A REVIEW ON CURCUMIN LOADED NANO DRUG DELIVERY SYSTEMS: NANO FORMULATIONS AND RECENT ADVANCES

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ABSTRACT

Turmeric (Zingiberaceae) rhizomes have been used for centuries in the indigenous medicine system to treat various inflammatory conditions and other diseases. Its medicinal properties have been attributed mainly due to Curcumin amongst the curcuminoids and the other phytochemicals present in the rhizomes and possess a range of pharmacological activities, including anti-inflammatory, anticancer, antioxidant, wound healing and antimicrobial effects. The other salient feature of turmeric/curcumin is that despite being consumed daily for centuries in Asian countries, it has not been reported to cause any toxicity.The only therapeutic limitation of curcumin is its bioavailability. Curcumin needs be bioaccessible before reaching systemic circulation since bioaccessibility is directly proportional to the solubility of the drug in gastrointestinal fluid. A fraction of curcumin would get intracellular space after it has been ingested. Through a Michael reaction α,β-unsaturated C=O group can produce covalently bonded intracellular protein conjugates with protein thiols. This, could be a reason for a small amount of free curcumin in circulation. To enhance the bioavailability and thus its therapeutic efficacy, researchers are making several efforts all over the globe to develop novel nano-drug delivery systems. This review is concentrated on describing issues linked to curcumin's poor bioavailability based on its chemical factors, physiological barriers and pharmacokinetics, focusing on its degradation as well as many unformulated and formulated ways utilized to improve its therapeutic effects such as inhibition of p- glycoprotein pump, enhancing tight junction integrity as well as the incorporation of curcumin in nanocrystals, cyclodextrin nanoparticles, nanospheres, nanofibers, nanoemulgels,intelligent films, quantum dots etc.

Keywords: *curcumin; bioavailability*; *nanocurcumin; nanoformulation; liposome; robotics*

INTRODUCTION

Curcumin is a bright yellow plant pigment obtained from *Curcuma longa* L.commonlyknown as Turmeric, belonging to the Zingiberaceae family(Fig 1A). *Curcuma longa, Curcuma amada, Curcuma zedoaria, Curcuma aromatica, Curcuma raktakanta*are all members of the Curcuma genus that contain curcumin predominantly. Turmeric is a popular spice and food additive widely used in South Asian and Middle Eastern countries. The powdered rhizome (or Turmeric) is used in traditional medicine to cure various kinds of diseases such as cancer,diabetes, arthritis,and Alzheimer as shown in Fig 2. It is also used asa colouring agent in beverage industries. 'Curcuminoids', is a diferuloylmethanecomplex present in curcumin and contains three major compounds; Curcumin-1,7-bis[4-hydroxy-3-

methoxyphenyl]-1,6-heptadiene-3,5-dione(80%), dimethoxy-curcumin-1,7-bis[3,4-dimethoxyphenyl]-1,6-heptadiene-3,5-dione (17%), and bisdemethoxycurcumin -1,7-Bis[4-hydroxyphenyl]-1,6-heptadiene-3,5-dione(3%) as shown in Fig 1B.

Fig 1: A. Curcumin Rhizomes and Powder

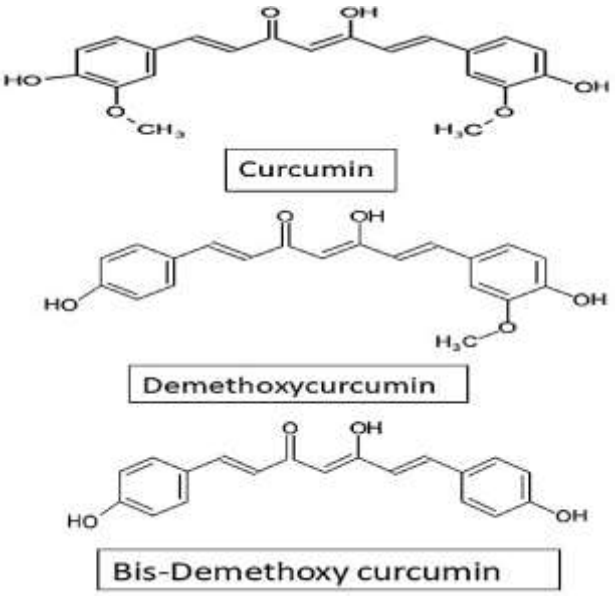

Fig 1 B. Chemical Structure of Curcuminoids

Modern medicine has shown that curcumin exhibits a broad range of biological and pharmacological activities, including antioxidant, anti-inflammatory, anti-tumour and chemo sensitizing, hepatoprotective, lipid-modifying and neuroprotective effects and is suggested to improve mental illnesses due to its ability to modulate numerous signalling molecules. (Fig 2). It is a Biopharmaceutical Classification System class IV polyphenol. Though have been acclaimed for multiple therapeutic benefits, its poor solubility, poor bioavailability, and low pharmacokinetic profile are still not regarded as a potential phytopharmaceutical for systemic use\. (Bao et al., 2021)(Eckert et al., 2021)(Jabczyk et al., 2021)

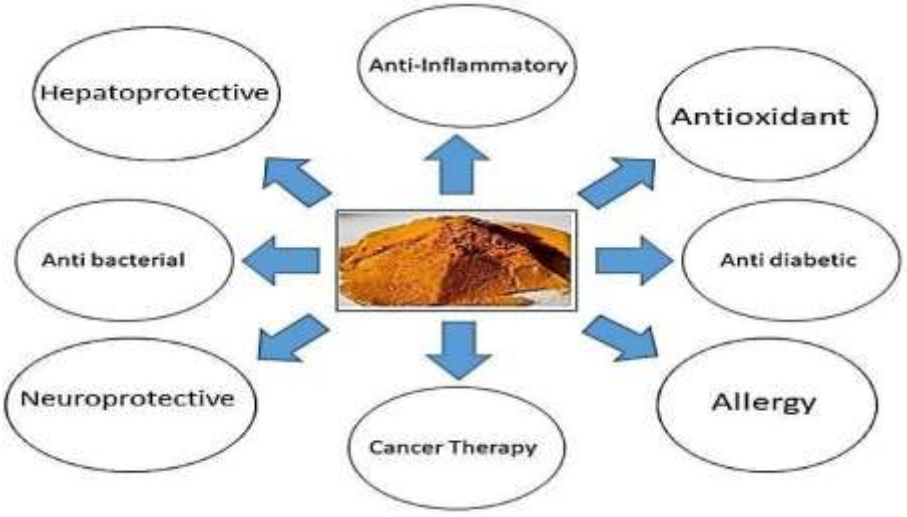

Fig 2 :-Pharmacological and Biological activity of curcumin.

