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REVIEW

Lipid-Based Nanocarriers for Curcumin Delivery: A Promising Strategy in The Management of Inflammatory Diseases

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Abstract: Inflammation is a key pathophysiological process underlying a broad spectrum of chronic disorders, including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, neurodegenerative diseases, and metabolic syndrome, and is closely linked to oxidative stress, immune dysregulation, and sustained production of pro-inflammatory mediators. Curcumin, a bioactive polyphenol derived from *Curcuma longa*, has been extensively studied because of its pleiotropic anti-inflammatory mechanisms, however, its therapeutic translation is substantially limited by poor aqueous solubility, chemical instability, rapid metabolism, and low systemic bioavailability. In this context, lipid-based nanocarriers, notably liposomes, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes, ethosomes, niosomes, nanoemulsions, self-nano-emulsifying drug delivery systems (SNEDDS), transfersomes, lipid nanocapsules, lipid micelles, spanlastic, and cubesomes, have emerged as promising formulation strategies to improve curcumin delivery. These platforms can enhance the solubility, stability, absorption, and pharmacokinetic performance of curcumin and, in selected cases, facilitate more efficient accumulation at inflamed sites. This review critically appraises recent advances in lipid-based nanocarrier systems for curcumin delivery in inflammatory diseases and addresses the principal formulation, translational, and clinical challenges that remain to be resolved.

Keywords: phytosome, SLN, psoriasis, alzheimer

Introduction

Inflammatory conditions have emerged as significant global health issues, affecting millions of people worldwide and playing a critical role in illness and death rates. Chronic systemic inflammation is implicated in leading causes of death, including cardiovascular disease, cancer, diabetes, chronic kidney disease, and neurodegenerative disorders, which together account for more than 50% of global mortality.[1] In addition, immune-mediated inflammatory diseases (IMIDs), such as asthma, atopic dermatitis, inflammatory bowel disease, multiple sclerosis, psoriasis, and rheumatoid arthritis, contribute significantly to global disability-adjusted life years (DALYs), with notable regional variations in incidence and disease burden.[2,3] Specific inflammatory conditions further illustrate this growing burden. For instance, inflammatory bowel disease affects approximately 3.8–4.9 million people worldwide, with the highest prevalence in high-income regions such as North America and Europe, while rapidly increasing in newly industrialized areas.[2,3] Rheumatoid arthritis affects an estimated 17.8 million individuals globally and is projected to reach 31.7 million by 2050, with disability accounting for the majority of its burden.[4] Moreover, periodontal disease, a chronic inflammatory condition, affects over one billion people worldwide and has been associated with systemic complications, including cardiovascular disease, diabetes, adverse pregnancy outcomes, and neurodegenerative disorders.[5]

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Inflammation is a crucial protective mechanism that protects the body from infections, tissue injury, and other harmful factors. Although acute inflammation is vital for repairing and healing tissues, when it becomes chronic, it is closely linked to the onset of numerous health problems, such as heart diseases, metabolic diseases, neurodegenerative illnesses, and autoimmune diseases.[6] Several factors can lead to this state of inflammation, including aging, smoking, poor diet, obesity, stress, hormonal imbalances, and disrupted sleep patterns. The process of Aging is associated with a decline in immune function, which hampers the body's ability to eliminate pathogens and fosters a pro-inflammatory environment, whereas mitochondrial dysfunction leads to an increase in reactive oxygen species production (ROS).[7] Cigarette smoke contains numerous harmful chemicals and reactive oxygen species that can damage airway cells and initiate inflammatory pathways.[8] Unhealthy eating habits, especially diets high in saturated fats and refined sugars, but low in fiber, disrupt the gut microbiota, resulting in increased intestinal permeability and toxin release. This can trigger immune responses and increase the levels of pro-inflammatory cytokines.[9] Psychological stress activates the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to overproduction of cortisol and catecholamines. This imbalance fosters glucocorticoid resistance and promotes the release of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, which maintain chronic inflammation.[10] Additionally, lifestyle-related factors, such as obesity, exacerbate long-term inflammation by creating an imbalance in adipokines and activating immune cells, eventually leading to insulin resistance and metabolic diseases.[11]

Given the significant role of inflammation in the development of these diseases, anti-inflammatory medications have attracted considerable interest.[12] Among the natural substances, curcumin, the main active ingredient in *Curcuma longa*, has demonstrated extensive therapeutic promise because of its ability to reduce inflammation by influencing several molecular targets and signaling pathways. Curcumin inhibits the activation of NF-κB, lowers the levels of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and hampers the production of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Through these actions, curcumin can significantly reduce inflammation.[13] Despite its wide-ranging therapeutic capabilities, curcumin encounters significant challenges, such as limited solubility in water, instability in chemical composition, rapid metabolism in the intestines and liver, and low systemic availability, even at high dosages.[14]

To overcome these challenges, various formulation techniques have been investigated, with lipid-based nanocarriers being one of the most promising methods.[15] To clarify the scope of this review, we have specifically focused on selected inflammatory disease settings in which curcumin-loaded lipid based-nanocarriers have been investigated: inflammatory skin disorders, joint inflammation, pulmonary inflammation, neuroinflammatory conditions, gastrointestinal inflammation, and liver fibrosis. The discussion primarily emphasizes preclinical evidence, particularly in vitro and in vivo studies, while clinical findings are considered only when available, as the translational evidence for these systems remains limited. Lipid-based carriers, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes, and ethosomes, were chosen as the main analytical lens because they are particularly well suited to address the major biopharmaceutical limitations of curcumin, such as poor aqueous solubility, low stability, rapid metabolism, and limited bioavailability, while also offering advantages in encapsulation efficiency, tissue penetration, controlled release, and site-oriented delivery. Accordingly, this review does not attempt to cover all inflammatory diseases or all nanocarrier platforms, but rather provides a focused critical overview of representative lipid-based systems for improving curcumin delivery in selected inflammatory disease models.

Inflammation and Its Role in Human Diseases

Inflammation is a natural and essential biological response that activates both immune and non-immune cells to defend the body against infection, toxins, and tissue damage. Its main purpose is to restore normal tissue function. However, when this process fails to resolve properly, it can become harmful, leading to chronic inflammation, fibrosis, and tissue dysfunction.[16] Acute inflammation is an immediate and highly regulated response to tissue injury or infection. It involves the activation of immune cells, the release of inflammatory mediators, and various mechanisms designed to eliminate harmful agents and initiate tissue repair. This phase includes processes such as neutrophil recruitment, production of cytokines and chemokines, and eventual resolution of inflammation through neutrophil apoptosis and macrophage polarization, all of which work together to promote healing and restore balance.[17] In contrast, chronic inflammation is a prolonged and dysregulated immune response

that fails to resolve, causing continuous tissue damage and disease progression. This persistent inflammatory state often underlies the development of numerous chronic conditions, including rheumatoid arthritis, osteoarthritis, cardiovascular diseases, inflammatory bowel disease, and neurodegenerative disorders.[18]

Inflammation process is tightly regulated by biochemical substances known as inflammatory mediators. These include vasoactive amines and peptides such as histamine, serotonin, and bradykinin, which increase vascular permeability and promote vasodilation resulting in redness, swelling, and pain. Other important mediators are eicosanoids, derived from arachidonic acid, such as prostaglandins, thromboxanes, and leukotrienes, which help control vascular tone, platelet aggregation, and recruitment of immune cells. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) play major roles in driving systemic effects, such as fever and acute-phase responses. Additionally, acute-phase proteins produced by the liver, including C-reactive protein (CRP), fibrinogen, and serum amyloid A, contribute to immune regulation and tissue repair.[19]

In the initial stages of inflammation, neutrophils adhere tightly to endothelial cells via carbohydrate-based ligands. When endothelial cells are activated, they express various membrane-bound and soluble adhesion molecules that reinforce this attachment. These interactions enable neutrophils to leave the bloodstream and migrate across the endothelial barrier to the site of tissue injury. This movement is directed by cell adhesion molecules (CAMs), their activators, and chemotactic signals that precisely guide neutrophils to damaged tissue.[20] At the tissue level, inflammation results in increased blood flow, enhanced vascular permeability, and infiltration of white blood cells, along with the release of numerous inflammatory mediators.[21] These mediators stimulate the production of key pro-inflammatory cytokines such as TNF, IL-1, IL-6, and various chemokines, which further amplify the inflammatory response and may contribute to tissue injury. Once neutrophils complete their functions, they undergo programmed cell death (apoptosis) and are cleared by phagocytes. This clearance triggers the release of anti-inflammatory cytokines, guiding the tissue toward resolution and restoring homeostasis.[22,23]

Curcumin as an Anti-Inflammatory Agent

Curcumin (Cur), known as 1,7-bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane,[24] is a naturally occurring polyphenolic compound derived from the rhizome of turmeric (*Curcuma longa*), a plant belonging to the *Zingiberaceae* family. It has garnered significant scientific interest owing to its diverse pharmacological properties.[25] Over the past few decades, numerous studies have highlighted the broad therapeutic potential of curcumin, including its anti-inflammatory, antioxidant, antimicrobial, antiviral, and neuroprotective properties.[26] These wide-ranging biological activities have made curcumin one of the most extensively researched natural compounds given its potential role in the management of chronic inflammatory diseases.[27]

Curcumin inhibits the synthesis of inflammatory mediators and controls inflammatory signaling pathways to exert anti-inflammatory effects. Curcumin binds to toll-like receptors (TLRs) and modifies downstream nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases (MAPK), activator protein 1 (AP-1), and other signaling pathways to regulate the inflammatory mediators and treat inflammatory diseases. Curcumin downregulates NF-κB[28,29] by acting on peroxisome proliferator-activated receptor gamma (PPARγ). Curcumin can also exert anti-inflammatory effects by regulating the Janus kinase/signal transducer and activator of transcription (JAK/STAT) inflammatory signaling pathway.[30] Furthermore, many inflammatory diseases are related to the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, a cytosolic multiprotein complex. A sensor protein, an apoptosis-associated speck-like protein with a caspase recruitment domain, and a protease caspase-1 form the NLRP3 complex. Curcumin may be used to treat inflammatory illnesses by either directly preventing the assembly of NLRP3 inflammasome from assembling or by blocking the NF-κB pathway, which prevents the activation of NLRP3 inflammasome.[31] Curcumin reduces pro-inflammatory mediators, including interleukin-1 (IL-1), IL-1β, IL-6, IL-8, IL-17, IL-27, tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), NO, granulocyte colony-stimulating factor (G-CSF), and monocyte chemotactic protein-1 (MCP-1), and regulates the activation of normal T cell expressed and secreted factors (RANTES).[32–35]

The regulatory effect of curcumin on immune cells is useful for the treatment of inflammatory disorders.[36] Curcumin mainly acts on dendritic cells, T helper 17 cells, and T regulatory cells. Th17 cells are crucial pro-inflammatory cells that stimulate the inflammatory response by producing IL-17, IL-22, and IL-23. Treg cells suppress inflammatory responses,

and abnormal immune responses resulting in inflammation can be caused by changes in the quantity and function of Th17 and Treg cells. Therefore, maintaining the Th17/Treg balance is advantageous for the maintenance of immunological homeostasis and the treatment of inflammatory disorders.[37] Curcumin inhibits Th17 differentiation, and regulates Treg/Th17 imbalance by inhibiting the IL-23/Th17 pathway.[38] By utilizing lipid-based nanocarriers, the extensive pharmacological benefits of curcumin can be maximized. As summarized in Table 1, incorporating curcumin into lipid-based nanocarriers significantly enhances the therapeutic potential of curcumin across various inflammatory disease models. Compared with free curcumin, these nanocarrier systems improve drug stability, prolong drug retention at the target site, and enhance cellular uptake. Consequently, they more effectively suppress inflammatory mediators such as TNF-α, IL-6, and IL-1β, while promoting tissue repair and reducing oxidative stress.

Lipid-Based Nanocarriers for Curcumin Delivery

In this review, the term lipid-based nanocarriers is used as an umbrella category for the lipid-containing delivery systems investigated for curcumin, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes, ethosomes, niosomes, nanoemulsions, self-nano-emulsifying drug delivery systems (SNEDDS), transfersomes, lipid nanocapsules, lipid micelles, spanlastic, and cubesomes. Within this framework, the term lipid nanoparticles is used more specifically for matrix-type systems composed of a solid or partially solid lipid core, particularly SLNs and NLCs, and is not used interchangeably with vesicular carriers such as liposomes and ethosomes or with phospholipid-complex systems such as phytosomes. This distinction is important because these platforms differ in structural organization, drug incorporation mechanisms, release behavior, and biological performance, even though they all belong to the broader family of lipid-based nanocarriers relevant to curcumin delivery.[83]

Structurally, Lipid-based Nanocarriers (LBNs) often display non-spherical shapes because of the interactions between the polar or ionized phospholipid head groups and the solvent, as well as the hydrophobic behavior of the lipid chains.[84] Depending on their design, such as liposomal bilayers or solid lipid cores, these nanocarriers demonstrate excellent compatibility with biological systems, making them ideal for pharmaceutical use.[85] Typically, they are composed of uniform lipid bilayers or solid matrices that can encapsulate hydrophilic and lipophilic molecules. Water-soluble compounds are stored in aqueous regions, whereas fat-soluble compounds, such as curcumin, are integrated into the lipid layers. This dual capability allows LBNs to safely transport different types of molecules to the target sites, provide sustained release, and biodegrade naturally after drug delivery.[86]

Advances in nanotechnology have greatly expanded the possibilities for improving curcumin delivery.[87] Various nanocarrier systems, including protein-, polysaccharide-, and hybrid protein-polysaccharide-based systems, have been explored. However, lipid-based nanocarriers remain the most extensively researched and effective platforms for curcumin encapsulation.[88] LBNs include several formulations such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, phytosomes, and ethosomes (Figure 1). Among these, lipid systems are particularly advantageous for hydrophobic compounds such as curcumin, as they enhance both bioavailability and stability by efficiently integrating into lipid matrices.[88]

Before discussing individual carrier classes, it is important to outline the principal physicochemical attributes used to characterize lipid-based nanocarriers for curcumin delivery. These attributes commonly include particle size and size distribution, zeta potential, morphology, drug loading, entrapment efficiency, and colloidal stability. However, the relevance and interpretation of these parameters are platform-dependent and should be considered in relation to the carrier architecture, because vesicular systems and matrix-type lipid nanoparticles do not share identical structural features or performance criteria. The particle size plays a major role in influencing the nanocarriers stability, biodistribution, cellular uptake, and therapeutic performance.[89] Generally, smaller LBNs (< 100 nm) demonstrate better cellular uptake and longer circulation times, whereas larger particles (> 100 nm) can load more drug but are less efficiently absorbed by cells.[90] The most common and reliable method for determining the particle size is Dynamic Light Scattering (DLS), which provides an apparent hydrodynamic diameter.[91,92]

However, it is crucial to recognize that Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Atomic Force Microscopy (AFM) provide complementary, not interchangeable, views of nanostructures. While DLS reports a hydrodynamic, intensity-weighted size that includes the particle plus

Table 1 Therapeutic Effects of Curcumin-Loaded Lipid-Based Nanocarriers in Inflammatory Diseases

Inflammation in Organs	Diseases	Study	Dosage	Administration Route	Result	Reference
Skin	Psoriasis	In vitro	SLN were applied to cells at 0.5, 1, and 5 μg/mL		↓ Hyperproliferation and death of keratinocytes in psoriatic lesions ↓ The production of pro-inflammatory cytokines IL-23, IL-6, and IL-8, ↓ Lipid peroxidation markers such as MDA.	[39]
	Atopic Dermatitis	In vitro	0.5–5 μg/mL		↓ Pro-inflammatory cytokines (IL-23, IL-6, IL-8) ↓ Ferroptosis marker (TFRC, MDA)	[40]
	Psoriasis	In vivo (Psoriasis mice model)	10 mg/kg of IBR and 20 mg/kg of CUR	Topical	↓ Epidermal hyperplasia, ↓ Inflammatory cytokines (IL-17, IL-22, and TNF-α) ↓ Lesions due to psoriasis involving acanthosis	[41]
	Psoriasis	In vivo (Psoriasis mice model)	NR	Topical	↓ Inflammatory markers (TNF-alpha, IL-6, IL-22, and IL-23) Psoriasis severity score lower than the IMQ control group. ↓ In psoriasis-like lesions Restoration of normal skin structure.	[42]
	Psoriasis	In vitro	250 mg of CUR-NLC		Sustained release up to 24 hours Suitable pH Good spreadability	[43]
		Ex vivo (Rat abdominal skin)	1.0 g of nanogel	Topical	High retention in epidermis (750.67 ± 0.65 μg/cm²) Deliver curcumin efficiently into the skin and maintain localized therapeutic levels	
	Psoriasis	In vitro	NR		↑Curcumin penetration across the skin in vitro Stable encapsulation and prolonged drug availability.a	[44]
		In vivo	0.3 mL of the formulations containing 0.1% (w/v) (Psoriasis mouse model)	Topical	↓ TNF-α, IL-17A, IL-17F, IL-22, and IL-1β mRNA levels ↓ CCR6 protein expression	
	Ear inflammation	In vivo (Ear inflammation female mice model)	1 mL 1% curcumin	Per oral	↑ Inhibiton of mice ear edema	[45]
	Tinea capitis	Clinical (Human with tinea capitis)	1.25 mg/g NSV-Cur gel	Topical	↓ In scaling and erythema ↑ In clinical score (TSSS ↓ significantly) Hair regrowth	[46]
	Acne vulgaris	In vitro	NR		Sustained release (48 h) ↑ Solubility and stability vs free drugs	[47]
		In vivo (Acne induced rat model)	1 g nanogel	Topical	↓ Epidermal hypertrophy ↓ Inflammatory cell infiltration ↓ Skin congestion	

(*Continued*)

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Table 1 (Continued).

