Pleiotropic Phytochemicals

Pleiotropic Phytochemicals:

Delivery Problems and Nano/Micro Solutions

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PREFACE

Plant-derived phytochemicals possess a myriad of pharmacological impacts and holds significant clinical possibilities for the management of both chronic and acute diseases. However, their clinical translation is often hindered by intrinsic limitations such as poor aqueous solubility, low systemic bioavailability, speedy metabolic degradation, and lack of target-specific delivery. Advanced drug delivery approaches, particularly those utilizing micro- and nanotechnology-based systems, provide effective solutions to these challenges by enhancing pharmacokinetic performance, enabling site-specific delivery, reducing dosing frequency, and minimizing off-target toxicity—ultimately improving therapeutic outcomes and patient compliance.

This book, *Pleiotropic Phytochemicals: Delivery Problems and Nano/ Micro Solutions*, explores fifteen widely studied phytochemicals and presents current research on their pharmacokinetic obstacles, formulation development using micro/nano carriers, and associated preclinical and clinical evaluations. Each chapter provides an in-depth analysis of delivery challenges, formulation strategies, safety profiles, and translational prospects associated with the respective phytochemical

With contributionfrom diverse experts from leading institutions, this volume is intended for to all the stakeholders of the healthcare domain including pharmaceutical scientists, formulation developers, medicinal chemists, phytochemists, pharmacologists, biomedical technologistsand healthcare researchers. We hope it serves as a valuable reference in advancing phytochemical-based therapeutics through innovative drug delivery approaches.

We, the editors—Prof. Partha Roy, Prof. Suvadra Das, and Dr. Moumita Das Kirtania—extend our sincere thanks to all contributing authors and collaborators for their valuable input, and we warmly welcome constructive feedback from readers to help shape and strengthen future editions of this work.

The Editors

CHAPTER 1

CURCUMIN: DELIVERY CHALLENGES AND MICRO/NANO FORMULATIONS

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Abstract

Curcumin, a bioactive polyphenol extracted from Curcuma longa, demonstrates a range of pharmacological properties, including anti-inflammatory, antioxidant, antibacterial, and anticancer actions. Even though curcumin has a lot of potential as a treatment, it has not been able to be used in clinical settings yet since it is hard to supply. This is because it does not dissolve well in water, it is not very stable chemically, breaks down quickly, and isn't highly bioavailable. These constraints lead to insufficient therapeutic concentrations at target areas. To address these challenges, micro and nano based delivery technologies have developed as effective methods to improve pharmacokinetic and pharmacodynamic characteristics of curcumin. Formulations that contain nanoparticles, liposomes, micelles, nanoemulsions, polymeric carriers, and solid lipid nanoparticles make curcumin more soluble, keep it from breaking down, allow for regulated release, and make targeted delivery easier. Recent developments in micro and nano formulations have shown better cellular absorption, extended circulation duration, and increased therapeutic effectiveness in preclinical investigations. This review emphasizes important delivery obstacles of curcumin and thoroughly examines new micro and nano formulation strategies aimed at maximizing its clinical effectiveness.

1. Introduction on sources of curcumin and its applications

The scientific community recognizes curcumin as one of the primary compounds present in the rhizome of *Curcuma longa* (turmeric) and other *Curcuma domestica* (1,2). The rhizome of turmeric is widely used as spice which is otherwise known as Indian saffron and yellow beet root (2). Demethoxycurcumin and bis-demethoxycurcumin (Curcuminoids), two similar molecules, are also present in commercial curcumin at a concentration of about 77% (1).

Turmeric (*Curcuma longa*), a common spice from India, has been used for millennia in herbal treatments to treat a number of conditions, including anorexia, diabetic ulcers, sinusitis, rheumatism, and cough. Turmeric's primary curcuminoid, diferuloylmethane, is curcumin, which gives the spice its distinctive yellow color. Anti-inflammatory, antioxidant, anti-mutagenic, anti-carcinogenic, antithrombogenic, and anti-infective benefits have notably been linked to curcumin (3). Anorexia, biliary complaints, cough, hepatic illnesses, and sinusitis are only a few of the conditions that are treated with curcumin in conventional medicine (4). Curcumin also has anti-rehumatic, wound-healing, antiviral, hepatoprotective, and anti-HIV pharmacological effects (5). With an oral dosage of 12 g/day, curcumin exhibits no side effects in clinical trials (6). To specifically find pyrrole, the photoluminescent curcumin organogel was used as an optical sensor (7). With rising pyrrole content, the photoluminescence intensity from the curcumin organogel decreased (3).

2. Delivery challenges for curcumin

The dietary spice turmeric contains a polyphenolic molecule called curcumin, which has a variety of benefits, such as antiangiogenic, anti-inflammatory, antioxidant, and antiproliferative characteristics. From the clinical trials conducted in Phase I it was reported that Curcumin is safe to use in humans even when given in large doses of around 12 g/day, however, bioavailability of curcumin was found to be minimal. (8). Owing to its limited oral bioavailability, curcumin has not been a very prominent drug candidate, despite its strong pleiotropic properties and therapeutic potential (9). Rapid metabolism, quick systemic clearance, and poor absorption appear to be the primary reasons of lesser level of curcumin in plasma and tissue. Research to date has indicated that curcumin has a strong intrinsic activity and is therefore effective as a medicinal agent for a variety of

illnesses. However, research on distribution, metabolism, excretion, and absorption of curcumin over the previous thirty years has shown that its absorption is low and metabolism is fast, which significantly reduces its bioavailability. Extremely low serum levels have been noted as one of the main findings of studies on curcumin. In 1978, Wahlstrom and Blennow used Sprague-Dawley rats to do the first known study of absorption, distribution, and excretion with curcumin. Rats given 1g/kg of curcumin orally revealed negligible levels of the compound in their blood plasma, indicating inadequate absorption from the stomach (8,10).

2.1 Pharmacology of Curcumin

Curcumin's pharmacological effects have been investigated by several researchers from all over the world. Curcumin may be able to lessen inflammation, both acute and chronic. It lowers histamine levels and may boost the adrenal gland's natural production of cortisone, which reduces inflammation (11,12). Additionally, in vitro studies showed that curcumin has anti-inflammatory properties on human vascular cells. Curcumin has anti-inflammatory qualities because it inhibits human endothelial cells stimulated by TNF-α inflammatory response by interacting with NF-κB. Moreover, curcumin has the ability to inhibit platelet-derived growth factor (PDGF) (12).