PHARMACOKINETICS OF CURCUMIN

In a pilot study conducted by Patra *et al*. in 2021, a pharmacokinetic profile of orally administered curcumin capsule containing 36-180mg curcumin was evaluated, and the results stated that curcumin doesn't have dose-limiting toxicity after 16 weeks of capsule ingestion. (Patra et al., 2021)

Curcumin absorption is dose-independent and remains constant, i.e. 60-66% of the dose administered. After 60 minutes of administration, 3.6 g of curcumin by oral ingestion achieved a plasma curcumin level of 11.1 nmol/L in a human clinical trial.Curcumin is primarily metabolized in the liver and intestine. Curcumin glucuronidation product, tetrahydrocurcumin (THC) reduces lipid peroxidation in vitro generated by radiation and promotes antioxidant enzymes. Another metabolite, Octahydrocurcumin, has an excellent free radical scavenging activity than curcumin (Prasad et al., 2014).(Fig.3)

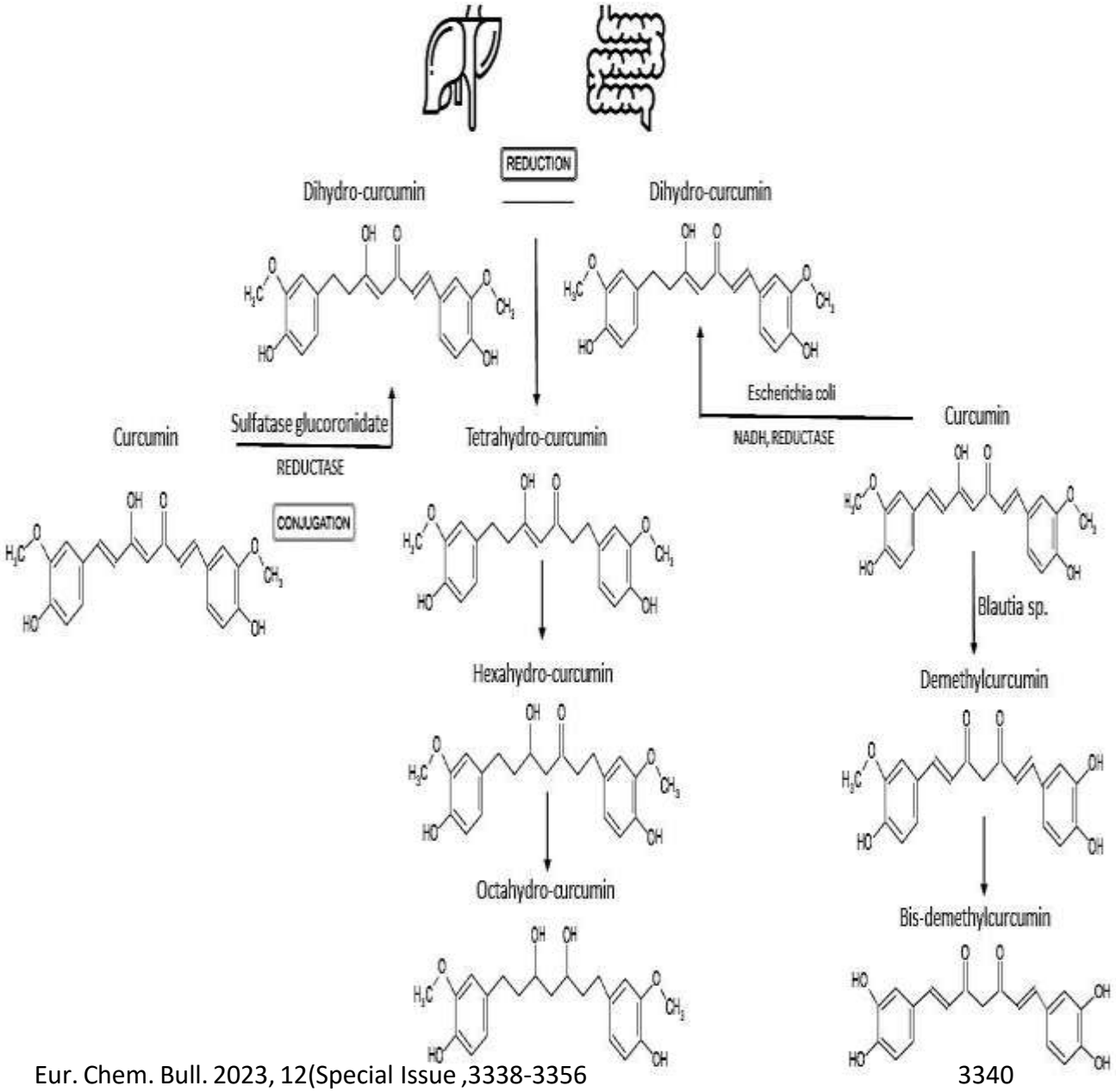

Fig 3 :- Metabolic products of curcumin

A physiological barrier in GIT affecting oral BA of curcumin

Physical- Drug transport is hindered by Upper mucus and intestinal epithelium. Absorption is blocked by tight junction of endothelial cells. Further diffusion is opposed by high moisture due to anionic glycoprotein mucin and water presence on the epithelium.

Chemical- metabolism by gastric acid, bile and digestive enzyme affects absorption.

Biochemical- metabolic enzyme and P-gp mediated efflux of curcumin in endothelial cells push it back to the lumen. Curcumin has three ionisable water protons, two phenolic and one enolic proton. Due to instability, Curcumin has limited solubility in neutral or acidic pH and gets hydrolysed at basic intestinal pH of 6.8. These conditions also add to low BA and absorption.

Strategies to improve oral Bioavailability of Curcumin-

Curcumin solubility in solvent

Log P of curcumin is 3.29 showing low water solubility (11ng/ml) and maximum solubility in dimethyl sulfoxide DMSO (20 mg/mL), making it the optimal solvent for developing curcumin Nano formulations. (Tomeh et al., 2019)

Increasing curcumin preparation stability in GIT-

Protection of curcumin destruction from the Gastrointestinalenvironment and making it more soluble with controlled release would be achieved via its conjugation with gastro-resistant polymer. Carboxymethyl chitosan was employed as P-gp mediated efflux and to boost gastrointestinal absorption. Heparin-all-trans-retinoid acid (LHR) as the loading material to enhance CUR polymeric micelle stability in physiological pH by a chemical conjugation technique. Coating of silica, a gastro-resistant polymer, has increased strength in the GI environment, which can preserve the interior structure of the nanoformulation. Due to its mucoadhesive property, Chitosan enhances absorption, and its coating on nanoemulsionavoids its phase separation and destruction of nanoparticles. Eudragit, a gastro-resistant polymer, blocks the destruction of curcumin in GIT.