Inflammation in Organs	Diseases	Study	Dosage	Administration Route	Result	Reference
Joint	Rheumatoid Arthritis	In vivo	NR	Per oral	↓ Paw swelling ↓ Inflammatory markers Improvement in phytosomes-treated animal group with no signs of arthritis	[48]
	Rheumatoid arthritis	In vitro	NR		Controlled drug release	[49]
		In vivo	100 μL CUR-NLC smart gel (2.5% w/v CUR) (Arthritis rat model)	Intra-articular	↓ Knee inflammation and swelling Provided sustained retention in the joint cavity Restored near-normal synovial histology ↑ Therapeutic efficacy and prolonged anti-inflammatory effect	
	Rheumatoid arthritis	In vivo (Arthritis mice model)	100 μL liposome suspension	Intravena	↓ Joint swelling and severity scores ↑ Antigen-specific FoxP3^{+} regulatory T cells (Treg) ↓ T cell proliferation ↓ IL-2, TNF and IFN-γ ↑ IL-10	[50]
	Osteoarthritis	In vitro	7-70 μM		↑ OPG/RANKL (indicative of inhibited osteoclast activity and reduced bone resorption) ↓ The production of pro-inflammatory mediators (COX-2 and MMP-3) induced by IL-1β in osteoblastic cells. ↓ Osteoclastogenic activity by inhibiting RANKL	[51]
	Arthritis	In vivo (Arthritis rat model)	1.75 mg/kg Cur LCN	Intraperitoneal	↑ The antioedematogenic activity ↓ Cartilage and bone damage ↓ Inflammatory cell infiltration	[52]
	Rheumatoid arthritis	In vitro	NR		Better in vitro skin penetration than plain curcumin.	[53]
		In vivo (CFA-induced rheumatoid arthritis model)	NR	Topical	↑ Clinical, histological and x-ray scores ↓ Pro-inflammatory cytokines through NF-κβ inhibition	
	Rheumatoid arthritis	In vitro	10 mL		Provide sustained drug release Have stable, uniform nanosized vesicles Show good compatibility	[54]
		In vivo (CFA-induced rheumatoid arthritis rat model)	4 mg	Topical	↓ Paw swelling reduced ↓ Pro-inflammatory cytokines ↑ Histological structure ↑ Radiological (bone/joint) condition Safe and non-irritant for topical use	

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Lung	Chronic obstructive pulmonary disease	In vitro	2.5 μM for liposomal curcumin		↓ Markers of cellular senescence (X-gal, p16) ↓ Inflammatory cytokines (osteopontin, FGF, uPAR) Maintaining cell viability	[55]
	Asthma	In vitro	1 μg/mL and 5 μg/mL of curcumin-loaded liposomes		↓ Pro-inflammatory cytokines IL-6, IL-8, IL-1β, and TNF-α Strong anti-inflammatory activity, suggesting potential as an adjuvant or alternative to corticosteroids for asthma therapy.	[56]
	Asthma	In vitro	5 mg of curcumin-SLNs		Effectively prolong the circulation time of curcumin, potentially enhancing its therapeutic efficacy	[57]
		In vivo (OVA-induced allergic asthma rat model)	400 mg/kg curcumin-SLNs	Intraperitoneal	↓ Airway hyperresponsiveness ↓ inflammatory cell infiltration ↓ Th2 cytokines (IL-4, IL-13)	
	Asthma	In vitro	5 μM Cur-RH60/F127-MMs		↓ IL-10, IL-6, and NO expression	[58]
		In vivo (Asthma mice model)	20 mg/kg Cur-RH60/F127-MMs	Per oral	↓ The expression of eosinophils ↓ Monocytes, lymphocytes, and granulocytes ↓ IgE levels Improved Th1/Th2 balance	
	Respiratory Syncytial Virus (RSV) Infection	In vivo (RSV mice model)	NR	NR	↓ Immune cell influx into lungs ↓ MIP-1α ↓ TNF-α ↓ IFN-γ	[59]

(*Continued*)

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Table 1 (Continued).

Inflammation in Organs	Diseases	Study	Dosage	Administration Route	Result	Reference
Nerve	Alzheimer	In vitro	Liposomal miR-101: 12.5 × 10^18 molecules/L + Curcumin: 0.7 g/L (added at 1:50 ratio)		The strongest and longest suppression of Aβ42 (~67% reduction up to 12 hours, max at 6 hours) ↓ TNF-α and IL-6 ↑ IL-10 levels	[60]
	Alzheimer	In vivo (Alzheimer mice model)	150 mg/kg SLNs-CUR	Intraperitoneal	↑ Cognitive performance and memory (step-down avoidance test) ↑ TG2-L (repair isoform) ↓ TG2-S (apoptotic isoform) ↑ Bcl-2 (anti-apoptotic) ↓ caspase-3 cleavage (apoptosis marker)	[61]
	Alzheimer	In vitro	8 μM and 20 μM		↓ Oxidative stress in SH-SY5Y cells ↓ Cells apoptosis	[62]
		In vivo (Zebrafish embryo model)	NR	Waterborne exposed/ immersion	Effective delivery without adverse developmental effects	
	Alzheimer	In vitro	50–200 μg/mL.		↑ Neuronal viability ↓ Reduced $A\beta_{1-42}$-induced toxicity ↓Aβ aggregation.	[63]
	Alzheimer	In vitro	NR		Show high affinity for amyloid deposits Inhibit Aβ aggregation ↑ Uptake across BBB models	[64]

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	Alzheimer	In vitro	20 μg/mL nanoliposomes for labeling		No cytotoxicity after 24 hours at 20 μg/mL CnLs. ↓ Aβ-induced cell death in cultured SH-SY5Y cells ↓ Aβ levels Strongly labeled Aβ plaques in human AD brain tissue.	[65]
		In vivo (Alzheimer mice model)	2 μL of 100 μg/mL CnLs suspension	Intraserebral / intracranial injection (stereotactic)	Strongly target and label Aβ plaques and successfully co-localized with Aβ deposits along the injection sites, confirming their specific binding capability within the brain tissue	
	Epilepsy	In vivo (Epilepsy mice model)	25 and 50 mg/kg liposomal curcumin	Per oral	↑ Seizure protection in all mouse models tested Delayed the onset of seizures ↓ The duration of seizures Strong anticonvulsant activity.	[66]
	Alzheimer	In vivo ($AlCl_3$-induced Alzheimer's disease-like mice model)	50, 25, 12.5 and 1 mg/kg C-SLNs	Per oral	↑ Neuroprotective and therapeutic effect in the aluminium-induced mouse model of Alzheimer's disease, outperforming free curcumin at similar doses Showing improvement on histopathology of the brain sections	[67]
	Alzheimer	In vitro	NR		The planar-curcumin liposomes howed very strong affinity for amyloid-beta (Aβ1-42) fibrils and supporting the potential for targeting Aβ fibrils in Alzheimer's disease	[68]
	Alzheimer	In vivo (Alzheimer animal model)	NR	Per oral	Significant dose-dependent therapeutic efficacy in an Alzheimer's disease animal model Outperforming the untreated group and demonstrating comparable effectiveness to the standard drug (donepezil).	[69]
	Alzheimer	In vivo (Malzheimer mice model)	10 mg/kg LNC	Per oral	↑ TNF-α ↑ IL-1β ↑ IL-6 ↑ IFN-γ Improved cognition Significantly inhibited NF-κB	[70]
	Alzheimer	In vivo (Alzheimer mice model)	10 mg/kg Curcumin + Meloxicam 5 mg/kg	Per oral	↓ COX-2 levels ↑ Cognitive impairment ↑ Long-term memory	[71]
	Alzheimer	In vivo (Alzheimer rat model)	20 mg/kg	Intraperitoneal	↓ NF-κB ↓ Brain damage ↑ Memory & cognition	[72]

(*Continued*)

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Table 1 (Continued).

Inflammation in Organs	Diseases	Study	Dosage	Administration Route	Result	Reference
Gastrointestinal	Ulcerative colitis	In vivo (Ulcerative colitis mice model)	NR	Per oral	↓ Clinical symptoms such as weight loss, diarrhea, and fecal bleeding) Prevent colon tissue damage and shortening ↓ Inflammatory biomarkers (MDA, MPO, IL-6, TNFα).	[73]
	Ulcerative colitis (inflammatory bowel disease)	In vitro	20 mg/kg C-SBLNs		↑ Cellular uptake and preferential localization in inflamed tissues compared to free curcumin Sustained drug release for up to 24 hours	[74]
		In vivo (Ulcerative colitis guinea pigs model)	15 mg/kg C-SBLNs	Per oral	↓ Leukocyte infiltration ↓ TNF-α ↓ Oxidative stress Better preservation of colonic structure, similar to healthy animals	
	Ulcerative colitis	In vitro			↑ Solubility ↑ Release ↑ Permeability (28.9× higher) ↑ Antioxidant activity	[75]
		In vivo (Ulcerative colitis mice model)	50, 100, 150 mg/kg RA-Cur	Per oral	↓ Inflammation in ulcerative colitis Shows dose-dependent therapeutic effect Effectively reverses colon damage	
	Inflammatory Bowel Disease	In vitro	20 μg/mL		↓ TNF- secretion	[76]
		In vivo (Ulcerative colitis mice model)	15 mg/kg/day	Per oral	↓ Neutrophil infiltration ↓ TNF- secretion ↓ Colonic inflammation	
	Inflammatory Bowel Disease	In vitro	NR		↓ TNF-α ↓ IL-6 ↓ nitric oxide (NO) High cell viability at all tested concentrations	[77]
Liver	Hepatic fibrosis	In vitro	10 μM per drug for most cell assays (MTT, uptake, migration) and 1 μg/mL per drug for the apoptosis assay		↓ Fibrotic markers α-SMA, Col1a1, and Col3a1 compared to free drugs ↑ Anti-fibrotic effect than each drug alone.	[78]
	Hepatic fibrosis	In vivo (Liver fibrosis in a rat model)	15 mg/kg	Intraperitoneal	↓ Liver enzyme markers (ALT, AST, ALP, T-Bil) ↓ Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). ↑ Cur-mNLCs improved hepatocyte growth factor (HGF) and MMP-2 expression, ↓ Collagen I and α-SMA Showed superior anti-fibrotic and hepatoprotective activity compared with Cur-NLCs and free Cur.	[79]

	Drug Induced Liver Injury (DILI)	In vitro			Higher and faster release Follows Higuchi diffusion model	[80]
		In vivo (Hepatotoxicity induced male rat)	25 mg/kg	Per oral	↓ ALT, AST, and TNF-α Nearly normal liver structure	
Bone	Osteomyelitis	In vitro	NR		Showed good stability and controlled release Suitable for localized drug delivery Has potential application in osteomyelitis	[81]
Ocular	Eye inflammation	In vitro	NR		Sustained release over 24 hours	[82]
		In vivo	50 µL per dose	Eye drops	Faster healing (4 days) Comparable as an anti-inflammatory effect with lower side effects (no IOP increase)	

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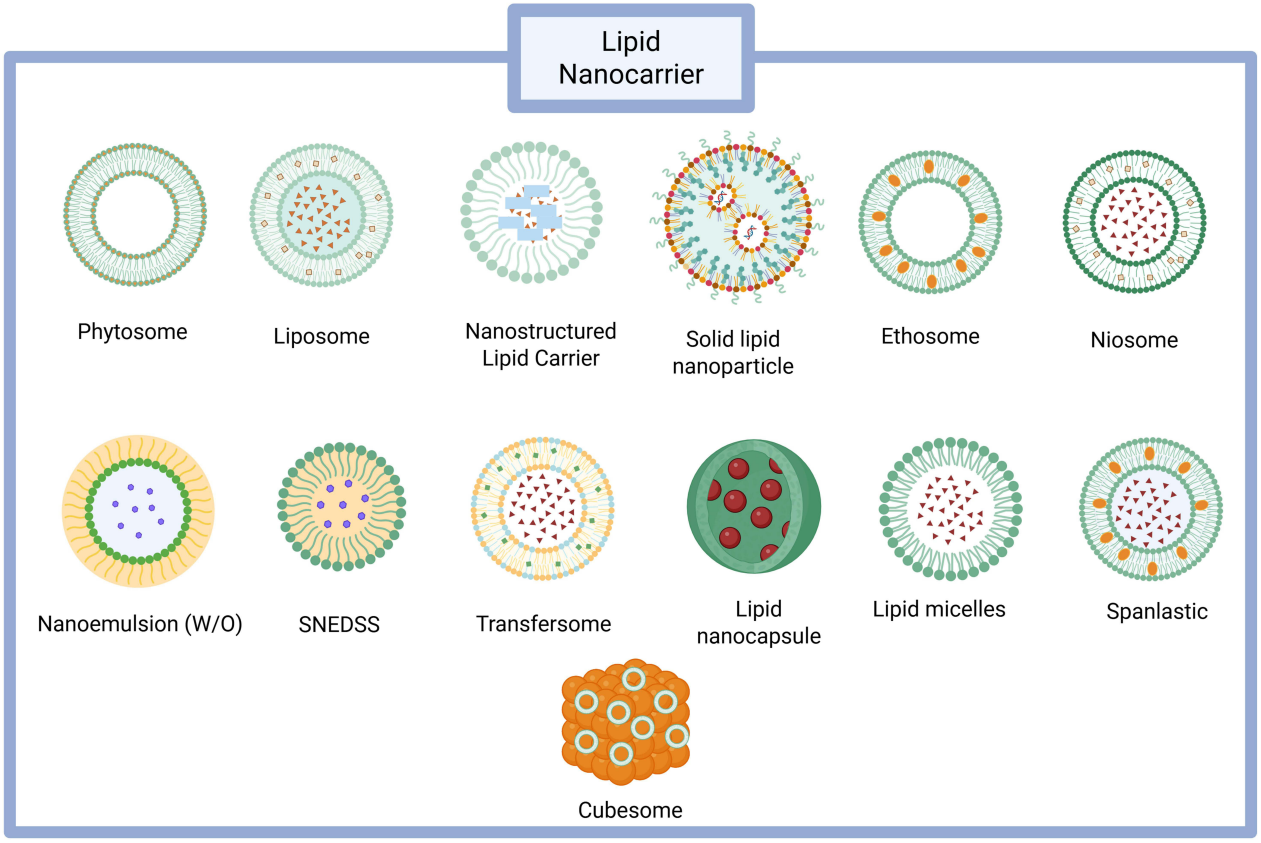

Figure 1 Types of lipid nanocarrier commonly used in drug delivery.

its solvation layer and any soft corona, microscopy techniques (TEM, SEM, and AFM) resolve the core size and morphology after particle deposition. Because the scattering intensity scales with the sixth power of the particle radius, DLS is strongly affected by aggregation and polydispersity, as the signal is dominated by larger particles.[92] In contrast, TEM and SEM provide high-resolution images of individual particle cores and their aggregation state on a substrate.[93,94] AFM further offers insights into surface topography and height, although it is less routine for size in dispersion. Therefore, the orthogonal use of both scattering and imaging techniques is highly recommended for the accurate characterization of nanomedicines.[73]

The surface charge of LBNs, expressed as the zeta potential, is another critical factor in determining their stability.[95] A higher positive or negative zeta potential signifies strong electrostatic repulsion between the particles, which helps maintain a stable suspension. Conversely, when the zeta potential was near zero, the repulsion weakened, leading to particle aggregation and eventual instability.[96] For curcumin nanocarriers, the pH-dependent charge and isoelectric point (pI) of the carrier materials govern colloidal stability, which in turn controls the physicochemical behavior, stability, and bioavailability of curcumin in biological media. Curcumin often becomes deprotonated and negatively charged at alkaline pH, interacting electrostatically with charged proteins or polymers to form more compact or aggregated structures depending on the charge balance.[93,97] Studies on various curcumin carriers, such as protein–polysaccharide complexes and liposomes, demonstrate that controlling pH relative to the carrier pI is essential to protect curcumin against degradation and enhance its bioaccessibility in simulated gastrointestinal or biological media.[94,98,99]

Surface morphology, examined using TEM, SEM, and AFM, provides further insights into the structure and texture of the nanocarriers.[100] Generally, a smooth and uniform surface improves stability, whereas rough or irregular textures can increase interactions with biomolecules, potentially altering biodistribution and reducing therapeutic efficiency.[101] Besides physical characteristics like size and morphology, the key parameters for optimizing LBN-based drug delivery

systems are stability, loading capacity, and entrapment efficiency. Stability refers to the ability of nanocarriers to retain their physical and chemical characteristics, such as size, shape, and lipid integrity under various conditions or during storage.[102] The loading capacity measures the total amount of drug encapsulated, whereas the entrapment efficiency reflects how effectively the drug remains within the nanocarriers after formulation.[89] Both are essential for ensuring consistent therapeutic outcomes and reliable formulation performance.

Despite the promising therapeutic potential of lipid-based nanocarriers, their clinical translation is significantly hindered by the critical challenge of sterilization. Common sterilization methods often prove problematic for these nanostructures due to their inherent physicochemical sensitivity.