Numerous investigations have demonstrated curcumin's potent capacity to reduce iron complex, impede lipid peroxidation, and remove nitric oxide (NO), hydrogen peroxide, and superoxide radicals produced by active macrophages. It has been demonstrated to scavenge several reactive oxygen species (such as anions of superoxide, radicals of nitrite and hydrogen peroxide) that are formed by macrophages both in *in vitro* and *in vivo* settings (13). These could be the main ways that curcumin demonstrates its antioxidant properties.

Curcumin may be able to stop newly identified cancers caused by radiation or chemotherapy. Curcumin has been proven to have anti-cancer capabilities by influencing many biological processes such as oncogene expression, mutagenesis, cell cycle control, apoptosis, tumorogenesis, and metastasis (14). Numerous studies have examined and proven the antitumor-promoting qualities of curcumin. These investigations demonstrated that curcumin had antitumor-promoting properties by causing human leukemia cells to undergo apoptosis (15). Research has demonstrated that dietary curcumin specifically inhibits the activity of cyclooxygenase (COX)-2 in the cancerous cells of colon and human breast (16,17).

Curcumin also has an impact on a range of cell adhesion molecules and growth factor receptors that are implicated in tumor metastasis, angiogenesis and growth.

Oxidative stress may have a variety of effects on HIV illness. A function for metabolites generated from plants that exhibit synergistic antioxidant action could shield patients against the spread of viruses and the cell death caused by oxidative stress. Antioxidants, namely turmeric, turmerin (a water-soluble extract), and curcumin (a lipid-soluble extract), have been studied for their potential effectiveness as anti-HIV medications. T_m (80 ng/ml) raised cell number by 60% and decreased infection by 26% when added to 3'azido 3'deoxythmidine (AZT) (5μM). Meanwhile, the combination increased cell number by 30% and inhibited infection by 37%. When T_m (800 ng/ml) was compared to AZT at 5 μM or 80 ng/ml in the proliferation experiment, lymphocytes from HIV-positive patients shown a greater reduction of mitogen responsiveness. Turmeric, when taken with AZT, decreased HIV-infected T-cell proliferation, infection, and improved cell survival. Combining turmerin with AZT at lower levels may result in effective anti-HIV therapy (18).

The antibacterial property of curcumin is very high. In vitro, curcumin blocks the growth of *Helicobacter pylori* strains and inhibits the growth of several other bacteria, including *streptococci, staphylococci, and lactobacillus* (12). Curcumin, at dosages ranging from 0.5 to 4 mg/ml, has been shown to reduce the ability of *Streptococcus mutans* to cause cancer. In endodontics, it will be helpful as a root canal medication since it is also potent against *Enterococcus faecalis* (19). Due to its effectiveness against *Penicillium digitatum*, *Aspergillus flavus*, *A. parasiticus*, and *Fusarium moniliforme*, it also functions as an antifungal agent (12). It is effective against *Plasmodium falciparum*, *Leishmania*, and *E. histolytica*, among other protozoa.

Curcumin has antihyperalgesic properties, among other medical effects. One study found that vanilloid moiety of curcumin activates TRPV1 and contributes to nociception. Vanilloid moiety of curcumin is thought to activate TRPV1, a key receptor for nociception. Curcumin inhibits capsaicin's activation of TRPV1, leading to reduced pain hypersensitivity (20).

It is believed that curcumin has minimal toxicity to both humans and animals. In one investigation, a phase one clinical trial comprised 25 volunteers. For three months, these 25 volunteers received up to 8000 mg

of curcumin daily, and no overt adverse effects were observed. Five more clinical trials including human subjects with 1125–2500 mg of curcumin daily validated the material's apparent safety (21). Curcumin and its equivalents have not been linked to any side effects, with the exception of a few isolated incidences of contact dermatitis, one of which affected a miller who worked in a spice shop.

3. Micro formulations for curcumin

Curcumin is formulated as a large-loading microemulsion that facilitates ease entry into the skin. Canales and her associates created curcumin-loaded microemulsions using an oil phase (oleic acid), surfactant (Tween 80) and co-surfactant (Transcutol HP). They identified the region for microemulsion production by creating pseudo-ternary diagrams for various ratios of surfactant and co-surfactant. In order to describe the microemulsions, the researchers also looked into a number of characteristics, including weight, size of droplet, viscosity, refractive index, conductivity, and in vitro skin penetration tests.

Upon preparation and characterization, nine microemulsions were observed, exhibiting distinct and consistent compositions where the size of the globules was contingent upon the component proportion. Based on the ratio of (40:40:10:10) including oleic acid, Transcutol® HP, and Tween® 80. water, the microemulsion with the maximum loading capacity (60 mg/mL) was able to permeate the viable epidermis and, at 24 h, the receptor medium contained 10.17 ± 9.7 μg/cm of overall curcumin. Confocal laser scanning microscopy enabled visualization of the distribution of curcumin in the skin, revealing that the greatest concentration was found between 20 and 30 μm. Curcumin can penetrate and enter the skin when it is included in a microemulsion. Curcumin's localization would be significant in circumstances when treating local diseases is the goal, particularly in the viable epidermis (22).

In 2021, Amuti and colleagues created water-in-oil-in-water (W/O/W) microemulsions and oil-in-water (O/W) emulsions to improve curcumin's water solubility and antioxidative characteristics. MEs were evaluated using particle size, viscosity, electrical conductivity, polydispersity index (PDI), and transmission electron microscopy. MEs were studied for their antioxidant properties and curcumin release in vitro. Proton nuclear magnetic resonance spectroscopy (^{1}H NMR) was used to determine curcumin localization inside MEs. Curcumin-loaded MEs had spherical

droplets with a PDI of 0.2-0.3 and an average particle size of 10.0-20.0 nm. ^{1}H NMR demonstrated the presence of curcumin within MEs. The authors observed combined effects of the MEs produced in this investigation significantly increased solubility of curcumin. Additionally, W/O/W ME demonstrated improved sustained release and antioxidant properties than O/W ME, according to assessments of the in vitro release and storage stability of the two experimentally produced MEs. For the two assessed ME, between storage conditions of 4°C and 25°C, there were no appreciable alterations.

Finally the authors concluded the suitability of O/W and W/O/W MEs for curcumin administration (23).