P-gp inhibition(P-glycoprotein)-

P-gp inhibition is intended to improve curcumin oral bioavailability. Chitosan and its derivatives have a P-gp suppressive activity that might be used to transport curcumin. (Sahu et al., 2016)

Improving epithelial Tight Junction integrity-

Chitosan, a mucoadhesive polymer, can shield a drug from intestinal and enzymatic destruction and improve curcumin absorption through mucosal barriers by interacting with tight epithelial junctions, increasing oral bioavailability.Curcumin's oral bioavailability can be increased by using the lymphatic transport pathway since lymphatic vessels can carry the drug into the thoracic duct, which is then transferred into the systemic circulation, skippingthe portal circulation.

Co-ingestion with adjuvants-

Piperine inhibits curcumin's metabolising enzymes, allowing it to bypass the first-pass metabolism(Baspinar et al., 2018). By altering the functions of UGT and catechol-O-methyltransferases, sesamin can also affect metabolism and bioavailability. Xanthohumolcan binds with sulphotransferases and UGT, thereby blocking curcumin degradation. Curcumin

has been co-administered with other adjuvants such as etoposide, docetaxel, and silybinin, to enhance its oral bioavailability, (Ma et al., 2019)

Curcumin combination with food may help boost BA –
Lecithin-rich foods like oil, egg, and vegetables.
Piperine blocks glucuronidation in the liver and small intestine and may enhance its BA by 2000%
Gender difference- 1.4high fold absorption in women may be due to reduced efflux and enzyme action. But this needs more research.

Bioavailability-
According to Abegg et al.2015,curcumin has been shown to covalently alter a signalling protein called casein kinase I gamma, which plays a vital role in curcumin's biological action.As a result, the generation of curcumin–protein adducts may add to curcumin's bioactivity.
The bioavailability of curcumin nanoformulations such as curcumin nanoemulsion, single-walled nanotube, and nanostructured lipid carrier is affected by milk, sugar, high-fat meal, and probiotic *Bifidobacterium lactis* Bb-12. Sugar increased SWNT BA is attributed to sugar complexation on the surface of the protein'which increased C_{max} and AUC; intestinal probiotics inhibited curcumin absorption due to breakdown, and a high-fat meal increasedNLC bioavailability. (Han et al., 2021)

Factors affecting & Reasons for low bioavailability-

The chemical degradation of curcumin is pH-dependent inan aqueoussolute. It is mediated by the redox mechanism resulting in generation of several substances such as alkaline hydrolysis metabolites like ferulic acid and vanillin, feruloyl methane, as well as autoxidation product like dicyclopentadione. At 3 to 6.5, the pH half-life of curcumin is 100-200 min and at 7.2 to 8.0 pH half-life is 1-9 min.
At physiological pH, the chemical degradation is carried out by a radical-dependent oxidation process; curcumin phenolic radical is formed by the removal of hydrogen from the phenolic ring, which reacts with the oxygen in the conjugated heptadienedione chain prominently to form dicyclopentadiene and different degradation product. This free radical goes to a new curcumin molecule causing rapid degradation by chain reaction. Curcumin solubility and bioaccessibilityare improved using medium-chain triglycerides (MCT) and long-chain triglycerides (LCT).

Absorption-
The lipophilic configuration of curcumin has two vinyl and twophenyl moieties, resulting in minimal aqueous solubility of curcumin. Ravindranath*etal*. 1980concluded that the Poor absorption cause of curcumin is poor bioavailability. Curcumin mainly gets absorbed in the small intestine. Still, because of its lipophilic phenolic nature, it gets difficult to absorb by intestinal epithelial cells when administered orally, as investigated by Prasad *et al*. 2014. When drank, it gets effluxed in the lumen due to its lipophilic nature (Ravindranath*et al*., 1980. However, Khajuria *et al*. 2002 found that piperinecan lower this by adjusting cell membranes and decreasing lipid fluidity because of its apolar nature.

Tissue distribution-
Ravindranath*et al.* administered 400 mg of curcumin in rats and found only traces of free-formed curcumin in the liver and kidney.

Metabolic transformation-

In phase 1, the four double bonds of the 7-carbon atom chain with two C=O moiety get reduced, initially generating dihydrocurcumin (DHC) and then decreasing to tetrahydrocurcumin (THC),later to hexahydrocurcumin and lastly octahydrocurcumin.

Phase 2 occurs inthe liver and intestinal cytosol. Since curcumin consists of two phenolic groups, it can be decomposed by Phase II enzymes likeglucuronosyltransferase and sulfotransferase, enabling the development of a significant amount of glucuronide and sulphate conjugates with a ratio of curcumin glucuronide to curcumin sulfate of 1.92:1.(Vareed et al. 2008)Hexahydrocurcumin is more stable than curcumin at aphysiological pH of 7.4 because of the same phenolic groups and diketo moieties as curcuminbut no olefinic double bonds.

Intestinal microflora may deconjugate phase II metabolites and turn them back to phase I compounds, resulting in the formation of fission metabolites like ferulic acid.Nicotinamide adenine dinucleotide phosphate NADPH-dependent reductase or dihydrocurcumin reductase (bacterial enzyme CurA), the enzyme involved in metabolism, was noticed by Hassaninasab et al.2011. Rection is catalysed by *E.coli* in the gut and found that only reduction of C=C happens and not C=O due to the absence of further metabolites other than dihydrocurcumin and tetrahydrocurcumin. Curcumin is demethylated by *Blautia* sp. into two different derivatives: demethylcurcumin and bis-demethylcurcumin.99% of plasma curcuminaresare less active due to their conjugated form with glucuronide and sulphate. Curcumin is stable at low pH of 2.5 to 6.5, so it can reach up to theintestine and undergo degradation.(Sanidad et al., 2019)

FORMULATIONS- (Fig 4)