Heat sterilization, such as autoclaving or moist heat, can trigger lipid melting, phase transitions, aggregation, drug leakage, and overall degradation of liposomes and other lipid-based nanocarriers.[103,104] While specific solid lipid nanoparticles or nanocapsules might tolerate carefully optimized high-temperature cycles depending on their formulation and stabilizers, this remains highly case-specific.[105,106] Sterile filtration (0.22 μm), although widely recommended, may be ineffective or result in significant material loss when the particle size approaches the filter pore size (≥200 nm), leading to membrane clogging and low drug recovery.[107] Furthermore, the structural integrity of these carriers is often sensitive to shear stress or interactions with the membrane, potentially causing size alterations or component loss.[108–110] Radiation techniques (γ, β, or UV) are also restricted where ionizing radiation can induce lipid oxidation, chain scission, and the formation of reactive oxygen species (ROS), leading to changes in particle size, zeta potential, and biological activity.[107,110] Although some NLCs may tolerate specific low doses of radiation, the effects are strictly formulation- and dose-dependent.[108] Finally, chemical or gas methods, such as ethylene oxide, are generally unsuitable due to concerns regarding toxic residues.[111] Collectively, these sterilization constraints directly impact the actual viability and scalability of lipid-based systems for biomedical applications.

Liposomes

Liposomes are lipid-based vesicles that self-assemble and are primarily composed of phospholipids. They can form many concentric bilayers (multilamellar) or a single bilayer (unilamellar), encasing an aqueous core that can contain pharmaceuticals or biomolecules.[112] Each phospholipid bilayer has a thickness of approximately 4–5 nm, and its size can vary greatly from 30 nm to the micrometer scale.[113] Alec D. Bangham and his associates at Babraham, Cambridge, first proposed the idea of liposomes in the mid-1960s, and the first structural model was released in 1964.[114,115] Since then, liposomes have emerged as one of the most researched and adaptable nanocarrier systems for the delivery of numerous therapeutic agents including proteins, nucleic acids, small chemicals, and imaging compounds.[116,117] To enhance their therapeutic efficacy, many delivery methods have been investigated, including parenteral, pulmonary, oral, transdermal, ocular, and nasal delivery.[118,119] Structurally, liposomes are spherical vesicles that develop independently when phospholipids are distributed in water. They self-assemble because they are amphiphilic. The creation of bilayer structure is driven by the hydrophilic (polar) head and hydrophobic (nonpolar) tail of each phospholipid molecule.[120] The hydrophobic tail is composed of long fatty acid chains with variable degrees of unsaturation, usually 10–24 carbon atoms in length, whereas the polar head commonly comprises phosphoric acid bound to an alcohol. Phospholipids align to form lamellar sheets that curve and close into stable spherical vesicles when subjected to water and energy inputs such sonication, heating, or homogenization.[121] These structures are thermodynamically stable through balanced interactions between lipids and water.[122] Owing to their bilayer structure, liposomes can include lipophilic substances, such as curcumin in the lipid membrane and hydrophilic medications in the aqueous core.[123,124] Biocompatible lipids, such as cholesterol, glycolipids, sphingolipids, long-chain fatty acids, and membrane proteins, are commonly found in liposomes and contribute to their stability and structural integrity.[123] Consequently, they can effectively prolong the circulation half-life of encapsulated medications, prevent enzymatic and oxidative degradation, and permit controlled or sustained release.[125] Additionally, owing to their flexibility, a variety of medicinal compounds, including peptides, antibiotics, enzymes, hormones, and other biomolecules, can be encapsulated.[124]

Several studies have demonstrated the therapeutic potential of liposomal systems. For instance, Jain et al investigated a topical liposomal gel co-loading ibrutinib and curcumin for psoriasis treatment. The optimized formulation exhibited a particle size of 128.53 ± 1.18 nm with a PDI of 0.174 ± 0.08, indicating a uniform and stable dispersion, along with high

entrapment efficiency (83.15 ± 1.91% for ibrutinib and 86.69 ± 3.80% for curcumin). In an in vivo imiquimod-induced psoriasis model, this formulation significantly reduced epidermal hyperplasia, ear thickness, and psoriasis severity index, as well as suppressed inflammatory cytokines and acanthosis, demonstrating enhanced skin permeation and localized anti-inflammatory effects.[41] Similarly, Wang et al evaluated curcumin-loaded liposomes (CUR-LPs), which exhibited a particle size of 167 nm, zeta potential of −34 mV, and a low PDI of 0.09, indicating high stability and uniformity. These systems demonstrated good resistance in simulated gastric fluid and a slower rate of degradation in simulated intestinal fluid. In a dextran sulfate sodium (DSS)-induced ulcerative colitis model, CUR-LPs significantly reduced clinical symptoms such as weight loss, diarrhea, and fecal bleeding, while also decreasing inflammatory and oxidative stress markers, including MDA, MPO, IL-6, and TNF-α. These findings highlight the potential of liposomes for colon-targeted delivery and anti-inflammatory therapy.[73]

Based on the studies summarized in Tables 1 and 2, liposomes exhibit broad applicability across inflammatory diseases, with Alzheimer's disease being the most frequently studied condition. As the most established and FDA-approved lipid nanocarriers, liposomes possess a distinct clinical advantage over other lipid systems that remain largely in the preclinical stage, particularly due to their well-documented safety profile and low immunogenicity derived from their cell-membrane-like phospholipid bilayers.[126,127] In addition, liposomal systems have been successfully applied in conditions such as osteoarthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriasis, and ulcerative colitis, highlighting their versatility in targeting both systemic and localized inflammation. Most formulations utilize curcumin as a model hydrophobic compound, however, liposomes have also been employed to deliver a wide range of therapeutic agents, including small molecules such as ibrutinib and cyclopamine, nucleic acids including miRNA, as well as essential biomolecules such as cardiolipin and nerve growth factor. This unique structural configuration, featuring both an aqueous core and a lipid bilayer, allows for the simultaneous loading of hydrophilic and hydrophobic compounds, a level of dual-delivery efficiency that many matrix-type lipid particles cannot achieve.[127] This demonstrates their ability to encapsulate diverse drug types and support combination therapies. Across different disease models, liposomal formulations consistently exhibit anti-inflammatory and immunomodulatory effects, as evidenced by the reduction of pro-inflammatory cytokines including TNF-α, IL-6, IL-17, inhibition of pathological processes such as amyloid-β aggregation, and modulation of immune responses, including increased IL-10 levels and regulatory T cell activity. In neurodegenerative models, liposomes further demonstrate the ability to cross the blood–brain barrier (BBB), improve neuronal viability, and reduce neurotoxicity. Physicochemical analysis across the included studies indicates that liposomes typically exhibit particle sizes in the range of 80–200 nm with high entrapment efficiency, generally ranging from 70% to 90%. These parameters are critical as they directly support formulation stability, drug loading capacity, and enhanced cellular uptake. Moreover, the structural flexibility of liposomes facilitates multiple routes of administration including oral, intravenous, topical, and intracranial delivery, enabling both systemic and targeted therapeutic effects across diverse inflammatory models.

Solid Lipid Nanoparticles (SLNs)

Müller and Lucks first presented solid lipid nanoparticles (SLNs) in the early 1990s as a substitute for traditional colloidal carriers such as emulsions, liposomes, and polymeric nanoparticles.[129] SLNs are often composed of physiologically appropriate solid lipids distributed in an aqueous phase and stabilized by surfactants or co-surfactants. Triglycerides, steroids, and fatty acids often comprise the lipid phase of SLNs. These substances remain solid at room and body temperatures, creating a stable core that permits regulated and prolonged drug release.[130]

The development of SLNs is largely driven by the limitations associated with conventional drug delivery systems, including low solubility, high metabolic rate, and systemic toxicity.[131] By modifying drug release and distribution, SLNs offer the potential for site-specific delivery and enhanced bioavailability, particularly for poorly soluble and labile drugs. SLNs combine the benefits of different colloidal carriers while minimizing certain drawbacks. However, their performance is often formulation-dependent. While SLNs provide improved drug stability and the capability to encapsulate both hydrophilic and lipophilic pharmaceuticals, their drug loading capacity can be limited by lipid crystallization during storage, a challenge that led to the subsequent development of NLCs. Nevertheless, SLNs remain highly regarded due to their biocompatibility, ease of scale-up, and cost-effectiveness.[132–136]

Table 2 Formulation and Characterization of Curcumin-Loaded Lipid-Based Nanocarriers

Lipid Nanocarrier	Drug	Base Composition	Characterization	Result	Reference
Liposomes	Curcumin	Phosphatidylcholine	NR	↑ Therapeutic effects compared to free curcumin	[55]
	Curcumin + miR-101	Phospholipids and cholesterol	NR	Liposomal miR-101 + CUR combination demonstrates synergistic effects Showed a delayed or less pronounced effect.	[60]
	Curcumin + Ibrutinib	Glyceryl monostearate Capryol PGMC Pluronic F-127 Carbopol 940	Particle size = 128.53 ± 1.18 nm Zeta potential = NR PDI = 0.174 ± 0.08 EE (%) = 83.15 ± 1.91% (Ibrutinib) and 86.69 ± 3.80% (Curcumin)	Controlled drug release Uniform and stable dispersion Strong synergistic interaction between the two drugs	[41]
	Curcumin	Liposomes composed of anionic phospholipids forming pseudo-pH-sensitive nanoparticles	Particle size = 167 nm Zeta potential = −34 mV PDI = 0.09 EE (%) = NR	Provided colon-specific delivery Prolonged curcumin release ↑ Stability, and significantly reduced inflammation and oxidative stress	[73]
	Curcumin + Cyclopamine	Lipoid S100 Cholesterol mPEG2000-DSPE	Particle size = 80–120 nm Zeta potential = 6.93 ± 1.4 mV PDI = 0.204 ± 0.002 EE (%) = 99.59 ± 0.06 (Curcumin) and 74.07 ± 0.41 (Cyclopamine)	Stable nanosystem with high drug loading Sustained and controlled release profile ↑ cellular uptake compared to free drugs Showed the strongest inhibition of HSC-T6 cell migration and invasion.	[78]
	Curcumin	Soy lecithin Cholesterol Tween 80	Particle size = 271.3 ± 3.06 nm Zeta potential = −61.0 mV PDI = NR EE = 81.1%	Stable High-encapsulation formulation that shows strong anti-inflammatory activity	[56]
	Curcumin + Cardiolipin + Nerve growth factor (NGF)	Cholesterol DPPC (1,2-Dipalmitoyl-sn-glycero-3-phosphocholine)	Particle size= 110–170 nm Zeta potential = −5 mV to −15 mV PDI = NR EE (%) = −14.73 ± 0.42%	Showed good biocompatibility in HBMECs, HAs, HBVPs, and SK-N-MC cells with no significant toxicity. Enhanced NGF and CUR transport across the HBMEC/HA BBB model, with controlled and sustained release. Stable nanoparticles suitable for BBB penetration	[63]

(*Continued*)

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Table 2 (Continued).

Lipid Nanocarrier	Drug	Base Composition	Characterization	Result	Reference
	Curcumin	Egg phosphatidylcholine (EPC)	Particle size = NR Zeta potential = NR PDI = NR EE (%) = 80–90% (Curcumin and quercetin)	No toxicity or apoptosis caused by the liposomes Strong inhibition of NF-κB activation, and enhanced induction of FoxP3 regulatory T cells. ↑ Entrapment efficiency	[50]
	Curcumin + Bisdemethoxycurcumin (BDMC)	Soybean phosphatidylcholine (SPC)	Particle size = 95–120 nm Zeta potential = NR PDI = NR EE (%) = 69.5% (Curcumin) and 71.4% (BDMC)	↑ Drug safety, stability and bioavailability, (high entrapment efficiency and stable particle size over time) ↑ Intracellular delivery	[51]
	Curcumin	DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) DSPE-PEG2000-CURC (Lipid–PEG–Curcumin conjugate) Cholesterol	NR	↑ Uptake by BBB transport systems	[64]
	Curcumin	DPPC (1,2-dipalmitoyl-sn-glycerol-3-phosphatidylcholine) Cholesterol DPS Curcumin (curcumin phospholipid conjugate)	Particle size = 207.2± 8.0 nm Zeta potential = −10.5 ± 1.2 mV PDI = 0.255 EE (%) = NR	Stable, non-toxic, neuroprotective, and reduces Aβ secretion.	[65]
	Curcumin	Lecithin Glycerin	NR	↑ Bioavailability and anticonvulsant activity in mice models, effectively crossing the blood brain barrier	[66]
	Curcumin	Phospholipid and DODAP (1,2-dioleoyl-3-dimethylammonium-propane)	Particle size= <200 nm Zeta potential = NR PDI= 0.2 EE (%) = 93.60 ±4.26	↑ Curcumin stability and neuroprotective effects Successfully deliver curcumin into cells and potentially across the BBB	[54]
	Curcumin	DPPC (1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine) DPPG (1,2-dipalmitoyl-sn-glycero-3-phosphatidylglycerol) Cholesterol	Particle size = 131–207 nm Zeta potential = NR PDI = NR EE (%) = NR	Effectively enhances their binding affinity and stability	[68]

Solid Lipid Nanoparticles	Curcumin	Glyceryl monostearate, PEG-40 stearate, Linolenic acid	NR	↑ The delivery and effectiveness of curcumin	[39]
	Curcumin + α-linolenic acid (LNA)	Curcumin monooleate Resveratrol monooleate Capsaicin oleates	NR	Excellent stability Controlled and sustained release	[40]
	Curcumin	Compritol 888 ATO (glyceryl behenate), Lutrol F68 (poloxamer 188), soy lecithin, DSPE-PEG2000	Particle size = 150–180 nm Zeta Potential= −29 to −24 mV PDI = 0.26 EE (%) = NR	Suitable for parenteral administration Good stability	[61]
	Curcumin	Lipid matrix: Stearic acid; Surfactant: Poloxamer 188 (1% w/v); prepared by hot homogenization and ultrasonication.	Particle size = 164.2 ± 5.6 nm Zeta potential = −26.3 ± 1.2 mV PDI = 0.211 ± 0.017 EE (%) = 82.6 ± 2.3%	Stable nanosystem with sustained drug release (80% at 48 h) ↑ Cellular uptake	[74]
	Curcumin	Lecithin Tween 80 Stearic acid	Particle size = 190 nm Zeta potential = −20.7 mV PDI = NR EE (%) = 75%	↑ The systemic bioavailability Prolongs its retention in the bloodstream Improves its efficacy for therapeutic applications	[57]
	Curcumin	Soy lecithin Tween 80 Compritol 888 ATO (Glyceryl behenate)	Particle size = 134.6 ± 15.4 nm Zeta potential = NR PDI = NR EE (%) = 81.92 ± 2.91%	↑ Increase in bioavailability ↑ Permeability across the blood-brain barrier (BBB) More effective therapeutic outcomes	[67]

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Table 2 (Continued).

