei, L.; Hong, D. A New Biocompatible Microemulsion Increases Extraction Yield and Bioavailability of *Andrographis paniculata*. *Chinese Journal of Natural Medicines* **2016**, *14*, 683-691, https://doi.org/10.1016/S1875-5364(16)30081-4.
26. Asasutjarit, R.; Sooksai, N.; Fristiohady, A.; Lairungruang, K.; Ng, S.F.; Fuongfuchat, A. Optimization of Production Parameters for Andrographolide-Loaded Nanoemulsion Preparation by Microfluidization and Evaluations of Its Bioactivities in Skin Cancer Cells and UVB Radiation-Exposed Skin. *Pharmaceutics* **2021**, *13*, 1290, https://doi.org/10.3390/pharmaceutics13081290.
27. Zou, L.; Ding, W.; Huang, Q.; Yang, X.; Li, J.; Huang, T.; Li, Z.; Lin, S.; Feng, J. Andrographolide/Phospholipid/Cyclodextrin Complex-Loaded Nanoemulsion: Preparation, Optimization, in Vitro and in Vivo Evaluation. *Biol. Pharm. Bull*. **2022**, *45*, 1106–1115, https://doi.org/10.1248/bpb.b22-00154.
28. Piazzini, V.; Landucci, E.; Graverini, G.; Giampietro, D.E.P.; Bilia, A.R.; Bergonzi, M.C. Stealth and Cationic Nanoliposomes as Drug Delivery Systems to Increase Andrographolide BBB Permeability. *Pharmaceutics* **2018**, *10*, 128, https://doi.org/10.3390/pharmaceutics10030128.
29. Li, M.; Zhang, T.; Zhu, L.; Wang, R.; Jin, Y. Liposomal Andrographolide Dry Powder Inhalers for Treatment of Bacterial Pneumonia via Anti-inflammatory Pathway. *International Journal of Pharmaceutics* **2017**, *528*, 163-171, https://doi.org/10.1016/j.ijpharm.2017.06.005.
30. Metkar, S.P.; Fernandes, G.; Nikam, A.N.; Soman, S.; Birangal, S.; Seetharam, R.N.; Joshi, M.B.; Mutalik, S. Mannosylated-Chitosan-Coated Andrographolide Nanoliposomes for The Treatment of Hepatitis: In Vitro and In Vivo Evaluations. *Membranes* **2023**, *13*, 193, https://doi.org/10.3390/membranes13020193.
31. Tu, S.Y.; Sun, D.M.; Zhang, J.J.; Jiang, Z.Q.; Chen, Y.X.; Zeng, H.; Huang, D.E.; Yao, N. Preparation and characterisation of andrographolide niosomes and its anti-hepatocellular carcinoma activity. *Journal of Microencapsulation* **2014**, *31*, 307-316, https://doi.org/10.3109/02652048.2013.843727.
32. Jamaludin, R.; Daud, N.M.; Sulong, R.S.R.; Yaakob, H.; Aziz, A.A.; Khamis, S.; Salleh L.M. *Andrographis paniculata*-loaded niosome for wound healing application: Characterisation and in vivo analyses. *Journal of Drug Delivery System and Technology* **2021**, *63*, 102427, https://doi.org/10.1016/j.jddst.2021.102427.
33. Bothiraja, C.; Pawar, A.; Munde, P.; Shaikh, K. Preparation, Optimization and In-Vitro Evaluation of Andrographolide Loaded Floating Cavilink™ Beads for Phytotherapy. *Nanosci. Nanotechnol. Lett*. **2012**, *4*, 445, https://doi.org/10.1166/nnl.2012.1337.
34. Mandal, D.D.; Mandal, T.; Hazra, M. Strategic Approach in Hepatic Delivery of Andrographolide: Key Challenges and New Insights. *Journal of Herbal Medicine*, **2020**, *24*, https://doi.org/10.1016/j.hermed.2020.100411.
35. Su, C.; Liu, Y.; Li, R.; Wu, W.; Fawcett, J.P.; Gu, J. Absorption, Distribution, Metabolism and Excertion of The Biomaterials Used in Nanocarrier Drug Delivery Systems. *Advanced Drug Delivery Reviews*, **2019**, *143*, 97-114, https://doi.org/10.1016/j.addr.2019.06.008.