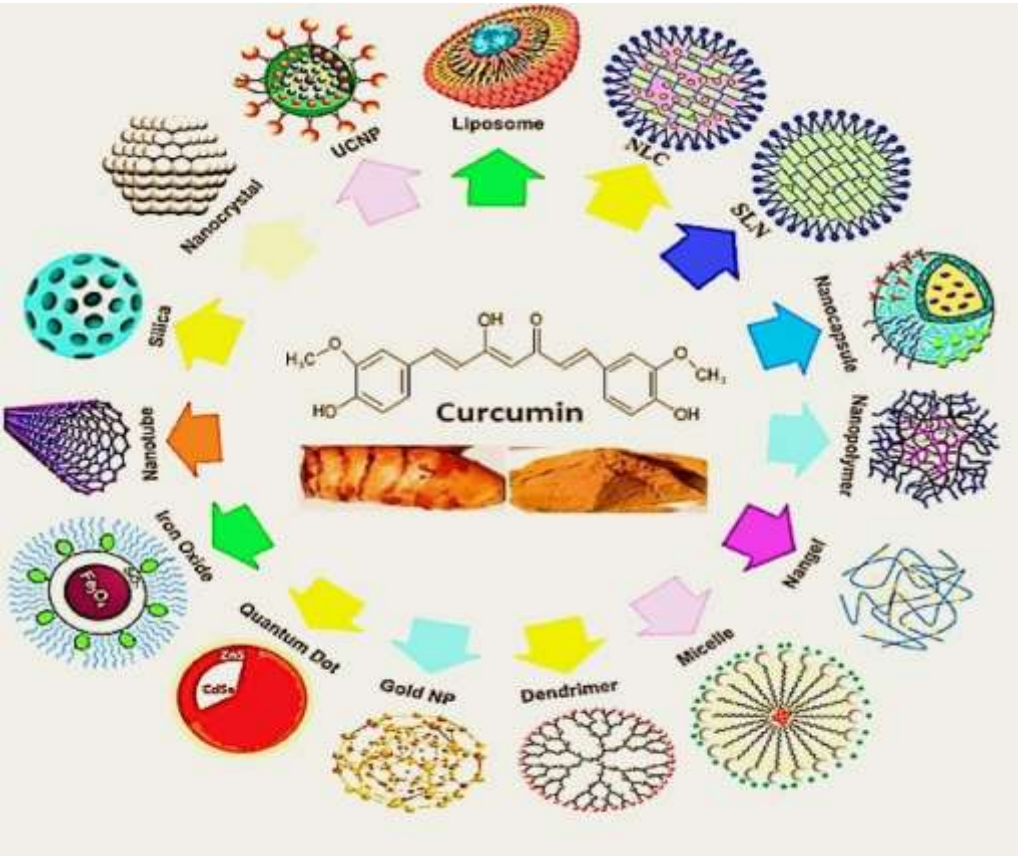

Fig 4:- Novel Formulations of Curcumin

Nanoparticles-

Yuanhong Zhang and co-workers developed novel soy-peptide nanoparticles (SPN) for lipophilic drug delivery. These nanoparticles were created using a pH-driven approach, which increased curcumin bioavailability by 10^5 times by increasing its water solubility. After deprotonation under a high basic pH, lipophilic phytochemicals like curcumin can be encapsulated in a self-assembled protein nanostructure during neutralization. Curcumin - digestive enzyme complexation was observed to increase in vitro bioavailability in curcumin-loaded SPN, avoiding curcumin metabolism and increasing retention rate by more than 90%.(Zhang et al., 2021)

SoumitraShome and colleagues studied the effect of conjugation of micro/nanocurcumin particles to ZnO nanoparticles on antibacterial activity and antioxidant activity.Electrostatic interaction between ZnO- curcumin micro/nanoparticle conjugation resulted in stabilization of nanocomposite. It showeda marked enhancement in antibacterial action of ZnO and curcumin micro/nanoparticles because of synergistic effectas well as high zeta potential aided in better bacterial wall penetration due to small hydrodynamic size.Curcumin-ZnO nanocomposites have also shown higher antioxidant activity than bulk curcumin because the small hydrodynamic diameter and high hydrophilicity showed an elevated bioactive surface to volume ratio. (Shome et al., 2021)

Manik N. Waghmare and co-workers studied the β-Lactoglobulin-gold nanoparticles interface and its conjugation with the anticancer agent curcumin for drug targeting. They revealed that curcuminbinds to BLG via one of its di-ketone groupthrough lipophilic and lipophobic bonding with BLG lipophilic central calyx, which can avoid curcumin auto-oxidation. This AuNP-BLG conjugate is a suitable carrier for drug design in targeted drug delivery for loading anticancer therapeutics. (Waghmare et al., 2021)

Nanocapsules-

Nanocapsules are 0 to 1000 mm in size and composed of one or more active components (core) and a protective matrix (shell) in which the therapeutic ingredient can be enclosed. Curcuminimparts an anti-inflammatory effect by lowering IL-17, IL-6, and TNF-alpha levels and an anti-autophagic action by lowering regulating the gene expression, which can help treat colitis inflammatory bowel disease. Curcumin-containing nanocapsules have indicated effectiveness in treating IBD due to intestinal retention.(Fallahi et al., 2021)

Felipe Barbosa de Carvalho and co-workers evaluated the effect of curcumin-loaded polymeric nanocapsules on angiogenesis, teratogenesis and oxidative stress using chick embryo. They used Chitosan low-molecular-weight (CS), polysorbate 80 (P80), Eudragit® RS100 (EUD), poly (ϵ-caprolactone) (PCL). Results showed that curcumin nanocapsules (P80, PEG, EUD and CS) do not have teratogenic, anti-angiogenic and catalase (CAT)activityand are effective on thiobarbituric acid reactive species (TBARS), nonprotein thiols (NPSH) reactive oxygen species (ROS), and thiobarbituric acid reactive species (TBARS). (de Carvalho et al., 2021)

Nanoemulsions-

Nanoemulsions (NE) are thermodynamically unstable microscopic particles with a radius of 100 nm and composed of two immiscible liquids, one of which is dispersed in the other with enhanced transparency and the increased surface area leading to more excellent absorption physical stability to gravity separation, flocculation and coalescence, and bioavailability. HeeJoungJoung and his colleagues developed a food-grade curcumin nanoemulsion using high-pressure homogenization and investigated its antioxidant properties in vitro. More

surface-active agent improves antioxidant property due to the solubilization of curcumin in the oil phase, according to the in-vitro antioxidant property by DPPH and ABTS assay.(Jounget al., 2016)

Rajshree L. Shinde and Padma V. Devarajan investigated the transport of curcumin to the brain using a docosahexaenoic acid (DHA)-rich oil microemulsion. The targeting effectiveness achieved by DHA-mediated transport across the blood-brain barrier is attributedto curcumin-DHA microemulsion's elevated brain concentration.(R. L. Shinde & Devarajan, 2017)

K. Margulis and colleagues developed and investigated the in-vitro effectiveness of a curcumin cyclopentanone-in-water microemulsion on the pancreatic cancer cell line, PANC-1. Spray drying was used to turn the microemulsion into nanometric powder containing amorphous curcumin, which was devoid of lipids and polymers. It was easily dispersed in water to form nanoparticles. The improved solubility, as well as stability of C-NP in the cell medium, possibly account for higher potency. The technique might allow additional water- insoluble compounds to create nanoparticles increasing their activity.(Margulis et al., 2014)