Lipid Nanocarrier	Drug	Base Composition	Characterization	Result	Reference
Nanostructured Lipid Carriers	Curcumin + Ibrutinib	Capryol PGMC Glyceryl Mono Stearate Pluronics-F-127	Particle size = 95.12 ± 3.39 nm Zeta potential = NR PDI = 0.285 ± 0.009 EE (%) = 86.04 ± 2.86% (IBR) and 87.25 ± 2.14% (Curcumin)	Improved drug flux (permeation) compared to the plain drug gel Better skin penetration capability.	[42]
	Curcumin	Cetyl palmitate Labrafac PG Captex 200 Tween 80 Labrasol	Particle size = 165.12 nm Zeta potential = −21.67 mV PDI = 0.49 EE (%) = 72.15%	Excellent stability Easily injectable formulation with sustained release and excellent biocompatibility	[49]
	Curcumin	Precirol ATO 5 Capmul MCM C8 Tween 80	Particle size = 189.4 ± 2.6 nm Zeta potential = −21.45 ± 1.3 mV PDI = 0.262 ± 0.24 EE (%) = 58.15–86.25%	Stable formulation Sustained release	[43]
	Curcumin	Soybean phosphatidylcholine PS (phosphatidylserine; 1,2-diacyl-sn-glycero-3-phospho-L-serine) Cholesterol Cholesteryl oleate Trioleate glycerolerine	Particle size= 204.6±1.97 nm Zeta potential= −46.29 ± 0.48 mV PDI = 0.067±0.002 EE (%) = 89.06 ± 0.47%	↑ Liver targeting and bioavailability. Prolonged mean residence time and higher AUC ↑ Anti-inflammatory and anti-fibrotic efficacy compared to non-modified Cur-NLCs and free Cur.	[79]
	Curcumin	Precirol® ATO 5 (glyceryl distearate) Miglyol® 812N/F Tween 80 Kolliphor® P188	Particle size= 280 ± 8 nm Zeta potential = −10.6 mV ± 0.3 PDI = 0.40 EE (%) = 95 ± 3%	Stable and homogeneous NLCs with high drug entrapment Localized inside Caco-2 cells, indicating strong interaction with the epithelial barrier.	[76]
Phytosomes	Curcumin + Leflunomide	Phospholipid Cholesterol	Particle size= 760 nm Zeta potential= −55.7 mV PDI = NR EE (%) = >98%	High entrapment Sustained release profile	[48]
Ethosomes	Curcumin	HSPC (Hydrogenated Soybean Phosphatidylcholine) DOPE (Dioleoyl Phosphoethanolamine) DSPE-PEG2000 Cholesterol	Particle size= 181.3 ± 2.6 nm Zeta potential= −43.2 ± 1.1 mV PDI= 0.212 ± 0.03 EE (%) = 82.6 ± 2.8%.	↑ Penetration, skin retention and better stability	[44]
Nanoemulsion	Curcumin	Medium Chain Triglycerides (MCT) Tween 20 Water	Particle size = 79.5–618.6 nm Zeta potential = NR PDI = 0.249–0.369 EE (%) = NR	Good stability for 7 days ↑ The bioavailability of curcumin and improved its anti-inflammatory activity	[45]

SNEDDS	Curcumin	Isopropyl mysristate Labrasol Cremophor RH 40 Transcutol P	Particle size = 32–405 nm Zeta potential = −15.12 ± 0.44 mV to −18.12 ± 0.36 mV PDI = 0.104 ± 0.006 to 0.228 ± 0.024 EE (%) = 93.11–99.12%	↑ Curcumin solubility, stability, and dissolution rate	[128]
	Curcumin + Piperin	NR	NR	↑ The bioavailability of curcumin	[69]
	Curcumin + Mesalamine	Capmul MCM Tween 80 Transcutol P	Particle size = 137.54 ± 1.58 nm Zeta potential = −17.25 ± 2.83 mV PDI = 0.286 ± 1.41 EE (%) = 86.38 ± 2.18% (Mesalamine) and 79.63 ± 1.93% (Curcumin)	Stability in physical and chemical properties after 3 months Safe (non-toxic) Faster dissolution Effective as localised oral medication	[77]
Cubosome	Curcumin	Glyceryl monooleate Pluronic F-127 Ethanol Water	Particle size = 186.27 nm Zeta potential = −17.5 mV PDI = NR EE (%) = 71.24%	Showed good rheological properties, release characteristics and stability studies	[81]
Lipid miccelles	Curcumin	Span 80 Cremophor Tween 80 Ethanol Water	Particle size = 168.6 ± 19.2 nm Zeta potential = − 42.2 ± 7.2 mV PDI = NR EE (%) = 85% ± 6.3	Showed moderate efficacy, good safety and stability but still less effective than standard oral therapy	[46]
	Curcumin + Rebaudioside	Ethanol	Particle size = 4.186±0.231 nm Zeta potential = 0.194±0.013 mV PDI = −1.873±0.494 EE (%) = 99.43%±0.67%	Improved permeability and antioxidant activity Good long-term stability (25:1 ratio) Better encapsulation and prevention of crystallization ↑ Drug release	[75]
	Curcumin	Cremophor Pluronic F127	Particle size =11.23 ± 0.62 nm Zeta potential = −7.62 ± 0.13 mV PDI = 0.153 ± 0.007 EE (%) = 89.43%	↑ The permeability of Cur into the cell membrane Controlled and sustained drug release Effective stability in biological environments	[58]
	Curcumin + Fusidic acid	Lecithin Tween 80 Carbopol 934	Particle size =11.23 ± 0.62 nm Zeta potential = −18± 2.1 and −35± 3.72 mV PDI = 0.22 ± 1.5 to 0.54 ± 0.98 EE (%) = 59 ± 0.65% to 85 ± 0.79% (Curcumin) and 52.5 ± 3.1% to 88 ± 3.7% (Fusidic acid)	Good stability Sustained release ↑ Solubility and stability than free drugs	[47]
Lipid nanocapsule	Curcumin	Polysorbate 80 Sorbitan monostearate Poly(epsiloncaprolactone)	Particle size =247 ± 4 nm Zeta potential = −34.7 ± 3.1 mV PDI = NR EE (%) = near to 100%	↑ Bioavailability ↑ Brain delivery (likely crosses BBB)	[70]

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Table 2 (Continued).

Lipid Nanocarrier	Drug	Base Composition	Characterization	Result	Reference
	Curcumin + Meloxicam	Span 60 Polysorbate 80 Caprylic monostearate Poly(ε-caprolactone)	Particle size = 291 to 312 nm Zeta potential = 22–36 mV PDI = NR EE (%) = near to 100%	Good colloidal stability Efficient drug loading Suitable for brain delivery (BBB penetration)	[71]
	Curcumin + Resveratol	Poly(ε-caprolactone) Polysorbate 80 Sorbitan monostearate Grape seed oil	Particle size = 196 ± 7.5 nm Zeta potential = −11.4 ± 2.1 mV PDI = 0.10 ± 0.04 EE (%) = NR	↑ Curcumin stability (at pH 7.4) and bioavailability ↑ Anti-inflammatory efficacy	[52]
Niosome	Curcumin	Cremophore RH Lechitin Cholesterol	Particle size = 212.0 ± 0.1 nm Zeta potential = −5.1 ± 0.2 mV PDI = 0.3 ± 0.1 EE (%) = 96.0% ± 0.1	High entrapment, better corneal penetration, and stable	[82]
	Curcumin	NR	NR	Have anti-inflammatory potential and could be a promising candidate to alleviate RSV-associated immunopathology.	[59]
	Curcumin	NR	NR	Better efficacy in a shorter time	[72]
Spanlastic	Curcumin	Span 80 Tween 20 Cremophor EL	Particle size = 105.2 nm Zeta potential = −20.9 mV PDI = 0.19 EE (%) = 88.4%	↑ Solubility, stability, and cellular availability. A potential approach for hepatic targeting.	[80]
Transfersome	Curcumin	Carbopol-934	NR	Enhanced skin penetration compared to plain curcumin Optimal particle size, spherical morphology, high encapsulation efficiency and sustained drug release profiles	[53]
	Curcumin	Lecithin Cholesterol Tween 80 Plurol oleique	Particle size = 164 nm Zeta potential = −41 mV PDI = 0.365 EE (%) = 63% to 77%	Uniformity in the vesicle size distribution Without significant agglomeration, indicating good stability of the transfersomal system	[54]

Abbreviations: NR, Not reported; EE (%), Entrapment efficiency.

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To better understand their performance, it is important to consider the key physicochemical characteristics that define SLN systems. SLNs are characterized by their large surface area and small particle size. Particle size, polydispersity index (PDI), entrapment efficiency, and other metrics can be used to assess the quality of SLN formulations. The primary constituents of SLNs are surfactants, water, and solid lipids. SLNs typically have a particle size between 50 and 1000 nm, polydispersity index (PDI < 0.3),[137,138] and entrapment efficiency between 40 and 100%.[139] SLNs allow controlled drug release, increase drug stability, and boost bioavailability by encasing both lipophilic and hydrophilic medicines within a solid lipid matrix. SLNs can effectively target particular cells and tissues because of their small particle size, which enhances drug absorption and penetration through biological barriers. They are adaptable to a range of therapeutic applications because they can be delivered via parenteral, oral, cutaneous, and rectal channels.[140–142]

Wang et al (2012) created curcumin-loaded lipid nanoparticles (curcumin-SLNs) to overcome the low bioavailability of curcumin and improve its anti-inflammatory activity in allergic asthma. The formulation was created using a solvent injection approach, which allowed curcumin to be integrated into a solid lipid matrix for greater stability. The nanoparticles exhibited desirable physicochemical properties, with an average particle size of ~190 nm, a negative zeta potential of −20.7 mV, and a high entrapment efficiency of 75%, indicating efficient loading and colloidal stability. X-ray diffraction revealed that the encapsulated curcumin was amorphous, indicating increased solubility and dissolution. In vitro release studies demonstrated a biphasic release pattern, with an initial burst followed by a sustained release phase, indicating that the SLN system could provide long-term drug availability. Pharmacokinetic studies in mice have demonstrated that curcumin-SLNs significantly increase curcumin concentration in the plasma compared to free curcumin. Furthermore, tissue distribution investigations have revealed increased accumulation in various organs, including the lungs and liver, which are important sites for asthma pathogenesis. The therapeutic efficacy of the formulation was investigated in an ovalbumin (OVA)-induced allergic asthma rat model, and curcumin-SLNs exhibited antiasthmatic activity. The SLN formulation substantially reduced airway hyperresponsiveness, suppressed inflammatory cell infiltration, and significantly decreased Th2-associated cytokines, including IL-4 and IL-13, in bronchoalveolar lavage fluid. These improvements were considerably greater in the untreated asthma and free curcumin-treated groups. Wang et al demonstrated the high potential of solid lipid nanoparticles as a delivery method for improving the anti-inflammatory activity and pharmacokinetic behavior of curcumin.[57]

Across multiple in vitro and in vivo studies (Tables 1 and 2), curcumin-loaded SLNs consistently demonstrate enhanced therapeutic performance compared to free curcumin, primarily driven by improved delivery efficiency and modulation of inflammatory pathways. The core advantage of SLNs lies in their high biocompatibility and biodegradability, as they are constructed from physiological lipids (generally recognized as GRAS) that ensure low acute and chronic toxicity. Unlike many polymeric nanoparticles, SLN manufacturing processes, such as high-pressure homogenization, are industrially scalable, cost-effective, and often avoid the use of toxic organic solvents.[132,143] In inflammatory skin disorders such as psoriasis and atopic dermatitis, SLNs significantly reduce keratinocyte hyperproliferation and suppress key pro-inflammatory cytokines, including IL-23, IL-6, and IL-8. Similar anti-inflammatory effects are observed in asthma models, where SLNs decrease Th2-associated cytokines (IL-4 and IL-13) and attenuate airway hyperresponsiveness. These biological outcomes are supported by the SLN's solid lipid matrix, which remains solid at body temperature, providing superior physical stability compared to liposomes and simple emulsions. This solid core acts as a protective shield for labile phytochemicals like curcumin against light, oxygen, and enzymatic degradation.[144] Beyond anti-inflammatory activity, SLNs also exhibit cytoprotective and antioxidant effects. Several studies report reduced lipid peroxidation markers such as malondialdehyde (MDA), along with modulation of apoptosis-related proteins, including decreased caspase-3 activation and increased Bcl-2 expression. In neurodegenerative models, these effects translate into improved cognitive performance and neuroprotection, suggesting that SLNs may influence both inflammatory and cell survival pathways. A key advantage of SLNs lies in their ability to enhance drug delivery and bioavailability. Studies consistently report increased cellular uptake, prolonged systemic circulation, and improved tissue targeting, including enhanced permeability across the blood–brain barrier (BBB). Sustained and controlled drug release profiles further contribute to prolonged therapeutic effects, particularly in chronic inflammatory conditions. These biological outcomes are closely associated with the physicochemical characteristics of SLNs. Most formulations exhibit particle sizes in the range of 130–190 nm, negative zeta potentials (approximately −20 to −30 mV), low polydispersity indices (PDI < 0.3),

and relatively high entrapment efficiencies (typically above 70%). These properties collectively support colloidal stability and a sustained drug release profile, which is crucial for the chronic management of inflammatory conditions. However, despite these promising preclinical findings, the transition to clinical application remains limited, highlighting the urgent need for further investigation into long-term safety, manufacturing scalability, and human clinical trials.

Nanostructured Lipid Carriers (NLCs)

A second-generation lipid-based nanocarrier system called Nanostructured Lipid Carriers (NLCs) was developed to address the drawbacks of Solid Lipid Nanoparticles (SLNs), including drug ejection, low loading capacity, and instability during storage.[145,146] NLCs are colloidal carriers composed of a mixture of liquid and solid lipids that produce a disordered matrix, which increases the encapsulation effectiveness and permits the incorporation of more drug molecules.[147,148] While liquid lipids introduce flaws into the crystalline lattice to enhance flexibility and drug loading capacity, solid lipids preserve structural integrity. Even at room temperature, the solid-liquid lipid combination usually remains solid, creating a stable nanocarrier with enhanced physicochemical stability and regulated release properties.[149,150]

Biocompatible and biodegradable lipids such as fatty acids, triglycerides, and waxes are used to synthesize NLCs. The dispersion was stabilized by adding appropriate emulsifiers or surfactants.[151] Particle size, encapsulation efficiency, and release profile are all strongly influenced by the choice of lipid composition and procedural parameters.[152] Particularly in oral delivery systems, small NLCs (approximately 200 nm) typically show superior mucoadhesion and bioavailability compared to larger particles (>600 nm).[153] Both hydrophilic and lipophilic substances can be encapsulated using a combination of liquid and solid lipids, thus providing adaptability to a variety of bioactive molecules.[148]

NLCs are divided into three main categories based on their internal structure and lipid makeup.[154] The Type-I disordered lipid matrix (Imperfect Crystal Model) is created by combining liquid and solid lipids with different fatty acid chain lengths, resulting in voids that improve medication accommodation. Type II (multiple model) enhances medication solubility and stops leakage during storage by combining liquid and solid lipids to produce tiny oil nanocompartments inside the solid matrix. To preserve the amorphous, non-crystalline structure and reduce drug expulsion caused by crystallization, Type III (amorphous model) is created by carefully combining particular lipids such as isopropyl myristate or hydroxyoctacosanyl hydroxystearate.[155,156] These structural advantages translate into several functional benefits. NLCs exhibit improved drug stability, higher loading capacity, and more controlled and prolonged drug release compared to SLNs.[157] Additionally, they are compatible with multiple administration routes, including topical, oral, parenteral, ophthalmic, pulmonary, and transdermal delivery.[149] Their cost-effectiveness, scalability, decreased cytotoxicity, and biodegradability make them desirable options for both medicinal and cosmetic formulations.[158] To guarantee safety for long-term clinical use, potential negative effects such as lipid matrix-related cytotoxicity and surfactant irritations still need to be carefully optimized.[157]

Wang et al investigated phosphatidylserine-modified nanostructured lipid carriers (Cur-mNLCs) as a targeted method for delivering curcumin to treat liver fibrosis. Surface modification with phosphatidylserine (PS) was employed to enhance macrophage uptake, given the key role of hepatic macrophages in fibrosis progression. The Cur-mNLCs demonstrated favorable physicochemical properties, including a particle size of approximately 204 nm, very low PDI (0.067), high entrapment efficiency (~89%), and a strongly negative zeta potential (−46.29 mV), indicating excellent stability and uniformity. Functionally, Cur-mNLCs exhibited superior liver-targeting capability compared to unmodified NLCs and free curcumin, as confirmed by biodistribution studies. This enhanced targeting translated into improved therapeutic outcomes, including reduced liver enzyme levels (ALT, AST, ALP, and T-Bil), decreased pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), and suppression of fibrosis markers such as collagen I and α-SMA. Mechanistically, Cur-mNLCs promoted hepatoprotective pathways by upregulating hepatocyte growth factor (HGF) and MMP-2 activity, supporting tissue remodeling and fibrosis resolution.[79]

Beyond individual studies, a broader comparison of multiple NLC formulations (Tables 1 and 2) further highlights their versatility and superior performance across different inflammatory conditions. The distinctive advantage of NLCs lies in their mixed solid-liquid lipid core, which creates an imperfect or unstructured matrix. This disordered structure provides significantly more space for drug molecules, leading to higher drug loading and encapsulation efficiency while effectively reducing drug leakage or expulsion during storage, a common limitation observed in earlier lipid systems.[143]

In psoriasis models, NLC-based formulations demonstrated enhanced skin penetration, reduced inflammatory cytokines (TNF-α, IL-6, IL-22, IL-23), and improved restoration of skin structure compared to conventional formulations. Similarly, in rheumatoid arthritis models, intra-articular administration of CUR-NLC gels provided sustained drug retention in the joint cavity, significantly reducing inflammation and restoring synovial histology. In gastrointestinal inflammation, such as inflammatory bowel disease, NLCs showed strong interaction with epithelial barriers (eg., Caco-2 cells), leading to reduced neutrophil infiltration and decreased TNF-α secretion. These findings indicate effective localized drug delivery and anti-inflammatory action. Notably, across studies, NLCs consistently exhibited favorable physicochemical characteristics, including particle sizes typically ranging from 95 to 280 nm, low-to-moderate PDI values, negative zeta potentials, and high entrapment efficiencies (often exceeding 70–90%). These properties contribute to improved stability, enhanced bioavailability, and sustained drug release. When compared to SLNs, NLCs generally demonstrate superior drug loading capacity, reduced risk of drug expulsion, and more flexible drug release profiles due to their less-ordered lipid matrix. This makes NLCs particularly advantageous for delivering hydrophobic bioactive molecules, especially in chronic inflammatory conditions requiring prolonged and targeted therapy. Overall, NLCs represent a significant advancement over SLNs, offering improved physicochemical stability, enhanced therapeutic efficacy, and broader application potential. However, despite promising preclinical outcomes, further studies focusing on large-scale production, long-term safety, and clinical translation are still required to fully realize their potential in clinical settings.