In 2015 topical turmeric microemulgel was developed by Sarafian and her co-workers. They studied about an autoimmune, recurring, chronic, inflammatory skin condition, psoriasis, which is inflammatory. Approximately 1% to 3% of the global population is impacted. Symptoms of hyperproliferation of keratinocytes include redness, thickness, and scaling of the epidermis, as well as itching and lesion development. These lesions typically cause medical and psychological distress to the patients. Many oral and topical treatments are available to treat psoriasis symptomatically; however, they can have significant negative effects in certain patients. The efficacy of the topical product was evaluated on 34 patients affected with plaque psoriasis with mild to moderate level, through a randomized clinical test, which was double blinded.

The results were assessed using the Dermatology Life Quality Index (DLQI) Questionnaire, Psoriasis Area and Severity Index (PASI) score, and images taken before and after therapy. The findings indicate a significant improvement ($P<0.05$) in the clinical and quality of life indicators for treated lesions when compared to untreated lesions. The side effects that were documented were minor and were also noted. According to our research, the suggested microemulgel might be taken into consideration as a substitute in certain cases and, possibly as an extra therapeutic option for a large number of plaque psoriasis patients (24).

The solubility and bioavailability properties of curcumin were successfully increased with the development of a novel curcumin microemulsions system (CUR-MEs). A number of microemulsion formulations were established by (25) and assessed employing various ratios of surfactants, oils, and co-surfactants (S&CoS). Solubility of curcumin may be increased to 32.5 mg/mL by using the ideal formulation, which includes Transcutol P

aqueous solution, Cremophor RH40 (surfactant), and Capryol 90 (oil). Rats were used for the pharmacokinetic analysis of microemulsions in comparison to the comparable suspension. Following dilution, microemulsion stability was excellent. When compared to suspension, microemulsions exhibit a considerably higher AUC (area under the curve) and C_{max} ($p < 0.05$). Curcumin's relative bioavailability was 22.6 times greater in microemulsions than in suspension. According to the results, the CUR-MEs might be a good way to improve the oral bioavailability of curcumin.

Colon targeted curcumin microspheres with Eudragit S100 have been developed by Madhavi and her co-workers (26) and they assess the formulation for *in vitro/in vivo* properties. They developed microspheres via the "O/O solvent evaporation" method. After analyzing the impacts of several process variables, including the drug:polymer ratio, stirring speed, and emulsifier percentage, the formulation was optimized. The characteristics of the produced microspheres were evaluated in vivo as well as in vitro. Surface shape, drug release, drug polymer interaction, particle size, percentage yield, percentage drug entrapment, under conditions that replicated gastrointestinal transit, and stability were among the in vitro criteria that were investigated. Drug release into blood circulation and distribution studies to various organs were studied as in vivo characteristics using an improved formulation. Male albino rats were used to estimate in vivo parameters. The o/o solvent evaporation process was successfully used to create Eudragit S100 curcumin microspheres. The best formulation was determined to be microspheres made with a 1:2 drug:polymer ratio, 1000 rpm of stirring speed, and 1.0% w/v emulsifying agent concentration. The formulation increased curcumin's water solubility by eight times, according to release trials using the optimized formulation. FTIR analyses showed that the properties of drug did not alter after the microspheres were created. Therefore, rather than the drug changing into a different physical state, the increase in surface area of the drug ingredient is the one, which is responsible for the boost in solubility. Images of electron microspheres underwent scanning were used to confirm this. The drug release model used by Korsmeyer and Peppas was followed. According to accelerated stability experiments, the medication remains stable in its formulation at room temperature for a minimum of 14 weeks. Following oral administration of the formulation, in vivo experiments showed a sustained release of the medication into the systemic circulation. Additionally, the adjusted formulation effectively attained the colon aim. The majority of the drug load (79.0%) in eudragit microspheres was transported to the colon, but only 28.0% of the entire dose in plain drug liquid reached the intended site.

Novel polymer-encapsulated magnetic microspheres were prepared by Esthar and his associates that allow site specific control delivery to surpass therapeutic outcomes. Authors developed magnetic microspheres encapsulated in polymer and loaded with curcumin using a new emulsion-based method (27). The process entails creating a binary emulsion system (water-in-oil-in-water, or W1-O-W2), which is then followed by the aqueous phase (continuous phase) being evaporated to create polylactic acid (PLA) microspheres with magnetic properties that contain ferrite magnetic nanoparticles and curcumin (CUR) (FA-MMS). Using a variety of microscopic and spectroscopic methods, the produced Ferrite@FA-CUR-PLA-MMS drug carrier was described. The release of curcumin from the drug carriers which was pH-dependent, was distinctive and consistent in the produced Ferrite@FA-CUR-PLA-MMS medication. The authors observed that pH-dependent curcumin release from the drug carriers was distinct and consistent in the produced Ferrite@FA-CUR-PLA-MMS medication. The MTT assays used to determine the cytotoxicity of the Ferrite@FA-CUR-PLA-MMS medication revealed a minimally harmful effect on A549 and Hela cancer cells. The IC value for A549 cells was found to be 15 μg/ml during a 24-hour period, while the IC value for Hela cells was 12 μg/ml. The IC values for Hela and A549 cancer cells were discovered to be 8.8 μg/ml and 10.2 μg/ml, respectively, during a 24-hour period. Following a 10-day incubation period, the medication completely destroyed the Hela and A549 cells of malignancy. Their results show additional potential for the application of the magnetic nanoparticles for cancer treatment. Future studies on the usage of this medicine delivery system may focus on the site-specific and controlled distribution of additional cancer chemotherapy medications.

Characterizing the hydrogel macro- and microparticles intended to administer curcumin to human colon cancer cells (LoVo) was the goal of Wezgowiec and her co-workers. A total of six different types of sodium alginate-based vehicles were created: untreated, coated with chitosan or gelatin, and micro- and macroparticles. Ionotropic gelation was used in conjunction with two different techniques to create the uncoated macroparticles and microparticles: an emulsion-based technique and an extrusion technique. Using scanning electron microscopy, the surface morphology of the particles was examined, and the average size was determined. Calculations were made for the swelling index, moisture content, and encapsulation efficiency.