Micelles-

Sinacurcumin®,marketed curcumin loaded Nano micellesformulation,was studied in covid-19 infected patients. The effect of sinacurcumin on inflammatory cytokines showed it was able to regulate the rate at which inflammatory cytokines increased in patients with COVID-19, the expression of IL-1 and IL-6 mRNA, as well as cytokine production, may promote the clinical benefit and overall recovery. In patients with mild and severe COVID-19, the effects of Sinacurcumin® on the number and activity of Th17 cells (T helper cells). Studies concluded that Sinacurcumin® could reduce the number of Th17 cells and their frequency. Asa result, it could be seen as a possible modulator reducing the severity of the patient's inflammatory condition.(Dourado et al., 2021)

Sha Bao and colleagues studied the effect of Self-assembled micelles by oral delivery of curcumin for the management of alcohol-induced tissue injury. The absorption rate constant (Ka) and apparent permeability coefficient (P_{app}) of curcumin-loaded Soluplus® micelles (CUR-Ms) in intestines were 3.50 and 4.10 times higher with improved aqueous solubility of CUR-Ms and P glycoprotein suppression of Soluplus®, respectively more than the value of free curcumin. CUR-Ms considerably enhanced the oral bioavailability of curcumin, according to pharmacokinetic investigations. The AUC and C_{max} of CUR-Ms were alsoraised.(Bao et al., 2021)

Liposomes-

Liposomes are phospholipid layers having hydrophilic centre. Drugs can be encapsulated in this lipid vesicle structure either in the core or in the phospholipid layer, allowing encapsulation of both lipophilic and lipophobic drugs. These are chemically as well asphysically unstable systems. Elisabet Mart Coma-Cros and colleagues investigated the antimalarial activity of curcumin incorporated in liposomes containing either hyaluronan (Eudragit-hyaluronan liposomes) or the water-soluble dextrin Nutriose® FM06 (Eudragit- nutriosomes). The researchers discovered that Eudragit-nutriosomes increased curcumin's in vivo antimalarial effectiveness in a dose-dependent manner by increasing the survival of all Plasmodium yoelii-infected mice.(Coma-Cros et al., 2018)

Syed NaseeruddinAlvi and researchers formulated aiontophoresis mediated curcumin loaded liposomal gold nanoparticle for dual light irradiated acne therapy. These NP had positive zeta potential which helped them interact with anionic mucus layer which helped them exert mucoadhesive effect. Au LiposCUR NPs-mediated regional photothermal destruction of the sebaceous gland and suppression of microbial activity as a potential acne treatment method.

Associated with more positive zeta potential, the Au LiposCUR NPs were able to permeate skin when iontophoresis was applied.(Alvi et al., 2021)

Solid lipid nanoparticles(SLN)-

The therapeutic compounds are encapsulated inside the solid matrix of SLN, which are a combination of one or more solid lipids. Debora Santonocito and colleagues synthesised and studied the novel Curcumin Containing PEGylated Solid Lipid Nanoparticles (CUR-pSLNs) by Oxygen Radical Absorbance Capacity (ORAC) assays potent antioxidant for systemic administration that might be employed to manage a variety of CNS disorders having a deficiency in antioxidant defence.CUR-pSLNs had higher antioxidant activity with compared free curcumin, showing that encapsulation plays an important role in retaining and thus augmenting the antioxidant activity of highly active substances.(Santonocito et al., 2020)
Entrapment efficiency of curcumin in SLN is affected by chain length of hydrocarbon and molecular weight of drug. Entrapment efficiency of curcumin in SLN is directly proportional to chain length and inversely proportional to molecular weight of drug. The bioactive phytocompound like curcumin entrapment efficiency is molecular weight dependent. SLNs containing phyto-bioactive chemicals can move across the intervillar space, lymphatic system, or Peyer's Patch with little loss of active site. In addition to the delivery of bioactive substances, certain coated nanoparticles are transported by ileum absorption.(Ganesan et al., 2018)

Cyclodextrins-

Cyclodextrins (CDs) are oligosaccharides made up of 6 (α), 7 (β) and 8 (γ) D-glucopyranose units connected by a -1,4- glycosidic linkage to form macrocycles. Inner structure of CD is lipophilic due to oxygen ring formed from glucosidic bonds. Outer part is water-soluble due to the hydroxyl group. This 3-D allows to form drug-CD inclusion complex. Many researchers have recently discussed the significance of CUR-CD drug delivery with the goal of improving in vivo anticancer therapies.(Santos et al., 2021)

Nanospheres-

Ji-Yun Kim and researchers studied the role of curcumin nanospheres (CN) on suppressing GI cell death signaling mechanism induced by gram-negative *Vibrio vulnificus* pathogen in human gastrointestinal epithelial HT-29 cells and an ileal-ligated mouse model. Pathogen formed VvhA recombinant protein is responsible for cell death. In rVvhA-treated HT-29 cells, CN blocked the phosphorylation of c-Src and PKC triggered by intracellular Reactive Oxygen Species, which was responsible for the activation of the MAPKs. In mouse model,CN inhibits cell apoptosis caused by DNA fragmentation, Bax, Bcl-2, and cleaved caspase-3, indicating that CN has an useful role in the host apoptotic system by neutralizing action of bacterial toxin.(Kim et al., 2020)
XinlongHuo and colleagues encapsulated PLGA nanospheres with Curcumin and selenium nanoparticles to investigate its effect on amyloid-β loading AD in transgenic mice. Lipophilic cur chain via lipophilic binding conjugates to nonpolar regions of the Aβ oligomers. H- bonding between Aβ oligomers polar region and curcumin -OH group stabilises lipophilic bonding and thereby preventing Aβ plaques.(Huo et al., 2019)

Nanogels-

Nanogels are hydrophilic crosslinked hydrogel materials with both hydrogel and nanoparticle capabilities, as well as the capacity to release drug in a controlled manner. Zhigao Wang and workers formulated stable and self-assembling rapeseed protein nanogel via acylating and

denaturing rapeseed to deliver lipophilic curcumin and studied its cytotoxic activity against several cancer cell line. Rapeseed protein has high bioavailability however its poor water solubility can be reduced by addition of water-soluble succinic group (acylation) which is useful for drug delivery. Disulfide bond and lipophilicity helped in self-assembling of nanogel. Anticancer activity was studied by MTT assay usingbreast cancer cell line (MDA- MB-231), hepatocellular carcinoma cell line (HepG2) and gastric cancer cell line (MKN-28) and confirmed to have improved cytotoxicity to these cells compared to free curcumin.(Wanget al., 2019)

Fadak Howaili and colleagues formed dually thermo-pH-responsive plasmonic nanogel (AuNP@Ng) to offer drug delivery and photothermal treatment (PTT) at the same time. The cytocompatibility of plasmonic nanogel was tested using MDA-MB-231 human breast cancer and non-tumorigenic MCF 10A cell lines, and the formulation was shown to be cytocompatible. The pH-thermoresponsive plasmonic nanogel was discovered to exhibit effective toxicity against MDA-MB-231 cells, which enhanced when combined with photothermal treatment, AuNP has localised surface-plasma-resonance (LSPR) which absorb NIR light and convert it to heat which contracts nanogel and releases curcumin.(Howaili et al., 2021)