Phytosomes

Phytosomes, sometimes referred to as phyto-phospholipid complexes, are vesicular delivery systems intended to improve the biological performance and absorption of poorly soluble phytochemicals.[159] "Some" denotes a vesicle that resembles a cell, but "phyto" alludes to plants. They are created by a well-defined complexation process in which phospholipids, most frequently phosphatidylcholine, interact with naturally occurring plant components such as flavonoids, terpenoids, or glycosides in an aprotic solvent.[160] The resultant structures were typically spherical vesicles ranging in size from 50 to 100 nm. They are composed of a lipophilic inner layer that holds an herbal extract and a hydrophilic exterior layer made of phospholipid head groups.[161–163] The hydrophilic phytoconstituent is surrounded by the lipid-soluble part of phosphatidylcholine in this stable molecular complex, which improves membrane permeability and pharmacological and pharmacokinetic activites. Phytosomes exhibit enhanced bioavailability,[164] greater encapsulation efficiency, and stronger physicochemical stability because of their phospholipid head groups and phytomolecule forming chemical bonds.[165] Phytosomes also offer several medicinal and formulation benefits. They provide effective trapping without complicated production processes, facilitate targeted distribution to tissues, and shield delicate phytochemicals from degradation by stomach enzymes and gut bacteria.[166]

Phytosome formation is a result of the long-standing issues associated with herbal remedies. Many phytochemicals have poor oral bioavailability, which limits their therapeutic potential, even though medicinal plants and their active ingredients have been used to treat a variety of disorders.[159,167] Reduced lipid solubility, polyphenolic compounds with several aromatic rings, and large molecular weights are the common causes of reduced absorption.[160,168] Many formulation techniques, including emulsions,[169] liposomes, nano-formulations, structural alterations, and prodrug methods[170,171] have been investigated to address these issues. Phytosomes have demonstrated the greatest promise among these techniques for enhancing the bioavailability of herbal compounds.[168]

Despite these advantages, studies investigating phytosome-based delivery systems for curcumin in inflammatory diseases remain relatively limited compared to those for other lipid-based nanocarriers. Unlike liposomes, where the active ingredients are merely entrapped in the core or bilayer, phytoconstituents in phytosomes are chemically bound through hydrogen bonding to the phospholipid head groups. This creates a covalent-like complex in which the phytochemical becomes an integral part of the vesicle membrane rather than a simple guest molecule.[162] For example, Nashaat et al (2023) investigated the use of phytosomes co-loaded with leflunomide (LEF) and curcumin (CUR) as a novel therapeutic strategy for rheumatoid arthritis (RA). The researchers created several CUR/LEF phytosome formulations for this investigation and assessed their chemical and physical properties. The improved phytosome (F2) performed the best among all the evaluated formulations. This formulation showed good stability and uniform dispersion, with a

spherical shape, a particle size of approximately 760 nm, and a strong negative zeta potential (– 55.7 mV). Additionally, the phytosome formulation exhibited a sustained release profile, attributable to its exceptionally high entrapment efficiency (>98%). Compared with free curcumin (CUR), free leflunomide (LEF), and their physical mixture, the CUR/LEF phytosomes significantly reduced paw swelling and inflammatory markers. These findings are further supported by the phytosome's superior biopharmaceutical profile for topical and systemic use, demonstrating higher skin penetration and better physical stability in aqueous systems compared to liposomes, which frequently require freeze-drying to maintain integrity.[162] Histological examination revealed no discernible signs of arthritis, indicating marked tissue protection. Collectively, these findings suggest that CUR/LEF phytosomes represent a promising therapeutic strategy for the treatment of rheumatoid arthritis.[48]

Ethosomes

Ethosomes are advanced lipid-based vesicular structures designed to enhance drug delivery via the skin. Ethosomes, are composed of water, phospholipids, and a high ethanol content (20–45%).[172] Owing to their high ethanol concentration, ethosomes are significantly more flexible than traditional liposomes, which possess relatively rigid bilayers that often hinder deep skin penetration.[173] Ethanol content fluidizes the phospholipid bilayer and disrupts the tightly packed lipids of the stratum corneum, producing soft, ultra-deformable vesicles that can deform and pass through narrow intercellular skin pathways while retaining their drug cargo. Furthermore, ethanol facilitates the permeation of ethosomes across the epidermal barrier by loosening intercellular junctions and increasing overall membrane fluidity, thereby enhancing the delivery efficiency of curcumin into deeper skin layers.[174] Compared to conventional transdermal systems, the shape of ethosomes allows them to effectively transfer hydrophilic and lipophilic medications into deeper epidermal layers, thereby increasing bioavailability and improving therapeutic results.[175]

Inadequate penetration of previous transdermal systems, including liposomes and transfersomes, has led to the development of ethosomes. Transfersomes are highly deformable vesicles that pass through small apertures using osmotic gradients.[176] However, ethanol provides ethosomes with strong penetration-enhancing properties and excellent flexibility, making them one of the best vesicular carriers for transdermal drug delivery. Various ethosomes have been developed to maximize their effectiveness. Owing to their high permeability and affordability, classical ethosomes, which contain phospholipids, ethanol, and water, are the most straightforward and extensively utilized.[174] By synergistically fluidizing the stratum corneum, binary ethosomes, which include an additional alcohol, such as propylene glycol or isopropyl alcohol, improve skin permeability.[177] In addition to ethanol and phospholipids, transethosomes contain surfactants or edge activators (Tween 80, Span 80, and sodium cholate).[178] They can handle larger molecules, such as peptides and proteins, of up to 325 kDa, owing to the exceptional flexibility of this combination.[179]

There are two primary phases in an ethosome-based medication delivery system. First, ethanol reduces membrane density, increases lipid fluidity, and improves medication solubilization when it interacts with phospholipid heads and the lipid matrix of the skin. Because of this interaction, ethosomes can more readily pass through the stratum corneum. Second, flexible ethosomal vesicles fuse with skin lipids in the second stage, which is known as the ethosome effect, and release their medication content into the deeper layers of the skin. Ethosomes function as skin reservoirs in many formulations, enabling regulated and prolonged drug release, which helps sustain therapeutic drug levels for extended periods of time.[180] Ethosomal delivery technologies have shown promise in systemic therapy for chronic illnesses, such as cancer, diabetes, and neuropathic pain. Ethosomes are currently used for treatments beyond dermatological applications.

Despite these well-established advantages, studies evaluating curcumin-loaded ethosomes in inflammatory conditions remain relatively limited. However, as phospholipid vesicles with a high ethanol content, ethosomes offer distinctive mechanistic advantages over conventional liposomes, SLNs, and NLCs, particularly for dermal and transdermal delivery. The primary strength of ethosomes lies in their superior skin permeation and depth of penetration; ethanol serves a dual role by fluidizing both the vesicle bilayer and stratum corneum lipids. This process loosens intercellular junctions and imparts high deformability, allowing these unusually soft vesicles to squeeze through narrow skin pathways and reach deeper layers or even systemic circulation more efficiently than classic, rigid nanocarriers.[181] For instance, Zhang et al developed hyaluronic acid-modified ethosomes (HA-ES) for the targeted delivery of curcumin in psoriasis. The incorporation of hyaluronic acid aimed to improve stability and enhance targeting via CD44 receptors, which are

overexpressed in psoriatic skin. The optimized formulation exhibited favorable physicochemical properties, including a particle size of approximately 181 nm, low PDI (~0.21), a strongly negative zeta potential (−43.2 mV), and high entrapment efficiency (~82.6%), indicating good stability and uniformity. In vitro studies demonstrated enhanced skin permeation and prolonged drug availability, whereas in vivo evaluation in a psoriasis mouse model showed significant therapeutic effects following topical administration. Specifically, HA-ES reduced the expression of key pro-inflammatory cytokines, including TNF-α, IL-17A, IL-17F, IL-22, and IL-1β, as well as CCR6 protein expression, which is associated with inflammatory cell recruitment. These findings suggest that ethosomal systems can significantly enhance curcumin penetration, skin retention, and anti-inflammatory efficacy in topical applications.[44] However, similar to phytosome-based systems, the current evidence is limited to a small number of studies, restricting a comprehensive comparison with other lipid-based nanocarriers such as SLNs and NLCs. Therefore, further investigations are required to validate their long-term safety, optimize formulation parameters, and establish their clinical potential.

Nanoemulsion

Nanoemulsions are colloidal particulate carriers with droplet sizes typically ranging from 10 to 200 nm, offering significant therapeutic potential in fields such as oncology and immunology.[182] These systems are categorized into oil-in-water, water-in-oil, and bi-continuous types, each providing a transparent and stable platform for controlled and sustained drug release by shielding active compounds from premature degradation. A primary advantage of nanoemulsions is their ability to enhance the solubility and release profile of lipophilic medications, particularly for topical and skin treatments.[183,184] The stability of these emulsions is maintained by essential components, including oils, surfactants, and co-surfactants (such as ethanol or propylene glycol), which utilize electrostatic interactions and steric hindrance to prevent common physical instabilities like creaming, sedimentation, or flocculation.[185] The preparation of nanoemulsions involves both high-energy techniques, such as high-pressure homogenization and ultrasonication, and low-energy processes that exploit the system's intrinsic physicochemical properties (eg., EIP and PIT) to generate tiny droplets efficiently.[186] Because droplet size is a critical factor influencing stability, optical properties, and release behavior, nanoemulsions are highly adaptable for diverse administration routes, including ocular, transdermal, perioral, and parenteral delivery.[187,188] Furthermore, the small droplet size minimizes gravitational effects during storage and can be precisely controlled by adjusting the oil-to-surfactant weight ratio. This versatility and ease of large-scale production, which often requires less surfactant than other colloidal systems, position nanoemulsions as a highly promising strategy for modern drug delivery.[185,189]

The therapeutic potential of this platform is further driven by its high solubilization capacity and the ability to protect sensitive bioactive compounds from gastrointestinal acid, enzymatic degradation, and oxidation. By encapsulating drugs within oil droplets, nanoemulsions significantly enhance intestinal permeability and oral bioavailability.[190,191] Compared to micro or macroemulsions, they offer superior stability under harsh pH and temperature conditions, ensuring the protection of labile drugs throughout their transit. Furthermore, they serve as versatile and safe edible carriers in nutraceuticals while proving effective across multiple delivery routes, including nasal and intravenous administration.[111,192] In specific applications such as ocular and skin delivery, nanoemulsions increase residence time and permeation while reducing systemic toxicity compared to conventional suspensions. The practical efficacy of this platform is evidenced by the data summarized in Tables 1 and 2. For instance, in an in vivo model of ear inflammation, oral administration of a 1% curcumin nanoemulsion resulted in a significant inhibition of ear edema. This formulation, characterized by a particle size range of 79.5 to 618.6 nm and a stable PDI (0.249–0.369), maintained physical stability for seven days. The improved anti-inflammatory activity observed in this study is directly attributed to the system's ability to increase curcumin's bioavailability and shield it from premature degradation. Overall, the combination of small droplet size, high encapsulation efficiency, and relatively simple processing makes nanoemulsions a standout strategy for delivering hydrophobic drugs like curcumin.[45]

Self-Nanoemulsifying Drug Delivery Systems (SNEDSS)

One of the most effective strategies to overcome the poor solubility of lipophilic compounds is the development of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS).[193] SNEDDS are anhydrous mixtures composed of oils, surfactants,

and co-surfactants that can spontaneously form fine oil-in-water (o/w) nanoemulsions upon dilution in an aqueous environment, aided by mild gastrointestinal agitation.[194,195] In this system, the oil phase serves as a solubilizing medium for lipophilic drugs, while surfactants reduce interfacial tension to facilitate emulsification. Co-surfactants further enhance the flexibility of the interfacial film and contribute to the thermodynamic stability of the nanoemulsion.[196] The efficiency and stability of SNEDDS are largely determined by their physicochemical characteristics. Typically, stable and transparent nanoemulsions exhibit droplet sizes below 100 nm.[197] The uniformity of droplet distribution is evaluated using the polydispersity index (PDI), whereas colloidal stability is assessed through zeta potential measurements, where values greater than ±30 mV indicate good stability.[198] Additionally, high transmittance values (95–100%) suggest the successful formation of nanosized droplets. Despite substantial evidence demonstrating that SNEDDS can significantly improve drug solubility and bioavailability, most studies remain limited to single-drug optimization and in vitro evaluations. Comparative analyses across different drug classes, particularly Biopharmaceutics Classification System (BCS) Class II and IV drugs, are still scarce. Furthermore, challenges such as large-scale manufacturing, long-term stability, and regulatory considerations remain insufficiently addressed in current research.[199,200]

The therapeutic potential of SNEDDS in managing various inflammatory conditions is well-supported by the physicochemical and biological data summarized in Tables 1 and 2. As isotropic oil–surfactant pre-concentrates, SNEDDS stand out from preformed systems like liposomes, SLNs, or NLCs due to their ability to undergo spontaneous nanoemulsification upon contact with gastrointestinal (GI) fluids. This in situ formation avoids the long-term physical instability often associated with pre-dispersed products while providing a high interfacial area for drug release.[190,201] Across different studies, curcumin-loaded SNEDDS typically exhibit a particle size range of 32 to 405 nm, with a high entrapment efficiency (EE) often exceeding 90%. These formulations consistently demonstrate high polydispersity index (PDI) stability (0.104 to 0.228) and moderate negative zeta potentials (approximately −15 to −18 mV), which collectively contribute to enhanced curcumin solubility, stability, and dissolution rates. In the context of gastrointestinal inflammation, such as Inflammatory Bowel Disease (IBD), SNEDDS has proven effective as a localized oral medication. For instance, a co-delivery system of curcumin and mesalamine formulated as SNEDDS (particle size ~137 nm, EE >79%) showed significant reduction in pro-inflammatory mediators, including TNF-α, IL-6, and nitric oxide (NO). Notably, these formulations maintained physical and chemical stability for up to three months and exhibited high cell viability, confirming their safety for long-term localized treatment.

Furthermore, SNEDDS applications extend to neurodegenerative disorders, such as Alzheimer's disease. Studies utilizing curcumin combined with piperine in SNEDDS formulations have reported a significant increase in curcumin bioavailability when administered orally. In animal models, these systems demonstrated dose-dependent therapeutic efficacy that outperformed untreated groups and showed effectiveness comparable to standard drugs, such as donepezil. This enhanced performance is primarily attributed to the system's ability to protect the bioactive compounds from degradation and facilitate their absorption through the gastrointestinal barrier, thereby supporting sustained therapeutic levels in systemic circulation.[69]

Cubosome

A cubosome is a nanoparticle-based delivery system composed of lipid materials that can form a cubic liquid-crystalline structure when mixed with water.[202] Generally, cubosomes are prepared using lipids such as glyceryl monooleate, and a stabilizer to maintain the particle structure in dispersion. The internal cubic structure of the cubosomes, which provides a large surface area and a unique network of water and lipid channels, is what makes it special. This structure allows the system to efficiently load active compounds and protect them from degradation.[203] Compared with conventional formulations, cubosomes can provide better drug retention and support a more controlled release of the active substance. This is especially helpful for curcumin, as it can improve the solubility and stability of the compound in the formulation.

The mechanism of cubosomes is closely related to their small particle size, large surface area, and structured internal phase. When applied or administered, cubosomes interact well with biological membranes, which may improve the transfer of the drug to the target site. Its lipid-based composition also helps the system work well in biological environments. In addition, the internal structure of cubosomes can slow down drug release, which is useful for maintaining the effect of the active compound

for a longer time. In curcumin formulations, these properties offer important advantages, such as better protection from degradation, improved drug loading, and enhanced delivery efficiency.[204]

These cubosomes, formulated using glyceryl monooleate and pluronic F-127, were characterized for their particle size, entrapment efficiency, and zeta potential. The optimized formulation (F7) demonstrated excellent entrapment efficiency (71.24%) and sustained-release properties. In vitro studies confirmed that the formulation showed effective drug release, making it a promising approach for treating osteomyelitis with enhanced drug delivery and bioavailability.[205]

Lipid Micelles

Lipid micelles are small, spherical aggregates formed by lipid molecules, typically amphiphilic compounds, in an aqueous environment. These molecules have a hydrophilic (water-loving) head and a hydrophobic (water-repelling) tail. When placed in water, the hydrophobic tails of the lipids turn inward, while the hydrophilic heads face outward toward the water, forming a structure that resembles a ball.[1] This self-assembly process allows lipid micelles to act as solubilizing agents for hydrophobic compounds, making them an effective delivery system for poorly water-soluble drugs. The size and composition of the micelles can be tailored depending on the drug being delivered, which allows for customization of the delivery system. One of the key advantages of lipid micelles is their ability to improve the stability of drugs that are sensitive to environmental factors, such as light and oxygen. By encapsulating these drugs, lipid micelles can protect them from degradation, ensuring that the active ingredient remains intact until it reaches the target site. Additionally, the surface properties of lipid micelles can be modified to increase their ability to interact with biological membranes, facilitating the uptake of the drug by target cells.[2]

Lipid micelles are commonly formed using surfactants, which are compounds that lower the surface tension between two substances. These surfactants can be nonionic, anionic, or cationic, and they determine the properties of the micelles, such as size, charge, and stability. The composition of the surfactant also influences the drug-loading capacity of the micelles and their ability to release the drug at the appropriate site in the body. The mechanism of drug delivery via lipid micelles is primarily based on their ability to form stable, water-soluble complexes with hydrophobic drugs, enhancing their solubility in the bloodstream. Once administered, lipid micelles circulate in the body and can be taken up by cells through endocytosis. The drugs are then released from the micelles inside the cells, where they can exert their therapeutic effects.[3]

Lipid Nanocapsule

Lipid nanocapsules (LNCs) are nanosized spherical carriers comprising a solid lipid core surrounded by a phospholipid monolayer. LNCs offer several advantages over traditional drug delivery systems, such as liposomes and emulsions. One of the main benefits is their ability to protect encapsulated drugs from degradation due to factors, such as light, heat, and oxygen. This protection enhances drug stability, ensuring that it remains effective until it reaches the target site in the body. Additionally, the small size of LNCs (typically ranging from 50 to 200 nm) allows them to easily pass through biological barriers, such as the blood-brain barrier, thereby improving drug delivery to difficult-to-reach tissues.[4]