36. Duan, Y.; Dhar, A.; Patel, C.; Khimani, M.; Neogi, S.; Sharma, P.; Siva K.N.; Vekariya, R.L. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC Adv*, **2020**, *10*, 26777–26791, https://doi.org/10.1039/D0RA03491F.

37. Ghasemiyeh, P.; Mohammadi-Samani, S. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as Novel Drug Delivery System: Application, Advantages and Disadvantages. *Research in Pharmaceutical Science* **2018**, *13*, 288-303, https://doi.org/10.4103/1735-5362.235156.
38. Wang X.; Chen H.; Luo Z.; Fu X. Preparation of starch nanoparticles in water in oil microemulsion system and their drug delivery properties. *Carbohydr Polym.* **2016**, *138*, 192–200, https://doi.org/10.1016/j.carbpol.2015.11.006.
39. Yoon G.; Park JW.; Yoon IS. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. *J. Pharm. Investig.* **2013**, *43*, 353–362, https://doi.org/10.1007/s40005-013-0087-y.
40. Makwana V.; Jain R.; Patel K.; Nivsarkar M.; Joshi A. Solid lipid nanoparticles (SLN) of Efavirenz as lymph targeting drug delivery system: Elucidation of mechanism of uptake using chylomicron flow blocking approach. *Int. J. Pharm.* **2015**, *495*, 439–446, https://doi.org/10.1016/j.ijpharm.2015.09.014.
41. Yadav, H.K.S.; Almokdad, A.A.; shaluf, S.I.M.; Debe, M.S. Chapter 17 - Polymer-Based Nanomaterials for Drug-Delivery Carriers. In Nanocarriers for Drug Delivery, Mohapatra, S.S., Ranjan, S., Dasgupta, N., Mishra, R.K., Thomas, S., Eds.; Elsevier: **2019**; pp. 531-556, https://doi.org/10.1016/B978-0-12-814033-8.00017-5.
42. Diaz, M.R.; Mejia, P.E.V. Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing Nanoliposomes. *Pharmaceuticals*, **2013**, *6*, 1361-1380, https://doi.org/10.3390/ph6111361.
43. Badwaik, H.R.; Kumari, L.; Nakhate, K.; Verma, V.S.; Sakure, K. Phytoconstituent plumbagin: Chemical, biotechnological and pharmaceutical aspects. *Studies in natural products chemistry* **2019**, *63*, 415-460, https://doi.org/10.1016/B978-0-12-817901-7.00013-7.
44. Zielinska, A.; Carreiro, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Durrazo, A.; et al. Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. *Molecules* **2020**, *25*, 3731, https://doi.org/10.3390/molecules25163731.
45. Oseni, B.A.; Azubuike, C.P.; Okubanjo, O.O.; Igwilo, C.I.; Panyam, J. Encapsulation of Andrographolide in Poly(lactide-co-glycolide) Nanoparticles: Formulation Optimization and in Vitro Efficacy Studies. *Frontiers in Bioengineering and Biotechnology* **2021**, *9*, https://doi.org/10.3389/fbioe.2021.639409.
46. Scioli, M.S.; Muraca, G.; Ruiz, M.E. Solid Lipid Nanoparticles for Drug Delivery: Pharmacological and Biopharmaceutical Aspects. *Front. Mol. Biosci*, **2020**, *7*, 319, https://doi.org/10.3389/fmolb.2020.587997.
47. Yeh, Y.C.; Creran, B.; Rotello, V.M. Gold nanoparticles: preparation, properties, and applications in bionanotechnology. *Nanoscale* **2012**, *4*, 1871–1880, https://doi.org/10.1039/C1NR11188D.
48. Lee, K.X.; Shameli, K.; Yew, Y.P.; Teow, S.Y.; Jahangirian, H.; Moghaddam, R.R.; Webster, T.J. Recent Developments in the Facile Bio-Synthesis of Gold Nanoparticles (AuNPs) and Their Biomedical Applications. *International Journal of Nanomedicine* **2020**, *15*, 275-300, https://doi.org/10.2147/IJN.S233789.