Bilal Javed and team members evaluated the toxicity of curcumin and piperine in collaboration with gold Lignin-g-p (NIPAM-co-DMAEMA) nanogel on U-251 MG GBM cells. The results showed increased biodistribution and cytotoxic capabilities of curcumin and piperine encapsulated in gold nanogels, entry in glioblastoma multiforme cancer cells via lysosome endocytosis and spreading in the cytoplasm which restrictedcancer cell growth by living inside intracellular organelles to cause cell death.(Javed et al., 2021)

Smart film-

Ralph W. Eckert , Sabrina Wiemann and Cornelia M. Keck produced new technology to have effective dermal and transdermal penetration of curcumin.When a mixture of lipophilic amorphous drugs is dissolved in solvent and deposited to a cellulose matrix-like paper, the solvent evaporates, leaving the drug entrapped in the pores of the cellulose matrix, preventing recrystallisation. To improve oral administration, these smart films can also be manufactured into tablets. They investigated smartfilm CUR penetration by invitro and exvivo and concluded that SmartFilms are a very effective medication transport strategy for transporting lipophilic drugs to the dermis and transdermal sites.(Eckert et al., 2021)

Nanoemulgels-

NEG is formed from incorporation of NE droplets in hydrogel to have slow release and penetration through the transdermal route. Novel nanoemulgel bypasses 1st pass metabolism, enhances drug permeability in a controlled and sustained fashion through skin.

Wafaa E. Soliman and researchers studied curcumin efficacy in curcumin NEG and evaluated in vivo anti-inflammatory activity and skin irritation in rat. They added curcumin in myrrh oil-based NE to formulate CUR-NEG. Skin penetration of CUR-NEG was compared with CUR-loaded gel, emulgel and curcumin aqueous suspension and results showed CUR-NEG had maximum steady-state transdermal flux (SSTF) (108.6 ± 3.8 μg/cm^2 ·h) with maximum enhancement ratio (ER) (7.1 ± 0.2). small particle size provided large surface area and surface active agent helped to enhance curcuminpermeation.(Soliman et al., 2021)

Mohammed S. Algahtani and co-workers formulated curcumin nanoemulgel using high energy ultrasonic emulsification method to reduce amount of surfactant needed and tested it in vitro, ex vivo using Franz cell diffusion apparatus and in vivo in Wistar rats. curcumin-Nanoemulsion due to low viscosity's minimal retention time on applied area so incorporation of NE in hydrogel due to its ability of drug delivery in cutaneous open wound , non-

adhesiveness, moisture retention and air permeability forms innovative NEG. Curcuminloaded NE was prepared by ultrasonication and added in 0.5% Carbopol® 940 hydrogel to enhance skin permeability. They found that NEG has well dispersed curcumin and had similar in vivo wound healing capacity with marketed silver sulfadiazine cream. (Algahtani et al., 2021)

Quantum Dots (QD) -

Graphene QD (QGD) are zero-dimensional, formed from carbon nanostructure, togetherhaving necessary features of graphene and semiconductor QD. Drug conjugates via π-πstacking and lipophilic bonding with QGD which are stable in water due to the presence of oxygen-containing moieties which makes it available for further derivatisation. QGD are relatively less toxic than semiconductor QD and more bioavailable having inherent photoluminescence due to quantum confinement and edge effects, which is very advantageous in cell imaging, drug pathway monitoring, and cellular uptake making it advantageous for biomedical use. Hydrothermal, solvothermal, acidic exfoliation, chemical oxidation, and electrochemical oxidation used to synthesise QGD.

Narges Ghanbari and colleagues formulated glucosamine linked QD loaded by curcumin to investigate its effect on GLUTs over-expressed MCF-7 breast cancer cells. Graphene oxide used as starting material for QGD preparation. Invitro studies showed because GLUTs receptor is overexpressed due to high aerobic glycolysis in MCF-7 cells, GlcN-GQDs are endocytosed more than GQDs via receptor-mediated endocytosis. (Ghanbari et al., 2021)

Sana Mushtaq and teammates studied the effect of Curcumin-loaded Graphene Quantum Dots on Antimicrobial Photodynamic Therapy (PDT) to treat multidrug-resistant (MDR) microbes. aPDT involves a photosensitiser (PS) and nontoxic compound which gets activated by irradiation of light of specific wavelength.QGD acts as PS carrier, when PS exposed to light in presence of oxygen it convertslight energy to molecular oxygen and forms reactive oxygen species (ROS). The results showedcurcumin carrier-mediated delivery via GQDs not only eliminates the low solubility problem of curcumin, but also promotes specific targeting of curcumin, leading to enhanced bioavailability of curcumin which is confirmed by ROS detection assay in which curcumin-loaded formulation raised ROS levels by threefolds by decreasing colony-forming units due to intracellular ROS generation and accumulation that causes bacterial cell membrane damage and cell death(Mushtaq et al., 2022).

Nanocrystals-

Yang Wei and co-workers formulated innovativezein-cellulose nanocrystals core-shell microparticles for delivery of curcumin. Curcumin was fabricated in lipophilic zein core and the outer shell was made up of water-soluble cellulose nanocrystal (CNC) and Electrostatic interaction, lipophilic force, hydrogen bonding enabled layer-by-layer self-assembly between biopolymers. The study revealed the produced zein-CNCs core-shell microparticles were the most stable and properly shielded the encapsulated curcumin when the mass ratio of zein microparticles to CNCs was 2:1. Meanwhile, indigestible CNCs might create a tight shell around the centre of the microparticles, preventing proteases and bile salts from reaching the curcumin, thereby reducing curcumin discharge and bioaccessibility.(Wei et al., 2021)

Nanospray-

Yue Li and co-workers formulated EGF-modified curcumin/ chitosan nano-spray for wound healing. The Epidermal growth factor (EGF) being anionic gets absorbed on cationic chitosan nanoparticle conjugated with CUR to generate EGF@CCN which is then added to spray bottle. The results of EGF@CCN nano-spray on skin defects in rats shown its excellent efficacy in promoting wound healing confirming the ability of Nano spray to be safe and

shows wound repairing action due to combinatorial effect of EGF on wound healing by increasing the proliferative and migratory potential of fibroblasts and CUR fibroblast generation, granulation tissue production and fastening wound closure and epithelialisation.(Li et al., 2021)