A colon, intestine, and stomach simulation experiment was used to examine the release of curcumin from the particles. Human colon cancer cells were

tested for the cytotoxicity of carriers loaded and unloaded with curcumin in order to determine the anticancer qualities of such tailored drug delivery systems. The authors also observed that the payload of the microparticles was released over a longer period of time and substantially less was encapsulated than that of the macroparticles. In contrast to the unloaded carriers, which were not cytotoxic to LoVo cells, the curcumin-loaded carriers dramatically reduced the viability of the cells after incubation with microparticles as opposed to macroparticles. The most promising carriers were either uncoated or covered with gelatin, although further research is needed to fully understand their possible anticancer effects (28).

Bhatia and her co-researchers worked on the enhancement of Curcumin release rate by microsponges using ethylcellulose and PVA as carriers in a quasi-emulsion solvent diffusion method (29). SEM, DSC, XRD and FTIR studies were used to evaluate the microsponges before determining their total drug content and entrapment effectiveness. The generated microsponges were thereafter packed in a firm gelatin capsule shell and then injected in carbopol gel to test their potential for oral and topical drug administration. Furthermore, an 8-hour investigation on release rate revealed that microsponges inserted in firm gelatin capsule shells, that is the batch MS4, demonstrated 93.2% release of curcumin, but pure curcumin placed in capsules only released 11.7% of its contents. Additionally, 77.5% of the curcumin that was deposited onto the microsponges in carbopol gel was released within 24 hours of being tested for ex vivo drug deposition experiments. Franz diffusion cell analysis revealed that an estimated 207.61 ± 5.03 μg/cm^2 of medicine remained in the skin. In both situations, it was discovered that the mechanism of drug release followed zero order kinetic model with anomalous characteristics.

Sareen developed curcumin microsponges for colon-specific drug administration, avoiding the upper gastrointestinal tract (GIT) for better therapeutic outcomes (30). Using a 3(2) full factorial design, microsponges were created via the quasi-emulsion solvent diffusion method. The prepared microsponges were optimized to examine how the volume of ethanol and Eudragit L100, two independent variables, affected the drug release, particle size, and encapsulation efficiency. An in vivo investigation was conducted on the improved formulation in rats utilizing an acetic acid-induced colitis model. Based on factors including attractiveness factor (0.83), cumulative drug release (84.12%), entrapment efficiency (78.13%), and particle size (41.63 μm), the F7 formulation was chosen as the optimal one. According to release tests, microsponges blocked the drug's early release in the upper gastrointestinal tract and accurately released curcumin at colonic pH. A R^2

value of 0.9927 obtained for the batch F7 showed that the release mechanism followed Higuchi kinetics and thus it was concluded that that the drug release took place through diffusion.

A pharmacodynamic investigation demonstrated that, in comparison to free curcumin, curcumin-loaded microsponges significantly reduce colon bleeding, necrosis, and edema. This research establishes the potential of curcumin-loaded microsponges as a medication delivery method for the treatment of ulcerative colitis.

Sareen developed and assessed chitosan microspheres which were pH sensitive due to eudragit coating containing curcumin (CUR) for the treatment of ulcerative colitis, both in vitro and in vivo. Emulsion cross-linking was used to first create CUR-entrapped chitosan microspheres, which were then coated with enteric polymer Eudragit S-100. The in-vivo evaluation was conducted in mice through a colitis model generated by acetic acid. The created microspheres had high entrapment efficiency and a consistent spherical shape. The X-ray diffractogram of CUR-chitosan microspheres demonstrated less strong peaks than that of free CUR, indicating the presence of medication within the microspheres. Microspheres coated with Eudragit S-100 inhibited premature release of CUR and demonstrated regulated release up to 12 hours in accordance with the Higuchi model, but uncoated CUR-chitosan microspheres displayed burst release within the first 4 hours. A study on the in vivo biodistribution of organs revealed very little CUR in the stomach and small intestine, indicating that the microsphere in the upper gastrointestinal tract (GIT) is intact. When CUR-loaded microspheres were used instead of pure CUR, an in vivo study found a significant reduction in the severity and extent of colonic injury. This finding was supported by a histological investigation. Studies conducted in vitro and in vivo demonstrated the created formulations' potential as a pH-dependent medication delivery system to the colon in ulcerative colitis patients (31).

4. Nano formulations for curcumin

Curcumin nanoformulations (Fig. 1) significantly changed the way diseases are treated by modifying the drug's cellular absorption, permeability, and bioavailability while increasing its plasma concentration. At the location of injury, curcumin nanoparticles effectively disperse the precise therapeutic concentration of medication. Numerous studies that have been reported

have examined the nanoformulations of curcumin and their therapeutic effectiveness against various diseases (32).

Curcuma longa (L.) rhizome contains curcumin, which is an essential curcuminoid and a natural polyphenol, known as the "wonder drug of life". It is an important food for healing. This plant is commonly used to treat cancer, arthritis, discomfort, bruises, digestive difficulties, edema, and other ailments. Limited water solubility of curcumin limits its application in medicine due to low systemic bioavailability and quick breakdown, despite its significant therapeutic potential. Curcumin nanoformulation is gaining popularity as a promising alternative to boost its medicinal properties. It improves its targeted transport to the targeted tissue and its water solubility, which leads to improved drug administration, increased bioavailability, and faster treatment (33).

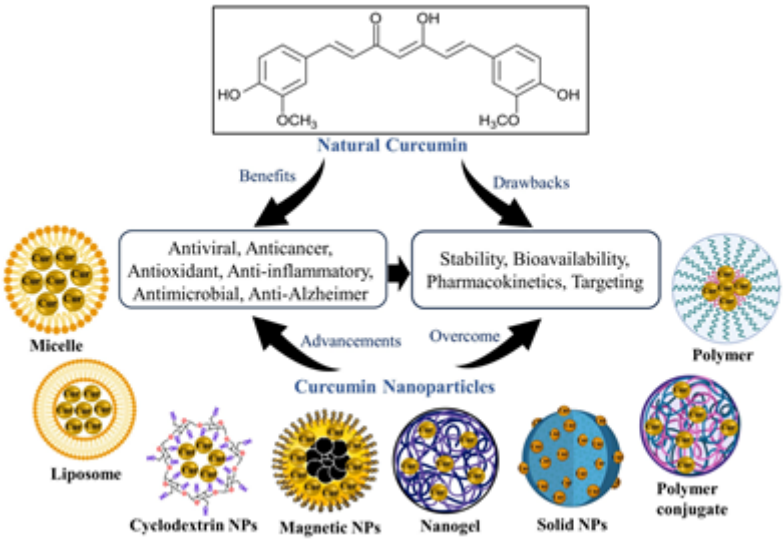

Fig. 1: Various types of curcumin nanoformulations

Nanoparticles encapsulating Curcumin and prepared with methoxy poly (ethylene glycol) poly (ε-caprolactone) was reported by Sasaki et al. to have higher oral bioavailability and effective drug administration (34).