49. Mikhailova, E. Gold Nanoparticles: Biosynthesis and Potential of Biomedical Application. *Journal of Functional Biomaterials* **2021**, *12*, 70, https://doi.org/10.3390/jfb12040070.
50. Khan, M. Y.; Roy, M. Synthesis, limitation and application of gold nanoparticles in treatment of cancerous cell. *International Journal of Scientific Research in Multidisciplinary Studies* **2019**, *5*, 8-14, http://dx.doi.org/10.26438/ijsrms.
51. Hassan, H.; Sharma, P.; Hasan, M. R.; Singh, S.; Thakur, D.; Narang, J. Gold nanomaterials–The golden approach from synthesis to applications. *Materials Science for Energy Technologies* **2022**, *5*, 375-390, https://doi.org/10.1016/j.mset.2022.09.004.
52. Rani, S.; Rana, R.; Saraogi, G.K.; Kumar, V.; & Gupta, U. Self-Emulsifying Oral Lipid Drug Delivery Systems: Advances and Challenges. *AAPS PharmSciTech* **2019**, *20*, 129, https://doi.org/10.1208/s12249-019-1335-x.
53. Gursoy, R.N.; Benita, S. Self-emulsifying drug delivery systems (SEDDS) for improved oral bioavailability of lipophilic drugs. *Biomed. Pharmacother* **2004**, *58*, 173-182, https://doi.org/10.1016/j.biopha.2004.02.001.
54. Cui, J.; Yu, B.; Zhao, Y.; Zhu, W.; Li, H.; Lou, H.; Zhai, G. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. *Int. J. Pharm.* **2009**, *371*, 148-155, https://doi.org/10.1016/j.ijpharm.2008.12.009.
55. Anand, S.; Gupta, R.; Prajapati, S. K. Self-micro emulsifying drug delivery system. *Asian J. Pharm. Clin. Res*. **2016**, *9*, 33-38, https://doi.org/10.22159/ajpcr.2016.v9s2.13180.
56. Dokania, S.; Joshi, A. K. Self-microemulsifying drug delivery system (SMEDDS)-challenges and road ahead. *Drug delivery* **2015**, *22*, 675-690, https://doi.org/10.3109/10717544.2014.896058.

57. Ohta, S.; Nitta, N.; Sonoda, A.; Seko, A.; Tanaka, T.; Takahashi, M.; Kimura, Y.; Tabata, Y.; Murata, K. Cisplatin-conjugated degradable gelatin microspheres: Fundamental study in vitro. *Br. J. Radiol*. **2009**, *82*, 380–385, https://doi.org/10.1259/bjr/27737783.
58. Nitta, N.; Ohta, S.; Tanaka, T.; Takazakura, R.; Toyama, T.; Sonoda, A.; Seko, A.; Furukawa, A.; Takahashi, M.; Murata, K.; Kurumi, Y.; Tani, T.; Sakamoto, T.; Tabata, Y. An initial clinical study on the efficacy of cisplatin-releasing gelatin microspheres for metastatic liver tumors. *Eur. J. Radiol.* **2009**, *71*, 519–526, https://doi.org/10.1016/j.ejrad.2008.06.006.
59. Toyama, T.; Nitta, N.; Ohta, S.; Tanaka, T.; Nagatani, Y.; Takahashi, M.; Murata, K.; Shiomi, H.; Naka, S.; Kurumi, Y.; et al. Clinical trial of cisplatin-conjugated gelatin microspheres for patients with hepatocellular carcinoma. *Jpn. J. Radiol*. **2012**, *30*, 62–68, https://doi.org/10.1007/s11604-011-0010-2.
60. Eghbal, N.; Liao, W.; Dumas, E.; Azabau, S.; Dantigny, P.; Gharsallaoui, A. Microencapsulation of Natural Food Antimicrobials: Methods and Applications. *Applied Science* **2022**, *12*, 3837, https://doi.org/10.3390/app12083837.
61. Gavali, K. V.; Kengar, M. D.; Chavan, K. V.; Anekar, V. P.; Khan, N. I. A Review on Microsphere and it's Application. *Asian Journal of Pharmaceutical Research* **2019**, *9*, 123-129, https://doi.org/10.5958/2231-5691.2019.00020.0.