Nanofibres-

Rajalakshmi Ekambaram and co-workers formulated electro spun SPEEK incorporated with aminated zirconia loaded with curcumin nanofibers for periodontal regeneration. The sulphonation of polyether ether ketone (PEEK) polymer resulted in bio-active SPEEK ionomers used to add drugs. To increase its biological characteristics such as cell adhesion and cytocompatibility, zirconia nanoparticles were functionalised with 3-Aminopropyltrimethoxysilane (APTMS). Using the electrospinning process, SPEEK ionomers were electrospun with amine-functionalised zirconia and curcumin to create nanofibers in a high electrostatic field by spinning a polymeric solution or melt.The nanofibers were evaluated for in-vitro for cytocompatibility and release of drug and shown to have increased biological activity, resulting in excellent cell survival and regeneration for periodontal regenerative applications. (Ekambaram et al., 2021)

Electrospun nanofibers (NFs)-based drug delivery is a promising implantable nanoplatform for targeted cancer therapy and addressing tissue defect post-surgery, providing on-site drug administration with minimal adverse effects to healthy cells. Liguo Xu and researchers formulated innovative nanofibrous scaffold CUR/CUR@MSNs-NFs, free curcumin co-encapsulated curcumin linked mesoporous silica nanoparticles (CUR@MSNs) via electrospinning using polycaprolactone and gelatine (PCL/GEL) hybrid. The results showed that there was an early burst release and a late steady release. In vitro anticancer investigations on MDA-MB231 breast cancer cells revealed that CUR/CUR@MSNs-NFs could efficiently showed increased cytotoxicity and greater apoptotic triggering.(Xu et al., 2022)

Dendrimers-

Dendrimers are 1-10nm size having dense dendritic branches as well as functional moiety at the terminal which makes it distinguish from monomer and oligomer. John Gallien and co-workers formulated surface-modified polyamidoamine (PAMAM) dendrimer loaded with curcumin to treat glioblastoma a CNS cancer. polyamidoamine (PAMAM) dendrimers have several components like core, internal branching and functional group on the surface, which can be changed to make newdendrimers of distinct morphology for certain therapeutic effects. In this experiment, the researchers synthesised fourth-generation dendrimer with 90%neutral 'OH' moiety and 10% cationic amine (NH^{3+}) to decrease toxicity which is unlike in the case of conventional dendrimers with 100% NH2 which gets protonated at physiological pH. This G4 90/10-Cys dendrimers centre has cystamine and two dendrons are connected by disulfide bond (-s-s-), which gets reduced to -SH by glutathione or other reducing agent upon entering cell by non-mediated endocytosis and release drug. The developed dendrimers were evaluated inmouse-GL261, rat-F98, and human-U87 glioblastoma cell lines and shown increased bioavailability of curcumin due to incorporation in the G4 90/10-Cys.(Gallien et al., 2021)

Nanostructured lipid carriers (NLC)-

NLC are comprised of solid and liquid lipid mixture. They improve drug incorporation, the incorporated product's long physical and chemical stability, surface functionalisation, and targeted delivery. Raquel F.S. Gonçalves and colleagues formulated and investigated the effect of lipid-based nanostructures on curcumin bioavailability, potential toxicity as well as

cellular transport in vitro using Caco-2 cells. Results state that, when compared to NE, NLC has greater stability because the mixture of liquid and solid lipids can result in increased tolerance to lipase adsorption and hydrolysis. and curcumin intestinal permeability by transcytosis due to lipid composition and physical state, as well as higher curcumin bioaccessibility than SLN because degradation products of oil can stimulate greater curcumin uptake in mixed micelles.(Gonçalves et al., 2021)

Chetan Shinde and co-workers formulated controlled release nanostructure lipid carrier-based smart gel by melt ultrasonication method to treat rheumatoid arthritis via intra-articular administration. To prepare NLC-CUR smart gel, amount of Pluronic F-127 and Pluronic F - 68 polymers adjusted to get optimum rheological properties of CUR-NLC. Pluronics are ABA triblock polymers made up of lipophobic poly-oxy-ethylene chains(PEO) and lipophilic poly-oxy-propylene chains(PPO) . Pluronic mixtures with ideal ratios change from sol to gel at or above gelation temperature, because of interaction between lipophilic PPO and lipophobic PEOblocks. Curcumin release is sustained as a result of the steady destruction of NLC spheres and curcumin diffusion into the outer polymer matrix. CUR-NLC smart gels, in-vitro, at 84 hours, released 94.32 % drug and showed a sol-gel transition at 33.21^0 C also found to be biocompatible and substantially minimised rat knee joint inflammation showing better efficacy when compared to free drug.(C. Shinde et al., 2021)

M. Akanda, G. Getti, D. Douroumis formulated curcumin loaded NLC by high pressure homogenisation to target prostate cancer. In vitro test shown CUR-LNC have sustainedrelease. in vivo investigation in mice xenograft of LNCaP tumour cells shown CUR-NLCs have a dose and time-dependent antiproliferative and cytotoxic effect than empty NLCs and pure CUR because after 24h incubation 12, 50, 75 and 100 g/ml concentration of curcumin- NLC LNCaP cell viability decreased to 91.5%, 37.8%, 21.4% and 9.2%,at 48h incubation at 100g/ml CUR cell viability was 0%. (Akanda et al., 2021)

Niosomes-

Niosomes are nano vesicular system to incorporate drug, thereby enhancing therapeuticaction and lowering side effects. These are two-layered comprised of nonionic surface-active agent and cholesterol encapsulating inner aqueous environment. These are stable and economic system. They can incorporate drug irrespective of solubility and penetrate through bacterial cell membrane by fusion to boost efficacy. Changes in structural components can be useful in their optimisation to get desired properties. ArefehAbolHassaniTarghi and colleagues incorporated curcumin loaded metal nanoparticles (AgNPs or CuNPs) in niosomes and investigated its physicochemical and antimicrobial activities. Metal NPs and niosomes were synthesised by chemical reduction and thin-film hydration method and then curcumin- metal np system were loaded in niosomes. The investigations revealed that dual-drug loaded liposomal formulations may provide prolonged antibacterial and anti-biofilm actions in vitro while demanding a smaller concentration. Additionally, in formulations involving curcumin- AgNPs or curcumin-CuNPs, suppression of arr and ebp genes associated in biofilm formationand binding to host elastin respectively, were stronger than in single drug-loaded niosomes because AgNP forms ROS and inactivate protein whereas in case of CuNP, cu can bind anionic bacterial membrane, deoxyribonucleic acid leads to formation of abnormal helical structure by crosslinking between nucleic acid strands finally cell death. Aromatic OH moietyof curcumin is electron-donating group which reacts with bacterial membrane and boosts drug penetration as well as methoxy and hydroxyl group on phenyl ring shows antibacterial activity.(Targhi et al., 2021)

