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# Novel Drug Delivery Systems to Improve Bioavailability of Curcumin

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## Abstract

Curcumin, the major component of common food spice, turmeric, is a potential compound for the treatment and prevention of a wide variety of human diseases and has wide spectrum of biological and pharmacological activities. Various studies have proven the safety and efficacy of curcumin at very high doses; however the relative bioavailability of curcumin is of major concern. It has extremely low aqueous solubility and it is still unclear if it metabolizes into active or inactive metabolites. In this review, we have discussed the various novel drug delivery systems of curcumin such as various nanoparticles, micellar formulations, liposomes and cyclodextrin inclusion complexes that have been reported in order to improve the solubility, bioavailability and efficacy of curcumin.

**Keywords:** Curcumin; Bioavailability; Nanoparticles; Liposomes; Micelles; Cyclodextrins; Nanoassembly; Nanogel

**Abbreviations:** 17β-HSD3: 17 β-hydroxy steroid dehydrogenase; ABCG2: Breast Cancer Resistance Protein; Akt: AKT8 Virus Oncogenecellular Homolog; AKT: Serine/threonine Protein Kinase; AP: Apical; AP-1: Transcription Factor Activator Protein-1; APP: Amyloid Precursor Protein; ATP: Adenosine Triphosphate; AUC: Area Under the Curve; BCRP: Breast Cancer Resistance Protein; BL: Basolateral; Caco-2: Heterogeneous Human Epithelial Colorectal Adenocarcinoma Cells; cAMP: Cyclicadenosine Monophosphate; CD: Cyclodextrin; CD13: Cluster of Differentiation 13 Enzyme; CSN: COP9 Signalosome; CYP3A4: Cytochrome P450 Isoenzyme 3A4; DLPC: 1,2-Dilauroyl-sn-Glycero-3- Phosphocholine; DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DNA: Deoxyribonucleic Acid; DOPC: 1,2-Dioleoyl-sn-Glycero-3-Phosphocholine; DSC: Differential Scanning Calorimetry; DSPE-PEG: 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol; $EC_{50}$: Median Effective Dose; EGF: Epidermal Growth Factor; EPC: Egg Phosphatidylcholine; FLICE: FADD Like Interleukin-1- β-converting Enzyme; FTIR: Fourier Transformed Infrared Spectroscopy; GI: Gastrointestinal; GTP: Guanosine Triphosphate; HER2: Human EGF Receptor 2; HPβCD: Hydroxypropyl-beta-cyclodextrin; i.p.: Intraperitoneal; i.v.: Intravenous; IAP: Inhibitor of Apoptosis; IL: Interleukin; IL: Interleukin; LLC-PK1: Pig Kidney Epithelial Cells-1 Cell Line; LPPC: Liposome-PEG-PEI Complex; MAPK: Mitogen-Activated Protein Kinase; MDCKII: Madin-Darby Canine Kidney II Cell Line; MK571: 5-(3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl)-8-dimethylcarbamyl-4,6-dithiaoctanoic acid sodium salt hydrate; MRP-1: Multidrug Resistance Protein 1; MRP-2: Multidrug Resistant Protein 2; MβCD: Methyl Beta-Cyclodextrin; NADP: Nicotinamide Adenine Dinucleotide Phosphate; NFE2: Nuclear Factor-Erythroid 2; NF-kB: Nuclear Factor-kappaB; NP: Nanoparticle; OATP: Organic Anion Transporting Polypeptide; p53: tumor protein 53; PCD/CUR: Poly(β-cyclodextrin)-Curcumin; PCL: Polycaprolactone; PEG: Polyethylene Glycol; PEGylated: Polyethylene Glycosylated; PEI: Polyethylenimine; P-gp: P-glycoprotein; PI3K: Phosphoinositide 3-kinase; $pK_a$: Acid Dissociation Constant; PLGA: Poly(lactic-co-glycolic acid); PSC833: 6-[(2S,4R,6E)-4-methyl-2-(methylamino)-3-oxo-6-octenoic acid]-7-L-valine-cyclosporin A; PVA: Polyvinyl alcohol; PVP: Polyvinyl Pyrrolidone; SA: L-glutamic acid, N-(3-carboxy-1-oxopropyl)-, 1,5-dihexadecyl ester; SEM: Scanning Electron Microscopy; S-M: Serosal to Mucosal; SMEDDS: Self-microemulsifying Drug Delivery System; STAT: Signal Transducers and Activators of Transcription Protein; SULT1A1 and 1A3: Sulfotransferase 1A1 and 1A3; $t_{1/2}$: half-life; UDP: Uridine-5' diphospho-; XRPD: X-ray Powder Diffraction; α-CD: Alpha Cyclodextrin; β-CD: β-cyclodextrin; γ-CD: Gamma Cyclodextrin