The mechanism of drug delivery using lipid nanocapsules is primarily based on their ability to encapsulate drugs in the lipid core while maintaining drug stability. When administered, lipid nanocapsules circulate in the bloodstream and can be taken up by cells through endocytosis. Once inside the cells, the drug is released in a controlled manner, often triggered by changes in pH, temperature, or enzymatic activity, allowing for targeted therapy. In pharmaceutical applications, lipid nanocapsules are increasingly being used to delivery a wide range of therapeutic agents, including anticancer drugs, vaccines, and gene therapies. Their ability to improve drug solubility, enhance stability, and provide controlled release makes them an attractive option for drug formulations. Additionally, lipid nanocapsules are considered biocompatible and biodegradable, which further increasing their appeal for clinical applications.[5]

The study presented quantitative results demonstrating the effects of curcumin and meloxicam co-loaded lipid core nanocapsules (LCNs) on cognitive impairment in a mouse model of Alzheimer's disease. The results from the memory tests, specifically the inhibitory avoidance test and the object recognition test, showed significant improvements in memory performance. In the inhibitory avoidance test, both meloxicam-loaded and curcumin-loaded LCN formulations (10 and 5 mg/kg, respectively) showed improvements in memory deficits caused by amyloid-beta peptide infusion,

compared to the control group. Additionally, curcumin and meloxicam co-loaded LCN (10 mg/kg) showed a significant reduction in non-aversive memory impairment, demonstrating its potential to attenuate cognitive decline.[6]

Niosome

Niosomes are vesicular delivery systems primarily composed of non-ionic surfactants and cholesterol, which interact to assemble into a stable bilayer.[206] The architecture of this bilayer creates a dual-compartment geometry consisting of a central aqueous core and a surrounding lipid domain. This unique structure enables niosomes to encapsulate a diverse range of bioactive molecules hydrophilic drugs are housed within the aqueous center, while lipophilic species are integrated into the lipid bilayer through partitioning.[206] The successful formation of these robust vesicles requires a precisely controlled hydration medium and, in certain formulations, the addition of charge inducers to prevent particle fusion and maintain long-term colloidal stability. The physicochemical properties of niosomes, including their dimensions, lamellarity, and surface charge are highly tunable and governed by several variables such as the hydration medium's pH, the specific properties of the surfactants, and the chosen synthesis method.[207] Rational design is therefore critical, as these parameters directly influence essential performance indicators such as encapsulation efficiency, polydispersity, and the controlled release profile of the drug.[208]

Due to their structural flexibility, niosomes have found broad applications ranging from gene therapy and drug delivery to the protection of sensitive cosmetic agents and antioxidants. Their ability to shield compounds from premature degradation and facilitate targeted delivery makes them indispensable for the development of personalized and advanced therapies.[209,210] By adjusting the niosomal design to the specific characteristics of the cargo molecule, these systems offer an innovative solution to overcome bioavailability and stability limitations, establishing them as a promising strategy for controlled release across scientific and technological fields.[211]

The practical application of niosomes in inflammatory therapy is demonstrated by their performance across ocular, respiratory, and neurological models, as shown in Tables 1 and 2. Compared to other lipid nanocarriers, niosomes offer broader cargo compatibility and superior structural tunability. They can effectively encapsulate diverse molecules, including proteins, genes, and vaccines, with adjustable size and surface charge, whereas SLN and NLC primarily favor hydrophobic drugs.[212] Furthermore, niosomes exhibit better stability than micelles, which often disassemble upon dilution and cause premature drug release, and they are more reproducible and stable at low temperatures compared to cell-membrane-based carriers.[213] A key highlight of this versatility is the use of curcumin-niosomes for ocular inflammation, which achieved a high entrapment efficiency of 96% and a particle size of 212 nm. This formulation provided a sustained drug release over 24 hours and demonstrated superior corneal penetration. In vivo evaluations revealed that niosomal eye drops facilitated faster healing within four days, offering an anti-inflammatory effect comparable to standard treatments but with a significantly improved safety profile, specifically by avoiding increases in intraocular pressure (IOP). Beyond ocular applications, niosomes have shown substantial potential in systemic and localized inflammatory conditions. In models of Respiratory Syncytial Virus (RSV) infection, curcumin-loaded niosomes served as a promising candidate to alleviate immunopathology by significantly reducing the influx of immune cells into the lungs and downregulating key pro-inflammatory mediators, including MIP-1α, TNF-α, and IFN-γ. Similarly, the neuroprotective capacity of niosomal curcumin is evident in neurodegenerative contexts. In Alzheimer's rat models, intraperitoneal administration of curcumin niosomes (20 mg/kg) resulted in enhanced memory and cognitive function while effectively reducing brain damage. This therapeutic outcome was closely linked to the suppression of the NF-κB signaling pathway. Collectively, these findings suggest that niosomes not only stabilize curcumin but also enhance its delivery to specific target sites, achieving better therapeutic efficacy in a shorter timeframe compared to conventional formulations.

Spanlastic

Spanlastic is an elastic vesicular system based on nonionic surfactants that has been developed to enhance drug delivery, particularly for compounds with poor solubility and limited bioavailability, such as curcumin. This system is designed to possess a more flexible membrane than conventional vesicles, enabling it to adapt more effectively to biological barriers[214] his flexibility makes spanlastic an attractive drug carrier because it can improve distribution, enhance interactions with biological membranes, and support more efficient delivery of active compounds to target tissues.[215]

In the case of curcumin, the use of spanlastic is particularly important because curcumin has substantial pharmaceutical limitations, including extremely low water solubility,[216] poor stability, and suboptimal absorption when administered in its free form.[217,218]

In general, spanlastic is formed from a primary surfactant as the vesicle-forming component and is combined with an edge activator to increase membrane elasticity.[219] Unlike more rigid vesicular systems, the presence of an edge activator in spanlastic reduces bilayer rigidity and allows the vesicles to deform without significant loss of structural stability.[214] This property is highly important because deformability plays a major role in enabling vesicles to cross biological barriers and maintain more effective drug delivery.[220,221] In addition, this system can enhance the ability of lipophilic active compounds to remain in a more readily dispersible form, thereby improving their pharmaceutical performance. Thus, spanlastic functions not only as a passive carrier but also as a system that directly supports improvement in the delivery profile of curcumin.[221]

The mechanism of spanlastic is primarily related to the elasticity of the vesicle membrane and its ability to interact more efficiently with biological surfaces.[219] Upon application, these flexible vesicles can more readily adapt to their surrounding environment, thereby optimizing contact with the tissue.[220,222] This supports greater transfer of the drug from the carrier system to the target site. In addition, the small vesicle size contributes to a larger surface area, which can ultimately enhance delivery efficiency. In curcumin formulations, these properties provide further advantages, including protection against degradation, improved loading efficiency, and the potential for more controlled drug release.[221,223]

In one curcumin-based spanlastic formulation, the particle size was 105.2 nm, indicating that the vesicles were within the nanometer range suitable for promoting favorable interactions with biological membranes. A PDI value of 0.19 indicates a narrow particle size distribution, suggesting that the formulation was relatively homogeneous. A zeta potential of −20.9 mV indicates sufficient surface charge to help maintain vesicle dispersion, while an entrapment efficiency of 88.4% shows that most of the curcumin was successfully incorporated into the system.[80] From a pharmaceutical perspective, the combination of these parameters indicates that spanlastic is capable of forming a stable, uniform, and efficient delivery system for carrying the active compound. Such a profile is highly important because it is directly related to formulation consistency, drug-loading capacity, and potential biological performance.

From a formulation development perspective, spanlastic shows strong promise as a nanocarrier for curcumin.[219,224] Its elastic vesicles, small particle size, uniform distribution, and high loading capacity indicate that this system has the potential to improve the performance of curcumin substantially compared to its free form.[80,221] Nevertheless, the development of spanlastic still requires further investigation, particularly regarding long-term stability, the safety of its constituent components, formulation reproducibility, and confirmation of biological effectiveness through in vitro, in vivo, and clinical studies.[80,225] Therefore, although the initial findings appear highly promising, further validation remains necessary to establish more firmly the potential of spanlastic as a curcumin delivery system.

Transfersome

Transfersomes are lipid-based vesicular systems designed to enhance drug delivery through the skin, particularly for compounds with limited permeation, such as curcumin. Transfersomes are composed of phospholipids and edge activators or surfactants that function to increase the elasticity of the vesicular bilayer.[226] Unlike conventional liposomes, which tend to possess more rigid membranes, transfersomes are highly deformable and can therefore pass through skin pores that are smaller than the vesicle diameter itself.[227] This ultra-deformable property makes transfersomes one of the most promising carriers for dermal and transdermal drug delivery, as the vesicles are able to adapt their shape without undergoing substantial structural damage. In the context of curcumin delivery, this system is particularly relevant because curcumin exhibits low aqueous solubility, limited stability, and poor bioavailability when administered in its free form.[228] By incorporating curcumin into transfersomes, the compound can be protected from degradation, remain in contact with the skin for a longer period, and demonstrate improved penetration into both the epidermal and dermal layers.[53]

The mechanism of transfersome penetration through the skin is primarily determined by the combination of vesicle deformability and hydration gradient across the stratum corneum.[226] Following topical application, water on the skin surface gradually evaporates, thereby creating a hydration gradient between the skin surface and the deeper epidermal layers. This gradient drives transfersomes toward tissues with higher water contents.[229] At the same time, edge activators

reduce interfacial tension and enhance vesicle membrane flexibility, enabling transfersomes to penetrate the narrow intercellular pathways of the stratum corneum.[230,231] Unlike ethosomes, which rely on a high ethanol content to fluidize both skin lipids and the vesicular bilayer, transfersomes primarily depend on the mechanical deformability of the vesicles themselves. Therefore, transfersomes are often considered superior in maintaining vesicle integrity during passage through the skin barrier, while also enabling more efficient drug delivery to target tissues.[226,232] In addition to enhancing penetration, this system may also support more controlled drug release, thereby maintaining therapeutic concentrations for a longer period at the site of application.[226]

Another advantage of transfersomes is in their formulation flexibility and ability to carry both hydrophilic and lipophilic compounds. The main components of this system generally include phospholipids, such as lecithin, which form the vesicular structure, as well as surfactants such as Tween 80, Span 80, sodium cholate, or other similar materials that act as edge activators. The inclusion of these components produces a membrane that is more flexible than that of conventional vesicular systems.[233,234] In curcumin delivery, this feature is particularly important because curcumin is a lipophilic compound that cannot optimally penetrate the skin when administered in the conventional form.[53] When incorporated into transfersomes, curcumin not only shows improved apparent solubility and entrapment efficiency, but may also achieve more uniform distribution, particle sizes suitable for topical application, and better dispersion stability.[53,235] From a pharmaceutical perspective, characteristics such as small particle size, narrow size distribution, adequate zeta potential, and high encapsulation efficiency are important parameters because they determine system stability, penetration capacity, and drug release performance.[229,230]

In one formulation using Carbopol-934, curcumin transfersomes were reported to exhibit enhanced skin penetration compared with pure curcumin, accompanied by optimal particle size, spherical morphology, high encapsulation efficiency, and a sustained drug release profile. These findings suggest that combining transfersomes with a gel base can improve formulation retention on the skin surface while maintaining gradual curcumin release, which is important for prolonging the local therapeutic effect.[53] In another formulation containing lecithin, cholesterol, Tween 80, and Plurol oleique, physicochemical characteristics were also found to support system quality, including a particle size of approximately 164 nm, a zeta potential of −41 mV, a PDI value of 0.365, and entrapment efficiency of 63–77%. These values indicate a relatively stable vesicular dispersion with a sufficiently uniform size distribution. In addition, uniform vesicle size distribution without significant agglomeration was also reported, indicating good stability of the transfersomal system.[54] Overall, these parameters reinforce the view that transfersomes are capable of producing a stable and deformable curcumin delivery system suitable for improving topical penetration.

Nevertheless, similar to other nanovesicular systems, transfersomes still have several limitations that should be considered. Long-term stability may be influenced by the surfactant composition, phospholipid-to-edge activator ratio, preparation method, and type of final dosage base used.[230,234] Moreover, although various studies have demonstrated enhanced penetration and favorable physicochemical characteristics, the number of studies that specifically evaluate the biological effectiveness of curcumin-loaded transfersomes under particular inflammatory conditions remains limited.[53,228] Thus, compared with other systems such as ethosomes, SLN, or NLC, the position of transfersomes still requires further support through broader comparative studies, whether in vitro, ex vivo, in vivo, or clinical.[228,236,237] However, based on their distinctive penetration mechanism, very high deformability, and promising formulation characterization results, transfersomes remain one of the most potential nanocarriers for improving curcumin delivery through the skin and enhancing its therapeutic effectiveness in both topical and transdermal applications.

Role of Lipid-Based Nanocarriers in Inflammatory Diseases

Inflammation in Skin

The human skin, the largest organ in the body, regulates inflammation, immunology, wound repair, and angiogenesis through tightly regulated interactions between keratinocytes, immune cells, and structural components.[238] This balance is disturbed and is responsible for major inflammatory skin illnesses including psoriasis and atopic dermatitis (AD). Psoriasis is a chronic autoimmune disorder caused by the abnormal activation of Th17 and Th1 cells. This causes excessive production of pro-inflammatory cytokines, such as IL-23, IL-17, and TNF-α, leading to uncontrolled

keratinocyte proliferation and plaque formation.[238] Similarly, AD and psoriasis are caused by a multifactorial interaction of skin barrier impairment, immune dysregulation, genetic susceptibility, and environmental triggers, resulting in chronic systemic inflammation characterized by higher circulating leukocytes, lymphocytes, cytokines, and chemokines, with Th2 pathways dominating AD and Th1/Th17 pathways in psoriasis.[239–242] Previously, treatment options were limited to topical agents or nonspecific systemic immunosuppressants with poor efficacy and safety. However, advances in the understanding of disease-driven cytokine pathways have enabled the development of modern targeted biologics that significantly improve therapeutic outcomes.

Drug administration through the skin can have two different therapeutic effects, local (dermal) and systemic (transdermal). While topical administration is the most effective route for achieving localized drug delivery, primarily targeting superficial tissues, transdermal delivery requires deeper penetration and regulated release into the systemic circulation. This approach has numerous advantages including avoiding first-pass metabolism, minimizing plasma concentration fluctuations, and increasing patient compliance.[243,244] The large surface area of the skin also allows for efficient drug distribution, contributing to its increased popularity in recent decades.[245,246] Despite these advancements, conventional transdermal distribution has always been restricted to lipophilic, low-molecular-weight, and non-ionic medicines. The advent of nanotechnology has expanded the scope of transdermal medicine by allowing the delivery of hydrophilic and ionic compounds, as well as larger macromolecules. Lipid-based nanocarriers have been shown to improve skin permeability, patient comfort, and reduce systemic side effects.[247,248] Lipid-based nanocarriers are one of the most widely recognized methods for improving skin delivery, owing to their capacity to improve drug stability, skin hydration, and retention, ultimately enhancing therapeutic efficacy. Drugs encapsulated in these systems can be transported via intercellular, transcellular, or appendageal pathways, depending on their molecular and carrier properties.[249] These features make lipid-based nanocarriers particularly useful for the treatment of inflammatory skin diseases, where good medication penetration and regulated release are required to reach deeper diseased areas.

However, despite these advantages, several physiological factors impose important constraints on the performance of lipid-based nanocarriers in topical and transdermal delivery. The skin surface exhibits a mildly acidic pH (≈4.2–5.6), which can significantly influence nanoparticle stability, including aggregation, lipid integrity, drug leakage, and surface charge (zeta potential), thereby affecting diffusion behavior. Accordingly, lipid-based nanocarrier formulations should be compatible with physiological skin pH to minimize instability and irritation.[250] In addition, pH-responsive systems have been developed to exploit local pH variations in inflamed skin (pH ~5.5–6.5), enabling controlled drug release and improved targeting efficiency.[251–253] Furthermore, the highly restricted structure of the stratum corneum limits nanoparticle penetration. Theoretical considerations suggest that only very small nanostructures (<5–7 nm for intercellular lipid pathways and <36 nm for aqueous pores) may diffuse through intact skin, although this remains under debate.[250] Since most lipid-based nanocarriers (eg., SLNs, NLCs, and vesicular systems) typically range from tens to hundreds of nanometers, they are unlikely to penetrate the skin as intact particles. Instead, their effects are mainly attributed to occlusion, enhanced hydration of the stratum corneum, and transfollicular delivery via hair follicles, where particles up to approximately 640 nm may accumulate effectively.[252] Notably, smaller nanocarriers (~20 nm) may exhibit improved penetration and pH-dependent partitioning in certain systems.[252] Collectively, skin pH and structural constraints play a critical role in modulating the stability, penetration, and overall performance of lipid-based nanocarriers, thereby directly influencing their functionality in topical and transdermal applications.