Tamer M. Shehata and co-workers formulated curcumin-niosomes from proniosomal gels to enhance anti-inflammatory action of curcumin in transdermal delivery. The proposed

niosomes were produced from proniosomal gel by simple water hydration method which serves as precursor for niosome formulation. The results showed that the skin penetration and efficacy of curcumin were markedly enhanced by 20 folds due to surface-active agents, oil and nanocarrier like niosomes. However long unsaturated chain of tween 80 increasedencapsulation of curcumin as well as small size niosomes. (Shehata et al., 2021)

Microspheres-

Himal Bhatt and researchers formulated chitosan-silica hybrid microspheres conjugated with curcumin by evaporation induced silica-NPs, chitosan and curcumin assembly via spray-drying. The silica anionic silanol moiety interacted with cationic chitosan via pH-dependent electrostatic conjugation. The assembly of curcumin incorporated microsphere is due todistinct inter-molecular conjugation and H-bonding. The produced chitosan-silica microspheres loaded with curcumin showed sustained release action and its anticancer effect investigated using human lung adenocarcinoma (A549) and cervical (HeLa) cancer cells and found to have potent anticancer effect. (Bhatt et al., 2021)

Kunal Pal and co-workers formulated curcumin loaded gum acacia microspheres conjugated with folic acid by co-precipitation method to determine cytotoxic effect on invitro triple-negative breast cancer cell (TNBC) lines and in-vivo BALB/C mice. Targeted drug delivery to cancer cells is achieved by bonding with folic acid. The in-vitro investigations revealed curcumin-induced tumour cell apoptosis is due to increased mitochondrial ROS production caused by intracellular acidic 5.5 pH mediated release of curcumin in tumour cell thereby producing reactive oxygen species (ROS) by 2.5 fold which cause destruction of DNA as well asmitochondrial membrane. In vivo study on mice also showed marked tumour volume reduction with non-toxicity to kidney as well as liver.(Pal et al., 2019)

Ethosomes(ES)-

Ethosomes enhance drug permeability through skin as well as allow incorporation of lipophilic and lipophobic drug in hydro-ethanolic solution containing core. Ethosomesare nanovesicular systems, can be derivatised by functionalised compounds, surface active agentsor permeability improving agents, which makes them innovative carrier for transdermal drug delivery. Teng Guo and co-workers formulated TPGS modified coincorporated curcumin and glycyrrhetinic acid-functionalised ethosomes for psoriasis. D-α-tocopherol acid polyethylene glycol succinate (TPGS) a vit.E derivative is permeability enhancer , emulsifying agent for ethosomes as well as role incounterbalancing oxidation-reduction in psoriasis was incorporated with Glycyrrhetinic acid (GA) in phospholipid layer and curcumin in phospholipid and centre of ethosome to provide synergistic treatment for psoriasis. Accordingto in vivo and in vitro pharmacodynamic experiments Cur@GA-TPGS-ES demonstrated significant anti-inflammatory and antioxidative effects on IL-6-induced HaCaT cells and IMQ-induced mice due to downregulation of NF-κB and STATs related proteins involved hyperproliferation and intense inflammation.(Guo et al., 2021)

Proliposomes-

Proliposomes are lipid vesicles formed with freely flowing dry powder formulation in which drug can be incorporated in bilayer. Having advantage of dry form these are highly stable and turn into liposomes under controlled condition, temperature and agitation environment by fast and simple hydration method and offers action regionally or systemic circulation if required. Islam M Adel and team-members formulated nano-spray dried proliposome for lung cancer targeting.To generate freely flowing powder, lecithin and cholesterol were used as vesicle matrix ingredients, stearyl amine (SA) as a cationic charge inducer, poloxamer 188 (PLX

188) as a surface acting agent, and hydroxypropyl-beta-cyclodextrin (HPCD) as a carrier. The investigations revealed the in vitro toxicity studies on lung tumour A549 cells showed increased action of curcumin-proliposomes due to less particle size, enhanced cellular uptake and targeting affinity towards tumour cell because cationic SA on the liposomal surface has a great attraction for the anionic phosphatidylserine on the tumour cell surface.(Adel et al., 2021)

Proniosomes-

Provesicular structure of niosomes are called proniosomes which are stable. Nonionic surface-active agents are applied on water-soluble carrier or as liquid crystalline gel. This duoby water hydration are transformed into liposomal dispersion. Farid A. Badria and colleagues produced dry curcumin incorporated dry proniosome via slurry method for Herpes simplex virus HSV-1 antiviral effect. Invitro studies shown proniosomes to have better drug release because of enhanced effective surface area due to adsorption of proniosomal lipid layer on water-soluble carrier Maltodextrin. The antiviral effect showed enhancement due to boosted permeability of curcumin by surfactant due to adsorption or fusion at interface which increases thermodynamic gradient of curcumin and elevated interaction between niosomal vesicle leads to fusion or endocytosis.(Badria et al., 2020)

F. A. Aboali, D. A.Habibb, H.M. Elbedaiwyb and R. M. Farid produced cremophore based-nonionic surfactant curcumin-loaded proniosomal gel by coacervation phase separation method for inflammation of eye. The ex-vivo analysis showed 3.2 fold increase in corneal penetration.(Aboali et al., 2020)

Recent Advancement-

Recently robots were invented for curcumin drug delivery in Alzheimers. Photodynamic therapy, fullerene chemistry, nanostructuring, x-rays, computers, pharmacokinetics, and robotics concepts are used to produce a modelling approach for nanorobot delivery of curcumin. Nanorobots have a number of benefits over current medicine delivery systems. These include enhanced bioavailability, focused therapy, reduced operative mistakes, the flexibility to target inaccessible parts of human anatomy, a wide surface area for masstransport, a non-invasive methodology, computer-controlled transportation, improved precision, minimal side effects, and faster drug action. Fullerenes acts as a vector which is entered in the body by intrathecal route for curcumins photodynamic therapy, fullerene-drug conjugatedegrades due to irradiation to activate and release curcumin. Moreover, these irradiations generate polyfullerene which absorbs irradiation. The pharmacokinetic model is used to calculate the time for medicine release. Curcumin efficacy can be seen as a set of nanoreactors used as plug flow reactor. (Sharma, 2013)

CONCLUSION

Despite its demonstrated effects, the potential health benefits of curcumin are limited by its poor solubility, low absorption from the gut, rapid metabolism and rapid systemicelimination. While the major portion of ingested curcumin is excreted through the faeces unmetabolized, the small portion that is absorbed is extensively converted to its water-soluble metabolites, glucuronides and sulfates. Different strategies have been pursued to improve the absorption of curcumin, including nanocrystals, emulsions, liposomes, self-assemblies and nanogels. This review summarises the contribution of several researchers towards improved bioavailability of curcumin for availing its multifold pharmaco-therapeutic benefits.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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