## Introduction

Curcumin (1,7-bis(4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione) (Figure 1), also called diferuloylmethane, is a hydrophobic polyphenol derived from the rhizome of the herb Curcuma longa and known by its common name Turmeric. Commercial curcumin contains

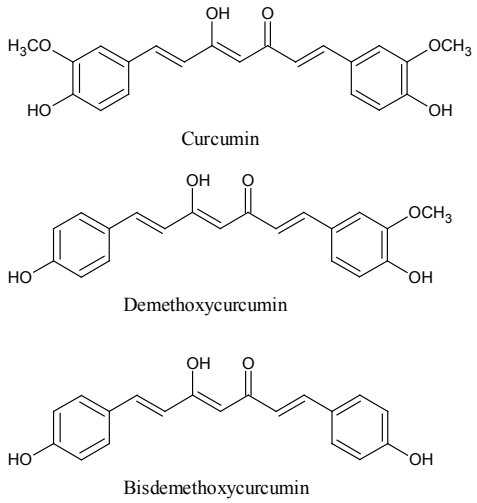


**Figure 1:** Chemical structures of curcumin, demethoxycurcumin and bisdemethoxycurcumin.

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approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bis demethoxycurcumin. It is also known to exhibit keto–enoltautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium [1].

It's an Indian spice known for its yellow food coloring in addition to its long history of use in Ayurvedic medicine [2]. The pharmacological safety and efficacy of curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseases. Curcumin has been found to have a wide spectrum of biological and pharmacological activities such as antioxidant,anti-inflammatory [1,3-7], antimicrobial,anticarcinogenic [1,8-12], hepato- and nephro-protective [1,13,14], thrombosis suppressing [1,15], myocardial infarction protective [1,16-18], hypoglycemic [1,19-21], and anti-rheumatic [1,22] effects.

Curcumin has been reported to modulate nuclear factor-kappaB (NF-kB), transcription factor activator protein-1 (AP-1), mitogen-activated protein kinase (MAPK), tumor protein 53 (p53), nuclear b-catenin signaling and serine/threonine protein kinase (AKT) signaling pathways [23,24]. It has been shown to suppress the expression of cancer associated epidermal growth receptor and estrogen receptors [23,25]. Curcumin has also been shown to overcome multidrug resistance to cancer therapeutics because of its downregulation of P-glycoprotein (P-gp), breast cancer resistance protein (ABCG2) and multidrug resistance protein (MRP-1) expression [23,26]. Table 1 shows the numerous molecular signals downregulated or upregulated by curcumin [27].

Various studies have been performed to prove the safety and efficacy of curcumin at very high doses, however the relative bioavailability of curcumin has been highlighted as a major problem [1,28-35]. It has an extremely low aqueous solubility of 11ng/mL at both acidic and neutral pH but solubilizes in alkaline pH. It has 3 $pK_a$s of 7.8, 8.5, 9.0 respectively, of the 3 acidic protons in the molecule [2].

The purpose of thisreview is to discuss in detail the possible novel drug delivery systems, more specifically nanoparticles, micellar formulations, liposomes and cyclodextrin inclusion complexes, to improve the bioavailabilityof curcumin.

## Bioavailability of Curcumin

Earlier pharmacokinetic studies ofcurcuminhave revealed poor absorption and rapid metabolismthat severely curtails its bioavailability, leading to extremely low serum levels [1]. Piperine is known to improve the absorption and bioavailability of curcumin [33]. Figure 2 shows the bioavailability of curcumin in humans with and without piperine [1]. In this randomized cross-over design study, six healthy adult male human volunteers took 2 g of curcumin with or without 5 mg of piperine (as bioperine). One week following initial drug administration, volunteers were crossed over to the opposite therapies, and blood samples were again obtained for evaluation. It was found the peperine almost doubled the AUC (Area under the curve) from 8.44 hr×ng/mL for curcumin alone to 15.55 hr×ng/mL for curcuminandpiperine combination.

Turmeric oil (Biocurcumax or turmerne) was also found to enhance the bioavailability of curcumin and AUC was 7–8 times higher when curcumin was combinedwith turmeric oil (Figure 3) [1,36].

Moreover, the serum levels of curcumin have been found to significantly depend on the route of administration. Table 2 shows the serum and tissue levels of curcumin in rodents and humans after different routes ofadministration [1]. The data shows that the serum levels of curcumin in rats and in human are not directly comparable. It is also indicated that curcumin pharmacokinetics observed in tissues after i.p. administration cannot be compared directly with those observed after gavage or dietary intake [1].