Using cholesterol as a carrier and mannitol as a cryoprotectant, Jourghanian et al. created solid-lipid nanoparticles encapsulating curcumin through high-

pressure homogenization, improving their stability and biocompatibility (35). Further research showed that the use of human serum albumin nanoparticles which were conjugated with folate and loaded with curcumin (F-CM-HSANPs), and prepared by chemical conjugation of folate to the surface of the developed nanoparticles, when given parenterally resulted in a longer retention time with targeted delivery in vivo in current clinical studies. (36).

The complex ß-cyclodextrin-curcumin nanosponge was produced and developed by (37) using cyclodextrin-based cross-linking of curcumin with dimethyl carbonate. This considerably increased the solubility and stability when compared to free curcumin. Additionally, curcumin's in vitro drug release effectiveness was discovered to be non-hemolytic and to be carefully regulated over an extended period of time.

To better encapsulate curcumin and inhibit the growth of colon/melanoma tumors in mice, (38) created a cationic liposome using PEI-PEG as a carrier isolate (LPPC). It was discovered that the complex of curcumin and LPPC has improved anti-proliferative properties and may enter cells quickly.

Curcumin-loaded chitin nanogels made of a cross-linked polymer network were evaluated in vitro on breast cancer cell lines in a different study by (39) and results showed improvements in bioavailability, anti-carcinogenic effects, greater -controlled release, and increased stability.

To improve the bioavailability of glioblastoma therapy, (40) reported on lipid nanoparticles encapsulating curcumin and studied anti-glioma activity in encephalon tissue. The findings of their study indicate that the glioma cells treated with curcumin-loaded nanoparticles exhibited apoptotic cell death to a higher level due to the inhibition of proliferation of cells, incursion and migration, as well as greater events of arresting cell cycle and inhibition of telomerase. Consequently, curcumin-loaded nanoparticles offer a promising approach to glioblastoma therapy by overcoming the difficulties associated with drug transport to the brain. Curcumin's water solubility, cellular absorption, and regulated release with increased dissolution rates were all considerably improved by these innovative techniques.

Researchers from the University of Delhi and the Johns Hopkins University School of Medicine have worked together to create "nano-curcumin," a polymer nanoparticle-encapsulated version of curcumin that is easily dissolved in aqueous environments. Using a hydrophilic polymer (N-

isopropyl acrylamide) and N-vinyl-2-pyrrolidone and poly (ethylene glycol) monoacrylate nanoparticles, they have coated regular hydrophobic curcumin particles. This nano composition improves water solubility and enters the bloodstream with ease. It has previously been evaluated *in vitro* on pancreatic cancer cells, where it was demonstrated to have comparable or superior effects to free curcumin on cancer cells extracted from human. These actions included down-regulating interleukin-6 (IL-6) and inhibiting NF-kB (41).

Using the water titration method, (42) synthesized amorphous nano-curcumin and assessed its anti-inflammatory properties both in vitro and in ex vivo condition in rats using the method of paw edema induced by carrageenan, with Diclofenac serving as the standard. The researchers concluded that NanoCur was significantly more effective than native curcumin.

In 2022, Pourreza and his colleagues developed a novel technique for measuring celecoxib in traces using fluorescence detection and curcumin nanoparticles (CurNPs) coated on multi-walled carbon nanotubes (MWCNT–COOH) containing carboxyl functional groups. Using ultrasonic vibrations, CurNPs were kept on carbon nanotubes for the synthesis of CurNPs–MWCNT–COOH. The sensing technique relies on tracking celecoxib's quenching of produced CurNPs–MWCNT–COOH fluorescence. Transmission electron microscopy (TEM) was used to examine the morphology of CurNPs–MWCNT–COOH in both the composite and celecoxib-containing conditions. Optimal conditions were achieved by evaluating the impacts of several parameters, including pH, MWCNT-COOH quantity, and Triton X-100 concentration, on the formation of CurNPs–MWCNT–COOH and celecoxib determination. For celecoxib in the starting solution, the calibration graph was shown to be linear in the 20–220 ng mL^{-1} range. Celecoxib's detection limit, calculated three times the blank standard deviation, was 5.8 ng mL^{-1}. Eight repeat measurements of 60 ng mL^{-1} and 180 ng mL^{-1} of celecoxib yielded relative standard deviations (RSD) of 3.6% and 1.8%, respectively. The technique was used to measure the amount of celecoxib in serum samples (43).

Farshidfar created a framework that closely resembled the composition and capabilities of the natural tissues' extracellular matrix (ECM). In order to achieve this goal, a scaffold with three-dimensional structure and biomimetic properties comprising curcumin (CUR), collagen (COL), and multi-walled carbon nanotubes (MWCNTs) was made by freeze-drying.

Pure COL solutions were treated with 0.5e1.5% MWCNTs and 5e15% CUR to create scaffolds, which were then freeze-dried. Evaluation studies including scanning electron microscopy (SEM), X-ray diffraction studies (XRD) and compatibility studies using fourier transform infrared spectroscopy (FTIR), were used to assess the scaffolds' physical and chemical characteristics. Animal models based on rats and Mesenchymal stem cells (MSCs) and biological research was primarily concerned with drug release, biodegradation, biocompatibility and in-vitro bioactivity. Further they have concluded that freeze-dried scaffolds COL-MWCNTs 1%-CUR 10% has proven to offer great potential for TE applications (44).

Hettiarachchi synthesized curcumin nanoparticles without the use of nanocarriers. Curcumin was soxhlet extracted from fresh turmeric rhizome in order to achieve this. Boiling water was treated with stock solutions of varying concentrations of curcumin produced in dichloromethane, added at varying flow rates, and sonicated for varying durations of time (45). With a concentration of 5.00 mg/mL in the stock solution, a flow rate of 0.10 mL/min, and a sonication time of 30 minutes, an average particle size of 82 ± 04 nm was achieved. Particle size tends to decrease with sonication time but increases with flow rate and curcumin content in the stock solution. Curcumin's identity and strong crystallinity are demonstrated by the crisp and powerful diffraction peaks seen in X-ray diffraction; nevertheless, nanocurcumins are amorphous. Fourier-transform infrared spectroscopy spectra verify that nanocurcumin contains all of curcumin's functional groups. Images from scanning and transmission electron microscopy demonstrate nanocurcumin's flawlessly spherical form. Curcumin is not soluble in water; however, formulations containing nano-curcumin readily dissolve in water.