62. Das, M. K.; Ahmed, A. B.; Saha, D. Microsphere a drug delivery system: A review. *Int. J. Curr. Pharm. Res.* **2019**, *11*, 34-41, https://doi.org/10.22159/ijcpr.2019v11i4.34941.
63. Casamonti, M.; Risaliti, L.; Vanti, G.; Piazzini, V.; Bergonzi, M.C.; Bilia, A.R. Andrographolide Loaded in Micro- and Nano-Formulations: Improved Bioavailability, Target-Tissue Distribution, and Efficacy of the ‘‘King of Bitters”. *Engineering* **2019**, *5*, 69-75, https://doi.org/10.1016/j.eng.2018.12.004.
64. Gibaud, S.; Attivi, D. Microemulsions for oral administration and their therapeutic applications. *Expert Opin. Drug Deliv* **2012**, *9*, 937–951, https://doi.org/10.1517/17425247.2012.694865.
65. Spernath, A.; Aserin, A. Microemulsions as carriers for drugs and nutraceuticals. *Adv. Colloid Interface Sci*, **2006**, *128–130*, 47–64, https://doi.org/10.1016/j.cis.2006.11.016.
66. Kale, S. N.; Deore, S. L. Emulsion micro emulsion and nano emulsion: a review. *Systematic Reviews in Pharmacy* **2017**, *8*, 39, https://doi.org/10.5530/srp.2017.1.8.
67. El-masry, J.F.; Hamdan, K.FB.; Abbas, A.H.; Martyushev, D.A. Comprehensive Review on Utilizing Nanomaterials in Enhanced Oil Recovery Applications. *Energies* **2023**, *16*, 691, https://doi.org/10.3390/en16020691.
68. Ojha, B.; Jain, V. K.; Gupta, S.; Talegaonkar, S.; Jain, K. Nanoemulgel: A promising novel formulation for treatment of skin ailments. *Polymer Bulletin* **2022**, *79*, 4441-4465, https://doi.org/10.1007/s00289-021-03729-3.
69. Liu, P.; Chen, G.; Zhang, J. Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives. *Molecules* **2022**, *27*, 1372, https://doi.org/10.3390/molecules27041372.
70. Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S., Joo, S. W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: classification, preparation, and applications. *Nanoscale research letters* **2013**, *8*, 102. https://doi.org/10.1186/1556-276X-8-102.
71. Maja, L.; Željko, K.; Mateja, P. Sustainable technologies for liposome preparation. *The Journal of Supercritical Fluids* **2020**, *165*, 104984, https://doi.org/10.1016/j.supflu.2020.104984.
72. Moghassemi, S.; Hadjizadeh, A. Nano-niosomes as nanoscale drug delivery systems: An illustrated review. *J. Control*. **2014**, *185*, 22–36, https://doi.org/10.1016/j.jconrel.2014.04.015.
73. Nguyen, V.H.; Pham, H.N. Current Nanocarriers in Therapeutic Improvement of Andrographolide. *Vietnam Journal of Sciences, Technology, and Engineering* **2022**, *64*, 62-68, https://doi.org/10.31276/VJSTE.64(3).62-68.
74. Rajera, R.; Nagpal, K.; Singh, S.K.; Mishra, D.N. Niosomes: A controlled and novel drug delivery system. *Biol Pharm Bull* **2011**, *34*, 945–53, https://doi.org/10.1248/bpb.34.945.
75. Mehrarya, M.; Gharehchelou, B.; Haghighi Poodeh, S.; Jamshidifar, E.; Karimifard, S.; Farasati Far, B.; Seifalian, A. Niosomal formulation for antibacterial applications. *Journal of Drug Targeting* **2022**, *30*, 476-493, https://doi.org/10.1080/1061186X.2022.2032094.
76. Umbarkar, M.G. Niosome as a Novel Pharmaceutical Drug Delivery: A Brief Review Highlighting Formulation, Types, Composition and Application. *Indian Journal of Pharmaceutical Education and Research* **2021**, *55*, https://doi.org/10.5530/ijper.55.1s.34.