Lipid-based nanocarriers are particularly effective for treating inflammatory skin diseases because they can improve drug delivery across the skin barrier and facilitate drug localization within epidermal layers. This technique is beneficial for two primary conditions, psoriasis and atopic dermatitis (AD), both of which are characterized by persistent inflammation and impaired keratinocyte activity. Psoriasis can be identified by prolonged immunological activation, increased keratinocyte proliferation, and aberrant differentiation, making medicines less effective on already-resistant skin surfaces.[254] Serini et al found that curcumin-linolenic acid solid lipid nanoparticles (CU-LNA-SLNs) effectively suppressed psoriatic inflammation by inhibiting key cytokines, including IL-23, IL-8, and IL-6, as well as by reducing keratinocyte hyperproliferation and cell death, and reversing increased ferroptosis markers associated with psoriatic lesions.[39] Atopic dermatitis is characterized by a weakened skin barrier, filaggrin deficiency, and Th2-driven inflammation, resulting in poor medication absorption.[255] Cassano et al created linolenic acid-loaded SLNs from curcumin, resveratrol, and capsaicin-derived lipid matrices, which demonstrated

sustained LNA release for 24 h, substantial antioxidant and anti-inflammatory effects, and a significant reduction in IL-6 levels in keratinocytes without cytotoxicity.[40] These results indicate that lipid-based nanocarriers have the potential to improve penetration, stabilize bioactive chemicals, and deliver targeted anti-inflammatory effects in both psoriasis and atopic dermatitis, indicating their potential for future topical treatments.

Topical delivery plays a central role in achieving effective curcumin targeting in inflammatory skin disorders, as it enables direct localization within the epidermis and dermis, the primary sites of pathological changes. Evidence from Tables 1 and 2 shows that lipid-based nanocarriers, particularly liposomes, SLNs and NLCs, enhance drug retention within these layers, allowing curcumin to remain concentrated at the site of inflammation. Rather than penetrating deeply into the systemic circulation, these nanosystems primarily interact with the stratum corneum through hydration effects and follicular pathways, facilitating localized deposition within the skin. This targeted accumulation has been shown to significantly increase epidermal drug retention compared to free curcumin, supporting a sustained presence in inflamed tissues. The ability to maintain curcumin within the epidermal and dermal layers is essential for modulating local inflammatory responses, including keratinocyte hyperproliferation and cytokine production. In chronic conditions such as psoriasis and atopic dermatitis, this localized delivery approach is therefore more critical than systemic exposure, as it enables prolonged therapeutic action directly at the site of inflammation.

Inflammation in Joint and Bone

Joints are highly specialized organs that allow for stability and locomotion by facilitating efficient force transfer, shock absorption, and smooth frictionless movement. Synovial joints are the most common type of joint in the human body and are frequently affected by arthritis. They are composed of two articulating bones covered in a capsule bordered by the synovial membrane, which produces the synovial fluid required for lubrication and nutrient exchange.[256] Importantly, the synovium does not cover the articular cartilage or meniscus, which are avascular structures that rely only on synovial fluid for metabolic support.

Joint inflammation usually starts in the synovial membrane, where immunological activation causes excessive cytokine production, synovial hyperplasia, and infiltration of inflammatory cells.[257] Sustained activation of T-cells, B-cells, and macrophages in rheumatoid arthritis (RA) leads to the overproduction of pro-inflammatory mediators including TNF-α, IL-1β, and IL-6, resulting in pannus, an aggressive fibroinflammatory tissue that erodes cartilage and bone.[258] Osteoarthritis (OA) involves persistent low-grade inflammation caused by mechanical damage and cartilage degradation, although it also generates DAMPs that excite synovial macrophages.[259] These inflammatory cascades gradually degrade the cartilage, thicken the synovium, disrupt subchondral bone remodeling, and cause clinically significant pain, stiffness, and functional degeneration.[260] Arthritis is characterized by chronic joint inflammation that causes swelling, limited movement, and persistent pain.[257,261] Among the various forms, OA remains the most frequent; however, RA is a systemic autoimmune illness characterized by bilateral synovial inflammation and progressive joint degeneration.[257,262]

In addition to synovial inflammation, bone tissue is actively involved in inflammatory musculoskeletal disorders and plays a critical role in disease progression. Bone remodeling is regulated by a dynamic balance between osteoclast-mediated resorption and osteoblast-mediated formation.[263] However, this balance is disrupted under inflammatory conditions. Pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 promote osteoclastogenesis while inhibiting osteoblast function, leading to progressive bone loss and structural damage. This imbalance is largely mediated through the RANK/RANKL/OPG signaling pathway, where immune cells and stromal cells enhance RANKL expression, thereby accelerating osteoclast differentiation and bone resorption.[264] Clinically, this contributes to periarticular bone erosion, systemic osteoporosis, and increased fracture risk in chronic inflammatory diseases. Bone tissue can also be affected by infectious conditions such as osteomyelitis, which presents distinct pathological and therapeutic challenges.

Osteomyelitis is characterized by microbial infection of bone tissue, leading to persistent inflammation, tissue destruction, and impaired healing. The presence of bacterial biofilms, combined with the dense and relatively poorly vascularized bone matrix, significantly restricts drug penetration and contributes to suboptimal therapeutic outcomes.[265] Recent studies have explored lipid-based nanocarriers to overcome these limitations. For instance, curcumin-loaded cubosomes have demonstrated promising physicochemical and functional properties for localized therapy in

osteomyelitis. The formulation exhibited a particle size of approximately 186 nm, a negative zeta potential (−17.5 mV), and an entrapment efficiency of 71.24%, indicating suitable nanoscale characteristics and efficient drug loading. In vitro evaluations further revealed good stability, favorable rheological behavior, and controlled drug release profiles, supporting their potential application for localized drug delivery in bone infections.[81]

In the context of intra-articular drug delivery, several physiological barriers within the joint environment must also be considered. Synovial fluid plays a critical role in nutrient transport, however, diffusion within this compartment is strongly influenced by molecular size, charge, and the dense extracellular environment, which can limit nanoparticle mobility.[266] In inflamed joints, nanoscale lipid systems may interact extensively with synoviocytes and immune cells, often resulting in preferential uptake within the synovium rather than direct penetration into cartilage tissue.[267,268] While this behavior may be advantageous for synovium-targeted therapies, it can limit effective drug delivery to deeper cartilage regions. Furthermore, the cartilage matrix presents an additional barrier due to its dense and highly organized structure. Studies have shown that smaller nanocarriers exhibit significantly better diffusion into cartilage compared to larger vesicular systems, which demonstrate minimal penetration under similar conditions.[268] The integrity of the extracellular matrix further influences this process, as matrix degradation can enhance nanoparticle transport.[3] At the cellular level, interaction with chondrocytes is also dependent on carrier design, surface modifications, such as cell-penetrating peptides or charge tuning, can significantly improve cellular association and uptake.[269–271] These findings highlight that both synovial interactions and cartilage diffusion barriers must be carefully considered when designing lipid-based nanocarriers for joint-targeted therapy.

Nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) are common pharmacological treatments that modulate cytokine activity and reduce inflammation. However, the use of these agents is frequently limited by serious side effects. NSAIDs can cause gastrointestinal discomfort, bleeding, kidney dysfunction, and a high risk of cardiovascular or thromboembolic events.[272] DMARDs can cause rashes, diarrhea, alopecia, interstitial lung disease, folate insufficiency, and hepatotoxicity.[273] Despite their potency as anti-inflammatory agents, corticosteroids have been linked to systemic complications such as weight gain, fluid retention, hypertension, diabetes, osteoporosis, increased susceptibility to infection, skin thinning, mood disturbances, and adrenal suppression when used long-term or at high doses.[274] These limitations highlight the need for safer therapeutic alternatives and have increased interest in natural anti-inflammatory compounds such as curcumin. In this context, curcumin-loaded lipid-based nanocarriers, including liposomes, ethosomes, phytosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have emerged as promising delivery systems because they may improve tissue penetration, enhance local retention, enable controlled release, and reduce off-target toxicity.[274]

Yeh et al successfully encapsulated curcumin, a poorly water-soluble polyphenol with established anti-inflammatory properties, in soybean phosphatidylcholine-based liposomes for osteoarthritis treatment. Curcuminoid-loaded liposomes showed approximately 70% entrapment efficiency, a consistent particle size, and much higher cellular absorption than free drugs. Cur-liposomes reduce macrophage-mediated inflammation and inhibit osteoclast differentiation. They also protect against osteoblast differentiation and mineralization. Curcuminoid liposomes inhibited osteoclastogenesis by decreasing the levels of inflammatory markers in osteoblasts and increasing the OPG/RANKL ratio when stimulated with IL-1β. These findings imply that curcuminoid-loaded liposomes may help reduce OA progression by decreasing inflammation and maintaining bone homeostasis.[51]

Similarly, positive outcomes have been reported in rheumatoid arthritis with intra-articular nanostructured lipid carriers (NLCs). Shinde et al developed curcumin-loaded NLC *smart gels* composed of cetyl palmitate, Labrafac PG, Captex-200, Tween 80, and Labrasol, which were disseminated within Pluronic F-127/F-68 matrices and optimized using a factorial design. Sterile syringeable CUR-NLC gels remained colloidally stable after gamma sterilization and were highly biocompatible. In an antigen-induced monoarthritis rat model, CUR-NLC therapy dramatically reduced knee inflammation compared to free curcumin, eradicating macroscopic swelling, redness, and stiffness. Histological investigation demonstrated no inflammatory infiltration in the intra-articular cavity, and the treated joints returned to near-normal morphology by the end of the trial. These findings indicate that lipid-based nanocarriers are promising for increasing curcumin delivery in both OA and RA, improving joint outcomes while minimizing systemic toxicity.[49]

Collectively, the data from Table 1 and Table 2 highlights that achieving therapeutic efficacy in joint inflammation is primarily governed by the ability of lipid-based nanocarriers to adapt to the unique physiological barriers of the joint microenvironment, particularly within the synovial compartment. The evidence consistently indicates that intra-articular administration and localized delivery systems, such as smart gels, are the most effective strategies for maximizing drug retention within the joint while minimizing systemic exposure. Rather than relying on extensive penetration into the dense and avascular cartilage matrix, most nanocarriers preferentially accumulate in the synovium, where they interact with synoviocytes and immune cells. This localized retention appears to be sufficient to exert significant therapeutic effects. From a design perspective, particle size and carrier architecture play a critical role in determining intra-articular behavior. Nanoscale systems generally demonstrate improved stability within synovial fluid and enhanced cellular interactions, whereas larger vesicular carriers tend to remain confined to the synovial space. In addition, sustained-release formulations, particularly nanostructured lipid carrier (NLC)-based gels, contribute to prolonged intra-articular residence time and continuous drug availability, which are essential for maintaining therapeutic efficacy.

Inflammation in Lung

Pulmonary inflammation is a complex pathological process that underlies a wide range of chronic respiratory diseases, including chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, and acute lung injury.[55,57] The major challenges in the treatment of lung inflammation include insufficient drug concentration at the target site, systemic side effects, and limited drug penetration across the epithelial and alveolar barriers. Bioactive compounds such as curcumin have demonstrated relevant anti-inflammatory and antioxidant activities capable of modulating pulmonary inflammatory pathways; however, their clinical application is hindered by poor aqueous solubility and low bioavailability. To address these limitations, liposome-based delivery systems have been developed to enhance curcumin stability and bioavailability in target tissues while protecting the active compound from degradation.

A critical consideration for pulmonary delivery is the interaction between lipid-based nanocarriers and the alveolar microenvironment, particularly pneumocytes. Upon inhalation, nanoparticles first encounter the pulmonary surfactant layer before reaching alveolar epithelial cells (AECs). This surfactant layer can significantly modulate cellular interactions, in some cases reducing nanoparticle uptake by AECs through the formation of mixed surfactant–nanoparticle aggregates that remain at the interface rather than entering the cells.[275] Beyond surfactant interactions, the formation of a protein or surfactant "corona" from bronchoalveolar lavage fluid (BALF) further influences nanoparticle behavior and uptake kinetics. For instance, while liposome uptake appears relatively insensitive to corona formation, other lipid nanostructures such as cubosomes are strongly affected by its composition.[276] The surface properties of these carriers, including hydrophilicity and charge, also determine their interaction with pneumocytes and their potential for systemic exposure. More hydrophobic liposomes tend to exhibit greater transcellular transport across the alveolar epithelium, whereas highly hydrophilic systems show prolonged lung residence with reduced epithelial transport and lower macrophage clearance.[277] Similarly, neutral or negatively charged liposomes are generally more stable in BALF and exhibit improved mucus permeation, while cationic systems tend to aggregate and undergo rapid phagocytosis.[276,278] Evidence from large animal models suggests that systemic exposure primarily results from drug or lipid components released and absorbed across the epithelium, rather than the transport of intact vesicles through lung lymphatics.[279] Despite these complex interactions, lipid nanocarriers have demonstrated favorable safety profiles in advanced lung models, showing effective uptake by both pneumocytes and macrophages without significant cytotoxicity or pro-inflammatory responses.[280,281]

These mechanistic considerations are supported by experimental studies demonstrating the therapeutic potential of lipid-based nanocarriers in pulmonary inflammation. Kokkinis et al demonstrated that liposomal curcumin significantly counteracted the effects of cigarette smoke extract by reducing the expression of pro-inflammatory proteins, including GM CSF, EGF, and ST2, which were otherwise up-regulated following cigarette smoke exposure. In addition, several cigarette smoke-induced markers of cellular senescence, such as p16, p21, osteopontin, basic FGF, and uPar, were markedly reduced following liposomal curcumin treatment.[55] This preclinical evidence indicates that curcumin formulated in liposomal systems is more effective than its free form in reducing the expression of inflammatory mediators and

markers of cellular senescence induced by irritant exposure, thereby highlighting the potential of this strategy in the management of inflammatory lung diseases.

Findings from Tables 1 and 2 indicates that the therapeutic efficacy of curcumin in pulmonary diseases is governed by how effectively lipid-based nanocarriers interact with key target cells in the alveolar region, particularly alveolar epithelial cells (pneumocytes) and alveolar macrophages. The findings highlight that, although inhalation enables direct local deposition in the lungs, systemic administration such as intraperitoneal (IP) injection in preclinical models can also play a critical role in enhancing systemic exposure and subsequent pulmonary accumulation. As shown in Tables 1 and 2, SLNs with a particle size of approximately 190 nm, delivered via the intraperitoneal route, significantly prolonged circulation time and increased drug levels in lung tissue. This enhanced distribution is closely associated with improved modulation of inflammatory pathways, including the suppression of Th2-associated cytokines (IL-4 and IL-13) and reduction of airway hyperresponsiveness. Such effects are attributed to the nanocarrier's protective function, which minimizes premature metabolic degradation and allows sustained delivery to deeper lung regions.

Inflammation in Nerve

Neuroinflammation plays a central role in the progression of neurodegenerative disorders, including Alzheimer's disease (AD), in which sustained inflammatory responses are closely linked to amyloid pathology and neuronal dysfunction.[65,66] The accumulation of amyloid beta peptides within senile plaques not only represents a pathological hallmark of the disease but also acts as a potent trigger for inflammatory cascades in neural tissue. Curcumin has attracted considerable interest because of its intrinsic anti-inflammatory and neuroprotective properties, as well as its natural fluorescence and high affinity for amyloid beta peptides. However, a significant obstacle for curcumin in neural therapy is its inability to effectively cross the blood-brain barrier (BBB).