Ubeyitogullari and Ciftci, 2019 developed low-crystallinity curcumin nanoparticles using a unique green method of nanoparticle creation, which would increase curcumin's bioavailability (46). Using supercritical carbon dioxide (SC-CO_2) as a mold, nanoporous starch aerogels (NSAs) with 0.11 g/cm^3 of density and 60 m^2/g of surface area, 93% of porosity with a pore size of 20 nm, were utilized to create curcumin nanoparticles. The curcumin nanoparticles had 66 nm of particle size on an average. Crystalline properties of curcumin were reduced upon encapsulation into NSAs, and no chemical interaction was formed between the nanoparticles of curcumin and the matrix of NSA. With 224.2 mg of curcumin/g of NSA, the highest impregnation capacity was achieved. Compared to curcumin in free state, curcumin nanoparticles greatly increased its bioaccessibility, nearly by 173 fold. By impregnating NSAs with curcumin, the bioaccessible fraction had

42 times higher amounts of curcumin, from a minimal concentration of 0.003 to a much higher concentration of 0.125 mg/mL. This is a novel method for producing curcumin nanoparticles which were of food-grade and possessed reduced crystallinity, which will boost curcumin's bioaccessibility and maximize its use.

The potential of cyclodextrin and nanosponges based on cyclodextrin to boost bioavailability of drug delivery systems has been extensively studied. The stability complexation as well as the solubilization of curcumin with β-cyclodextrin and nanosponges based on β-cyclodextrin were investigated (47). By crosslinking β-cyclodextrin with varying molar ratios of diphenyl carbonate, nanosponges were created. β-cyclodextrin cross-linking improved the solubilization effect and complexation efficiency of β-cyclodextrin polymer, suggesting that nanosponge formulation could be used in pharmaceutical applications for active substances that are poorly soluble. Mashaqbeh and his co-workers also demonstrated that curcumin could be successfully formed in cyclodextrin complexes when they were equilibrated in a 20% ethanolic solution. Additionally, the complexation stabilities of curcumin inclusion complexes with β-cyclodextrin in relation to cross-linked cyclodextrin nanosponges were reviewed. Curcumin in crosslinked β-cyclodextrin nanosponges resulted in a more notable augmentation of drug solubility and enhanced complexation stability as compared to the curcumin-β-cyclodextrin complex. The study's findings also showed that as the number of cross-linker increased, solubilization and complexation efficiency decreased. They demonstrated the detrimental impact of raising the molar ratio of β-cyclodextrin:cross-linker by more than 1:4.

Iriventi et al., 2020 developed a topical gel containing curcumin (CUR) and caffeine (CFN) based on nanosponges (NS) that may be used as a psoriasis therapy (48). They infused NS with Topical gels, which was made of beta-cyclodextrin (β-CD) as the polymer and dimethyl carbonate (DMC) as the crosslinker. The NS was synthesized using the hot melt method. To examine all nine potential experimental runs, they built a completely randomized factorial design (32). The gels were made by adjusting the concentration of the polymer guar gum (X2) and gelling agent carbopol-934 (X1). Viscosity (Y1) and in vitro percent drug release (Y2) of prepared gels were assessed in relation to these two independent variables; additional NS and nanogel evaluation studies were carried out; in vivo animal studies were performed for optimized formulation using a mouse model of imiquimod-induced psoriasis. It was demonstrated by Iriventi and his co-scientists that the produced NS and gels (F1-F9) displayed ideal physical and chemical

properties. Formulation N10 with 12,329.78cp viscosity and 69.72% in vitro drug release was achieved as a consequence of optimization. Studies on histopathology showed that the produced nanogel had a potentially effective anti-psoriatic effect. The findings showed that, in comparison to CUR alone, which took about 20 days, the CUR and CFN combination shortened the amount of time needed to demonstrate anti-psoriatic efficacy to 10 days. Furthermore, the drug release through 12 hours has been shown by the nanogel. Finally they concluded that the combination of CUR and CFN considerably increased the anti-psoriatic efficacy in comparison to the individual components and also shortened the time needed for the effect to take effect. Therefore, a more effective drug delivery method for anti-psoriatic therapy would be the suggested nanogel.

The wide range of biological applications of curcumin makes it a naturally occurring substance that has been investigated extensively. Yet, this substance has certain disadvantages, including poor stability, low penetration targeting performance, low bioavailability, low bioavailability, rapid systemic elimination, low water solubility, and poor pharmacokinetics. Curcumin is encapsulated in nano-carriers in order to circumvent these limitations. In order to increase solubility of curcumin in water, Kanwal et al., 2023 created curcumin nanoparticles in the current investigations without the use of nanocarriers utilizing a variety of techniques, including nano-suspension (Cur-NSM), sonication (Cur-SM), and anti-solvent precipitation (Cur-ASP). FTIR, SEM, and XRD analyses were used to characterize the produced nanoparticles. The water solubility, DPPH scavenging, amylase, α-glucosidase, and β-glucosidase enzymatic activity of these curcumin nanoparticles were examined (49). It was discovered that the range of nano-curcumin particle size was 47.4–98.7 nm. While, solubility of curcumin in water is just 0.98 μg mL^{-1}, solubility increases considerably when its particle size is reduced to 79.2 μg mL^{-1}. At 75.0 μg mL^{-1}, Cur-ASP had the maximum potential for scavenging free radicals (48.84 ± 0.98%), which was comparable to normal BHT (50.48 ± 1.11%). Cur-ASP also shown, at 100 μg mL−1, the best suppression of α-amylase (68.67 ± 1.02%), α-glucosidase (58.30 ± 0.52%), and β-glucosidase (64.80 ± 0.43%), which is comparable to the conventional medication acarbose. Because of their larger surface area, nanoparticles can prevent enzyme binding sites by exposing the different groups of curcumin. Using this approach could help develop curcumin as a powerful treatment for diabetes mellitus. Additionally, the potential binding mechanisms of curcumin in the binding pocket of every receptor were examined in order to evaluate the molecular interactions of curcumin with α-amylase, α-glucosidase, β-glucosidase, and polyphenol oxidase. Curcumin's optimal

binding mode was employed to form complexes with the target proteins, and 50 ns MD simulation was utilized to verify the stability of these structures.

Some of the clinical studies were undergone with nano curcumin formulations are showed in Table 1.

Table 1. Instances of curcumin nanoformulations being used for different ailments

Formulation	Amount/dose of curcumin	Rout(s) of administration	Duration of study	Animal	Disease	Observation
Curcumin encapsulated p(PEG-PLA) micelles	Weekly 22 mg/kg	Oral	3 months	Tg2576 transgenic mouse	Alzheimer	enhanced cue memory and working memory. increased brain bioavailability of curcumin (50, 51)
Curcumin and MRI contrast agent (GdHPDO3A) encapsulated apoferritin	63 mg/kg	Intraperitoneal	24h	C57BL mouse	Hepatitis	Shielded livers from hepatitis caused by thioacetamide. Decreased inflammatory scarring (52)
Curcumin-PEG-chitosan film	2.7 mg/3 cm^2	Topical	14 days	Adult male Spraguee Dawley) rat	Wound healing	Increased production of collagen. 90% decrease in wounds (53)
Curcumin encapsulated PEG-PCL micelles in hydrogel	1 mg	Topical	7 days	Adult male Spraguee Dawley) rat	Wound healing	Improved healing of wounds, Improved granulation, increased collagen content, and advanced wound maturity (54)
PLGA-curcumin nanoparticles	0.15 mg/30 ml of 0.9%w/v NaCl	Intradermal	16 days	RjHan:NMRI female mice	Wound healing	improved wound closure as a result of curcumin and lactic acid from PLGA working together. shown the development of granulation tissue, re-epithelialization, and an anti-inflammatory action (55).

Curcumin infused solid lipid nanoparticles	25, 50 mg/kg/day	Oral gavage and IV	8 days	Male Wistar rat	Cerebral ischemia	lipid peroxidation inhibition. elevated enzymes involved in endogenous antioxidant defense. enhanced absorption capacity (56).
Chitosan nanoparticles infused with curcumin	33 mg/kg daily for 7 days following a 3-day period of induced infection	Oral	10 days	Female Swiss mouse	Malaria	increased curcumin bioavailability. cured infection with *Plasmodium yoelii* (57).
Curcumin formulation using glycerin and gum ghatti	0.5 mg/kg/day	Oral	6 weeks	Adult male Sprague Dawley) rats	Heart failure	restoration of post-myocardial infarction left ventricular fractional shortening (58).

Toxicity of Curcumin

Acute toxicity study

The development of modified solid dispersions of curcumin-loaded nanocomplexes (CNCs) in gums by Jantawong et al. 2021 allowed for the sustained and extended release of curcumin. Using mice and hamsters, the acute and long-term toxicity of CNCs were evaluated. CNCs were given to the animals orally (59-61). Random assignment was used to place the female animals (a total of 29 mice and 23 hamsters) in either the intervention or non-treatment groups. According to OECD guideline 423 for Testing of Chemicals, acute toxicity testing was conducted with a few minor adjustments to the animal number used in the test, species of rodent used and dose level. The toxicity was evaluated using the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) 2003, according to which, the most severe toxicity is classified as category 1 ($LD50 \leq 0.005$ g/kg bw) and comparatively less toxicity level in category 5 ($LD50 > 2-5$ g/kg bw). Agents with minimal toxicity ($LD50 > 5$ g/kg bw) (Erhirhie et al., 2018)61 are categorized as unclassified risks according to OECD guidelines (Creton et al., 2009)60 and are indicated by the ∞ sign. According to the majority of earlier publications, the LD_{50} of curcumin in rats and mice is roughly 2 g/kg bw (in GHS category 5 of the OECD standards for oral toxicity research) (62,63). Thus, to ascertain the true dose

for transferring from animal to human subjects, the higher dose values employed from OECD Guideline 423. Mice and hamsters were chosen as the rodent species mentioned previously. For mice, 0.1, 1.1, or 11 g/kg bw (corresponding to 0.03, 0.3, or 3 g/kg bw of curcumin, respectively) and for hamsters, 0.2, 2.1, and 21.4 g/kg bw (corresponding to 0.06, 0.6, and 6 g/kg bw of curcumin, respectively) were the single doses of CNCs administered. The blank nanocomplexes (BNCs) group included mice and hamsters that were given a single oral dose of 7.9 g/kg bw BNCs and 15.4 g/kg bw BNCs, respectively. The oral gavage method was used to provide the single dosage at a volume of 10 mL/kg body weight. The powdered BNCs or CNCs that were going to be administered were diluted 10:1 w/v with distilled water. In less than 45 minutes, the diluted samples were forced through gavage tubes. The negative control group of animals did not receive any treatment. For 14 days after treatment, clinical indicators of toxidromes (morbidity, twitching, excitability, depression, increasing fur, tremors, salivation, and mortality) were noted and documented twice a day (59).

Chronic toxicity study

The protocol was followed in compliance with the OECD guidelines for Testing of Chemicals (Section 452), with a few minor adjustments made to the rodent species, dose levels, and number of animals used. The hamsters (13 per sex group), a total of 182 mice (80-100 g bodyweight) and 168 Swiss albino mice 25-40 g bodyweight (bw) were randomly assigned to seven groups. For six months, Groups 3–5 received daily oral gavages of CNCs at low, medium, and high levels. The doses for mice (0.09, 0.27, and 0.8 g/kg bw, equivalent to 0.025, 0.075, and 0.225 g/kg bw of curcumin, respectively) and hamsters (0.18, 0.54, 1.61 g/kg bw, equivalent to 0.05, 0.15, and 0.45 g/kg bw of curcumin, respectively) were used. Group 1 (control) received a normal diet and did not receive any treatment; Group 2 received oral gavage on daily basis with BNCs (0.58 g/kg bw/day in mice or 1.16 g/kg bw/day in hamsters). The recovery groups, which consisted of 24 mice and 26 hamsters, were assigned to groups 6 and 7, respectively, to receive either the high-dose CNCs regimen or 0.58 g/kg bw/day of BNCs for a duration of 6 months. After the treatments ended at six months, the animals in groups 6 and 7 were kept for an additional twenty-eight days. Each animal that was used received a dosage volume of 10 mL/kg bw. The outcomes of the acute toxicity tests were utilized to determine the dose levels to be employed for the chronic toxicity testing. In chronic toxicity testing, the medium and low doses were approximately three times lower than the high dose, indicating that the high-dose level was comparable to the medium dose level utilized in acute toxicity studies. Every day throughout the trial, the general health, body weight, illness, and death of

each animal were assessed. Prior to their deaths, the animals were starved for a single day (59)[59].