In AD, most nanostructures do not simply slip through the BBB via passive diffusion, instead, they must be engineered to exploit specific transport pathways under defined conditions. The primary mechanism for brain entry is receptor-mediated transcytosis (RMT), where nanocarriers are functionalized with ligands, such as antibodies or peptides targeting transferrin, insulin, or low-density lipoprotein receptors, that trigger endocytosis into endothelial cells and subsequent exocytosis into the brain parenchyma.[282–285] Examples include curcumin-conjugated nanoliposomes or polysorbate-80-coated particles that mimic endogenous lipoproteins. Additionally, adsorptive-mediated transcytosis (AMT) can be utilized, where cationic surface modifications enhance electrostatic interactions with negatively charged endothelial membranes.[284,286]

The feasibility of such crossing is governed by strict physicochemical design windows. Effective BBB-penetration typically requires a particle size <100 nm (ideally <50 nm for efficient transcytosis), a near-neutral or mildly negative zeta potential, and high hydrophilicity (often via PEGylation) to prolong systemic circulation.[284,285] While neuroinflammatory conditions such as Alzheimer's disease may increase BBB permeability, the barrier remains highly restrictive, blocking over 98% of small molecules, thus, rational and targeted design remains essential. It is important to acknowledge that only a small fraction of the administered dose typically reaches the brain parenchyma.[283,287,288] Despite this limitation, even low levels of accumulation may still exert therapeutic effects. Preclinical studies have shown that curcumin-loaded nanoliposomes are well tolerated, reduce amyloid peptide secretion, attenuate neurotoxicity, and selectively accumulate in pathological regions such as the hippocampus and neocortex.[66]

The intricate transport processes of liposome nanocarriers across the BBB are illustrated in Figure 2. The mechanism of direct penetration (A) is primarily driven by adsorptive-mediated transcytosis, where the electrostatic attraction between positively charged liposomal surface groups (such as cationic lipids or amino acids) and the negatively charged endothelial membrane facilitates endocytosis. This internalization can be further enhanced by incorporating cell-penetrating peptides (CPPs), such as the TAT peptide, to promote deeper membrane interaction. Alternatively, receptor-mediated transcytosis (B) utilizes specific ligands that bind to receptors overexpressed on the BBB surface, such as the transferrin receptor. This highly specific ligand-receptor interaction not only regulates the internalization of the nanocarrier but also governs its subsequent delivery into the brain parenchyma. Upon successfully bypassing the BBB, these multi-functional liposomes can be precisely directed toward amyloid-beta (Aβ) plaques (C), enabling targeted therapeutic intervention for Alzheimer's disease.[289]

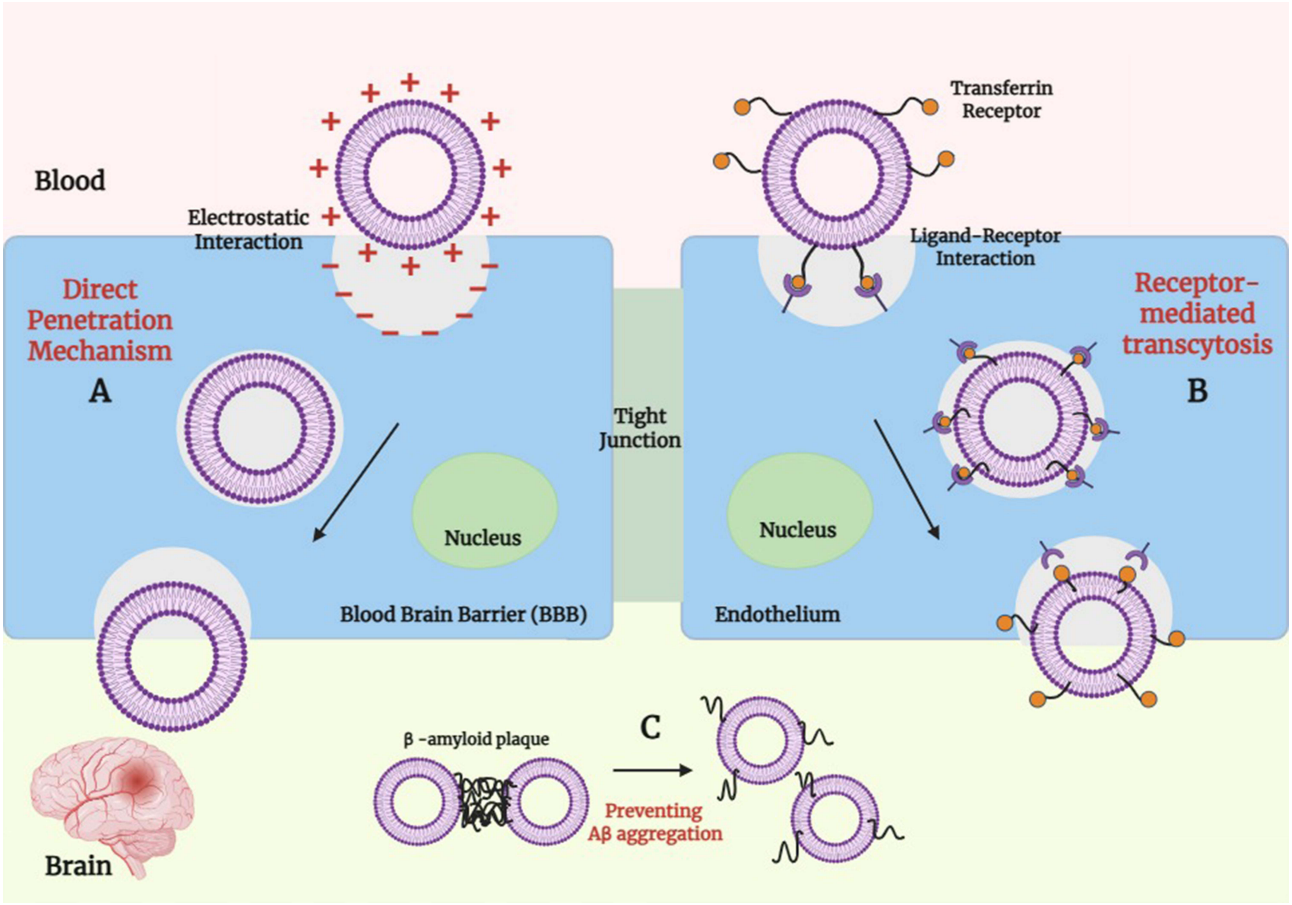

Figure 2 Transport process of liposome nanocarriers across the blood-brain barrier (BBB).

The therapeutic effectiveness of curcumin in neuroinflammatory disorders is primarily influenced by the choice of administration route and the ability of lipid nanocarriers to reach specific brain target sites, including the hippocampus, neocortex, and amyloid-beta (Aβ) plaques. The data from Tables 1 and 2 indicate that different delivery routes offer distinct advantages depending on the targeting objective. Systemic administration, particularly via intraperitoneal injection in preclinical models, enables distribution to brain tissue and supports accumulation in regions associated with neurodegeneration. The oral route also demonstrates potential for long-term management by facilitating brain exposure through systemic circulation. In contrast, localized approaches such as intracranial or intracerebral injection allow direct and precise delivery to specific brain regions, including areas with Aβ deposition. Across these strategies, effective targeting of brain parenchyma and associated pathological sites is essential for enabling localized therapeutic action. The ability of nanocarriers to reach and localize within these regions ultimately determines the success of curcumin delivery in neuroinflammatory conditions.

Inflammation in Gastrointestinal

Effective clinical management of gastrointestinal inflammatory disorders, particularly Inflammatory Bowel Disease (IBD) and Ulcerative Colitis (UC), is frequently obstructed by the formidable and fluctuating physiological landscape of the digestive tract. Therapeutic agents must navigate a treacherous path characterized by a vast pH gradient, ranging from a harsh acidic gastric environment to an alkaline intestine, along with enzymatic degradation and a defensive mucus barrier. These inherent challenges are further compounded by disease-associated pathophysiological alterations, such as accelerated intestinal transit time and microbial dysbiosis,[290] which collectively impede the retention and accumulation of drugs in inflamed mucosa. In this context, curcumin has emerged as a therapeutic paradox, and although it possesses potent anti-

inflammatory properties, its clinical utility is severely compromised by these biopharmaceutical barriers, resulting in negligible solubility, rapid metabolic clearance, and premature degradation.[291] Consequently, engineering lipid-based nanocarriers has become a critical strategy for shielding curcumin from this hostile environment. Solid Lipid Nanoparticles (SLNs), in particular, represent a leading approach that effectively circumvents these limitations, significantly enhancing curcumin's solubility and bioavailability to ensure optimal therapeutic efficacy in UC management,[291] The advantages of SLNs extend beyond formulation stability to include profound cellular-level mechanisms of action. Based on the findings of,[292] the enhanced anti-inflammatory activity observed with SLN systems is driven by superior cellular uptake by macrophages. This increased intracellular accumulation facilitates the precise blockade of the NF-κB signaling pathway. At the molecular level, SLNs function by preventing the degradation of the inhibitor protein IκBα in the cytoplasm, effectively halting the translocation of the p65 subunit into the nucleus. This inhibition of gene transcription has been proven to significantly suppress the production of crucial pro-inflammatory mediators, such as NO, IL-6, TNF-α, and IL-1β, while also improving cell viability through the prevention of apoptosis, which is difficult to achieve with free curcumin.

Complementing this particulate approach, vesicular systems, such as liposomes, offer targeting strategies that are responsive to the inflammatory microenvironment. However, the stability of liposomes in the gastrointestinal tract requires careful consideration. Although acidic gastric conditions (pH ~1–3) are often considered detrimental, several studies report that many phospholipid/cholesterol-based liposomes remain relatively stable at low pH, showing minimal leakage and preserving bilayer integrity despite some aggregation or structural changes.[293–295] Lecithin-based systems, for example, retain stability during the gastric phase and tend to destabilize mainly in the intestinal environment,[296] while certain optimized formulations even exhibit enhanced stability under acidic conditions. In contrast, greater destabilization typically occurs in the intestine, where bile salts and pancreatic enzymes induce membrane disruption, vesicle fusion, and significant drug release.[294,297] Therefore, current strategies focus on maintaining gastric stability while enabling controlled release in the intestinal environment through polymer coating or pH-responsive designs.[298] Liposomes can be engineered as "smart" systems that release their drug payload in response to specific stimuli such as temperature changes or elevated enzyme levels at inflammation sites. Basak and Das (2025) developed a zwitterionic liposomal system responsive to phospholipase A2, an enzyme associated with inflammation, to ensure site-specific release of curcumin.[299] In the context of IBD, this capability is crucial because it allows curcumin to be delivered directly to inflamed intestinal tissues to modulate inflammatory pathways and alleviate oxidative stress, positioning the integration of these lipid systems as a promising therapeutic modality.[300]

Oral delivery emerges as the dominant strategy for achieving effective curcumin targeting in gastrointestinal inflammatory disorders, as reflected by the data summarized in Tables 1 and 2. Lipid-based nanocarriers, including NLCs, SLNs, and liposomes, consistently facilitate the transport of curcumin through the gastrointestinal tract and promote its accumulation within inflamed intestinal regions. Rather than relying solely on systemic exposure, these systems enable localized deposition along the intestinal lining, particularly within the colonic mucosa. Experimental findings further show that such nanocarriers can closely interact with the intestinal epithelial barrier, as demonstrated by their uptake in Caco-2 cell models and preferential localization in inflamed tissues. This targeted distribution toward the intestinal epithelium and underlying mucosal layers plays a central role in supporting localized therapeutic action. The ability to retain curcumin at these sites is therefore a key determinant in addressing inflammation within the lower gastrointestinal tract.

Inflammation in Liver

The pathological landscape of hepatic fibrosis is significantly shaped by the dynamic nature of the immune response, which triggers a sustained inflammatory cascade through the release of potent pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β.[301,302] In this cellular interaction, macrophages especially Kupffer cells and their derivatives serve a crucial dual function, they can worsen disease progression by releasing fibrogenic mediators, yet they also have the capacity to promote resolution by degrading scar tissue.[303,304] The complex interactions among immune cells highlight the need to target the fibrotic milieu during treatment.[305] In parallel, the liver plays a central role in nanoparticle biodistribution and systemic elimination. Following systemic administration, nanoparticles are rapidly distributed into hepatic sinusoids lined by liver sinusoidal endothelial cells (LSECs), where they interact extensively with Kupffer cells,

hepatocytes, and other resident cells.[306–308] This results in substantial hepatic accumulation (30–99%), making the liver a primary site of nanoparticle sequestration. Kupffer cells and LSECs exhibit high phagocytic activity, capturing a large proportion of nanoparticles and thereby limiting their distribution to target tissues.[309–311] Nanoparticles that evade initial uptake may subsequently interact with hepatocytes and undergo biliary excretion, particularly in lipid-based systems via ApoE-mediated pathways. These interactions ultimately govern nanoparticle retention, biotransformation, and clearance.[308,312]

Due to the intricacy of this condition, curcumin is a prospective therapeutic candidate because of its capacity to mitigate inflammation through the NF-κB pathway and to decrease fibrogenesis via the TGF-β1/Smad axis. However, its clinical application is hindered by intrinsic physical constraints. Curcumin encounters difficulties in permeating dense hepatic tissues and demonstrates low bioavailability, resulting in insufficient quantities at the target cellular level. The use of lipid-based nanocarriers, particularly liposomes, has emerged as a key alternative to overcome these delivery issues. Liposomal formulations containing curcumin have demonstrated considerable improvement in anti-fibrotic efficacy by specifically targeting Hepatic Stellate Cells (HSCs). The advantage of this system is its ability to optimize cellular absorption, which enhances the intracellular accumulation of the drug to inhibit proliferation and induce cell death in activated HSCs. This liposomal intervention effectively inhibited essential TGF-β1 and NF-κB signaling pathways at the molecular level, resulting in the downregulation of significant fibrosis indicators, including α-SMA and Type I Collagen. The advantage of this formulation over traditional curcumin has been validated in vivo, as demonstrated by the repair of hepatic architecture via decreased collagen deposition and lowered levels of liver damage enzymes (ALT and AST).[78]

Systemic delivery plays a central role in directing curcumin toward hepatic tissues, as reflected in the data presented in Tables 1 and 2. Intraperitoneal administration, commonly applied in preclinical models, facilitates distribution into the liver, where lipid-based nanocarriers can accumulate within the hepatic microenvironment. Following systemic administration, these nanosystems preferentially localize within key liver compartments, including hepatocytes and hepatic stellate cells (HSCs), which are the primary cellular drivers of fibrosis. This accumulation is consistent with the liver's natural role in nanoparticle uptake and clearance, enabling the effective delivery of curcumin to sites of inflammation and fibrotic activity. In addition to systemic approaches, liposomal systems demonstrate strong affinity for hepatic stellate cells in in vitro models, highlighting their potential for more targeted cellular-level delivery. Across these strategies, the ability to reach and retain curcumin within fibrotic liver tissue is a critical determinant of therapeutic effectiveness.

Inflammation in Eye

Ocular inflammation can arise from a wide range of conditions, including infection, autoimmune disorders, surface dryness, trauma, surgical interventions, and degenerative diseases, affecting tissues from the ocular surface to the posterior segment of the eye.[313,314] Dysregulated immune responses, particularly in autoimmune conditions, can target uveal and retinal tissues, leading to elevated levels of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, IL-17, and CCL2. These cytokines contribute to the disruption of the inner blood–retinal barrier, promoting vascular permeability, edema, and progressive tissue damage that may ultimately impair vision.[315] Despite the need for effective therapy, ocular drug delivery remains highly challenging due to the presence of multiple anatomical and physiological barriers. The complex multilayered structure of the cornea, sclera, and retina significantly restricts the penetration and distribution of therapeutic agents. In particular, the transport of nanocarriers is strongly influenced by their physicochemical properties, including particle size, surface charge, and composition, which determine their ability to traverse ocular tissues.[316] In addition to these structural barriers, precorneal factors further limit drug availability. Topically administered formulations, including nanoparticle-based systems, are rapidly diluted and eliminated through tear turnover, reflex blinking, and nasolacrimal drainage, resulting in a short residence time on the ocular surface.[317] Consequently, effective delivery often requires strategies that enhance mucoadhesion or utilize in situ gelling systems to prolong contact time. Safety and formulation-related challenges must also be considered in the design of ocular nanocarriers. Certain polymers and surfactants may induce ocular irritation, toxicity, or transient visual disturbances, particularly at higher concentrations.[318] Furthermore, nanoparticle aggregation can disrupt the tear film and potentially obstruct lacrimal drainage pathways.

Recent studies have demonstrated the potential of lipid-based and vesicular nanocarriers to overcome the limitations of ocular delivery. For instance, curcumin-loaded niosomes have shown promising results for the treatment of eye inflammation. The formulation exhibited a particle size of 212.0 ± 0.1 nm, a zeta potential of −5.1 ± 0.2 mV, a polydispersity index (PDI) of 0.3 ± 0.1, and a high entrapment efficiency of 96.0% ± 0.1, indicating efficient drug incorporation and nanoscale stability. In vitro studies demonstrated sustained drug release over 24 h, whereas in vivo evaluation using eye drop administration (50 μL per dose) showed accelerated healing within four days. Notably, the anti-inflammatory efficacy was comparable to conventional treatments but with reduced side effects, particularly without an increase in intraocular pressure (IOP). These findings highlight that niosomal systems can enhance corneal penetration, prolong drug residence time, and improve therapeutic outcomes in ocular inflammation.[82]

Conclusions and Future Perspectives

Lipid-based nanocarriers have shown great potential for overcoming the inherent drawbacks of curcumin, such as poor bioavailability, fast metabolism, and limited aqueous solubility. Researchers have improved stability, entrapment efficiency, tissue penetration, and therapeutic efficacy by adding curcumin to lipid matrices such as liposomes, ethosomes, phytosomes, SLNs, and NLCs. These platforms have demonstrated better anti-inflammatory, antioxidant, and tissue-protective properties than free curcumin in both in vitro and in vivo experiments, indicating their potential in the treatment of a range of inflammation-related illnesses. In addition to lowering oxidative stress and inflammatory cytokines, these formulations also enhance tissue repair, reduce systemic toxicity, and offer targeted delivery to disease-specific locations, including psoriatic skin, arthritic joints, liver tissue, and inflamed intestinal mucosa. However, a critical and balanced analysis reveals that the clinical translation of these nanostructures is still hampered by significant functional and technical limitations. The actual performance of these carriers is intimately linked to the harsh physiological environments they encounter; for instance, the structural integrity of lipid vesicles is often challenged by the acidic "acid mantle" of the skin or the aggressive presence of bile salts and lipases in the gastrointestinal tract. Furthermore, crossing highly regulated biological barriers, such as the blood-brain barrier, remains restricted to a small percentage of the administered dose, requiring precise ligand-mediated engineering rather than passive accumulation.

From a manufacturing perspective, the sensitivity of lipid nanostructures to heat and radiation presents a major challenge for sterilization and large-scale production, often leading to material loss or chemical instability. Other key limitations include physicochemical instability during storage, batch-to-batch variability, and insufficient evaluation of long-term safety, particularly for repeated or chronic administration. To address these challenges, future research should prioritize the development of robust stability-indicating analytical methods, standardized characterization protocols, and reproducible quality control parameters. Scalable and reliable manufacturing processes must also be established to ensure consistency beyond laboratory-scale production. Moreover, future studies should incorporate clinically relevant, disease-specific endpoints rather than relying predominantly on general anti-inflammatory biomarkers, while systematically evaluating the long-term safety of lipid components and excipients. In conclusion, although lipid-based nanocarriers represent a promising strategy for enhancing curcumin delivery, their successful clinical translation will depend on addressing these critical translational barriers. A more integrated understanding of nanocarrier–biological interactions, combined with advances in formulation design and manufacturing, will be essential to transform these systems from promising experimental platforms into clinically viable therapeutic solutions.

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Disclosure

The authors report no conflicts of interest in this work.

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