In summary, the toxicity of high-dose CNC therapy was rated as extremely low, presumably as a result of the nanocomplex's constituent parts.

5. Future prospects

Over the years, curcumin has drawn a lot of attention due to its possible medical uses. it is important to note that the medicine containing curcumin was able to benefit from improved therapeutic value and improved pharmacokinetic features thanks to the use of nanoencapsulation techniques. Curcumin nano-formulation has made significant advancements over the past few decades and has been utilized to treat a wide range of human ailments. Nonetheless, the saying "there is always room for improvement" perfectly captures the speed at which advances are being made to curcumin in order to make it a viable therapeutic candidate. As a result, there are still a lot of obstacles to overcome before nanocurcumin can be considered a viable option for treating human illnesses. To date, a variety of curcumin nanoformulations have been developed to increase the drug's cellular absorption, tissue selectivity, and efficacy. This review highlights curcumin nanoformulations that effectively alter signaling pathways linked to many medical disorders. However, most formulations were only tested in pre-clinical models, with limited proof of concept investigations. The dangers of curcumin nanoformulation in humans remain unclear. Inquire about the safety of curcumin-based applications. Nanomedicine-based drug delivery methods can induce negative effects such as excitotoxicity, allergic responses, neuroinflammation, and DNA damage. This unusual cause necessitates accurate investigation and documentation of the biocompatibility of nanomedicines and biodegradability. Only a small number of clinical trials have been done thus far, but those that have show that nanocurcumin is consistently safe and has superior qualities than bulk curcumin, including bioavailability, chelating activity, and retention time. However, because there have been few clinical trials to evaluate the safety and effectiveness of curcumin nanoformulations in people, significant research gaps have been found. Therefore, before releasing curcumin nanoformulations onto the pharmaceutical market, numerous clinical trials involving a sizable patient population must be completed. It is also worthwhile to look into the possibility of using curcumin as a medication on its own or in an appropriate combination with another medication to expand the possibilities of chemotherapeutic approaches. According to this

theory, curcumin-loaded nanoparticles ought to be added to any other therapeutic intervention in order to lower the concentration of the primary medication and produce better therapeutic results with less toxicity. It can thereby reduce toxicity and enhance the therapeutic efficiency of curcumin-loaded nanoparticles. Nevertheless, increasing the commercial production of nano-encapsulated curcumin ought to be the top focus for researchers. Therefore, developing low-cost methods of nanoencapsulating curcumin is a business necessity in order to lower manufacturing costs and create intense rivalry with artificial additives and medications (64).

Curcumin, a polyphenolic molecule, is currently one of the most studied natural products. Its low hazardous profile and proven benefits in treating many human ailments have been documented. Many therapeutic targets for curcumin delivery have been identified over time, offering the molecular underpinnings of the pharmacological effect. Regrettably, bioavailability and transport of curcumin pose significant challenges to its efficacy, hindering its application in medical settings. More curcumin-based complexes with noteworthy pharmacological characteristics may soon be discovered and developed into potent therapeutic medicines for the treatment of human illnesses. The development of this science has enormous potential for using this polyphenol in medicine. Furthermore, because curcumin has a multifunctional profile, an effective delivery system may provide a better chance of effective prophylaxis or treatment in complex multifactorial disorders, like cancer and systemic inflammatory diseases. This supports the use of curcumin-based agents as therapeutics that can both prevent disease and modify it (65).

6. Conclusion

Due to its many health benefits, curcumin has drawn attention from all over the world. These benefits seem to be primarily attributed to its anti-inflammatory and anti-oxidant properties. The optimal way to reap these benefits from curcumin is to combine it with substances like piperine, which greatly boost its bioavailability. Curcumin may help cure oxidative and inflammatory disorders, metabolic syndrome, anxiety, arthritis, and hyperlipidemia, according to study. Furthermore, it may help reduce inflammation and soreness in the muscles caused by exercise, which would enhance recovery and ability for people who exercise. Furthermore, for those without medical diagnoses, a comparatively low dosage may be beneficial to their health.

7. List of abbreviations

1. HIV – Human Immuno Deficiency Virus
2. g – Gram
3. Kg – Kilogram
4. NF-κB- Nuclear Factor kappa-light-chain-enhancer of activated B cells
5. TNF-α- Tumor Necrosis Factor- alpha
6. NO- Nitric oxide
7. ng- Nanogram
8. ml- Mililitre
9. AZT- 3'azido3'deoxythmidine
10. Tm- Trabecular meshwork
11. µM- Micrometer
12. T-Cell- Thymus cell
13. TRPV1- Transient Receptor Potential Vanilloid type 1
14. O/W- Oil-in-water
15. W/O/W- Water-in-oil-in-water
16. PDI- Polydispersity index
17. ME- Microemulsion
18. NMR- Nuclear Magnetic Resonance
19. PASI- Psoriasis Area & Severity Index
20. DLQI- Dermatology Life Quality Index
21. CUR-MEs- Curcumin microemulsions system
22. S&CoS- Surfactants, and co-surfactants
23. AUC- Area under the curve
24. Cmax- Maximum concentration
25. O/O- Oil-in-oil
26. FTIR- Fourier Transform Infrared spectroscopy
27. PLA- Polylactic acid
28. CUR- Curcumin
29. MTT- Tetrazolium dye
30. GIT- Gastrointestinal tract
31. PEI-PEG- Polyethyleneimine-graft-Polyethylene Glycol
32. LPPC- Lipo-Polyethyleneimine-graft-Polyethylene Glycol
33. IL-6 – Interleukin-6
34. $CurNP_s$- Curcumin Nanoparticles
35. TEM- Transmission Electron Microscopy
36. MWCNT- Multi-walled carbon nanotubes
37. RSD- Relative standard daviation
38. ECM- Extracellular matrix
39. SEM- Scanning Electron Microscopy