Onceabsorbed, curcuminmay be subjected to conjugations like sulfationand glucuronidation at various tissue sites and/or undergo extensive reduction, most likely through alcohol dehdrogenase, followed byconjugation leading to various possible metabolites such as dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, hexahydrocurcuminol, ferulic acid, dihydroferulic acid, curcuminglucoronide, and curcumin sulfate (Figure 4) [1]. It is not clear yet ifcurcumin metabolites are as active as curcumin.Muruganet. al reported that tetrahydrocurcumin had better anti-diabetic and antioxidant activity than curcumin in Type 2 diabetic rats [37] where as Sandur et al. [38] reported lower anti-inflammatory and anti-proliferative activities of tetrahydrocurcuminas compared to curcumin. In another study, Ireson et al. [39] reported lesser anti-proliferative effects of curcuminglucuronides and tetrahydrocurcumin than curcumin.

Elimination half-life is also an important factor affectingcurcumin bioavailability. Shoba et al. [33] reported that the absorption and elimination $t_{1/2}$ of curcumin administered orally at a dose of 2 g/kg in rats to be 0.31 ± 0.07 and 1.7 ± 0.5 hrs, respectively, and the serum curcumin levels in humans were below the limit of detection. However, Yang et al. [40] reported the elimination $t_{1/2}$ values for i.v. (10 mg/kg) and oral (500 mg/kg) curcumin in rats to be 28.1 ± 5.6 and 44.5 ± 7.5 hrs, respectively. This variability in reported data warrants additional investigations on the pharmacokinetics of curcumin and the factors affecting it.

## Intestinal Absorption of Curcumin

Poor curcumin absorption from intestine might be due to its low water solubility, decomposition at neutral or alkaline pH, photosensitivity and a coordinately regulated alliance between metabolizing enzymes and transporters, all act in tandem with the net result of low curcumin absorption [24,41,42]. *In vitro* studies with Caco-2 cells, [24,41,42], MDCKII cells [41,43] and LLC-PK1cells [41,44], experiments with vesicles isolated from Multidrug Resistance Associated Proteins 1 and 2 (MRP-1 and MRP-2) transfected Sf8 cells [41,43] and CYP3A4 studies [41,44] identified P-glycoprotein (P-gp), MRP-1, MRP-2, Cytochrome P450 isoenzyme 3A4 (CYP3A4), sulfotransferase 1A1 and 1A3 (SULT1A1 and 1A3) [41,45], UDP glucuronyltransferases [39,41,46] and nonspecific oxydoreductases [39,41] as the key intestinal transporters and enzymes for hepatic pre-systemic metabolism of curcumin.

Berginc et al. [41] determined the permeability of curcumin through Transwell grown Caco-2 cell monolayers with 2% of albumin added to both sides of the monolayer. The permeability was determined in the absorptive (AP-BL; apical to basolateral) and the opposite (BL-AP; basolateral to apical) direction at acidic and neutral pH (i.e. 6.5 and 7.4) on the apical side of the cells, while the basolateral pH was kept constant at pH 7.4. The participation of efflux (Pgp, MRPs and Breast Cancer Resistance Protein (BCRP)) and absorptive (Organic Anion Transporting Polypeptide (OATP)) transporters were assessed by using appropriate inhibitors (PSC833 for Pgp, MK571 for MRPs and fumitromorgin C for BCRP) and appropriate pH conditions on

| **Transcription factors** | **Inflammatory mediators** |
|---|---|
| Activating transcription factor-3 ↓ | C-reactive protein ↓ |
| Activator protein-1 ↓ | Interleukin-1β ↓ |
| β-catenin ↓ | Interleukin-2 ↓ |
| CREB-binding protein ↓ | Interleukin-5 ↓ |
| C/EBP homologous protein ↓ | Interleukin-6 ↓ |
| Electrophile response element ↑ | Interleukin-8 ↓ |
| Early growth response gene-1 ↓ | Interleukin-12 ↓ |
| Hypoxia inducible factor-1α↓ | Interleukin-18 ↓ |
| Nuclear factor κ-B ↓ | Interferon-γ ↓ |
| Notch-1 ↓ | Inducible nitric oxide synthase ↓ |
| NFE2 related factor ↑ | 5-Lipoxygenase ↓ |
| p53↑ | Monocyte chemoattractant protein ↓ |
| Peroxisome-proliferator-activated receptor -γ ↑ | Migration inhibition protein ↓ |
| Specificity protein-1 ↓ | Macrophage inflammatory protein-1α↓ |
| STAT-1 ↓ | Prostate specific antigen ↓ |
| STAT-3 ↓ | |
| STAT-4 ↓ | **Protein kinases** |
| STAT-5 ↓ | Autophosphorylation-activated protein kinase ↓ |
| Wilms' tumor gene 1 ↓ | Ca2+, phospholipid-dependent protein kinase C ↓ |
| | c-jun N-terminal kinase ↓ |
| **Enzymes** | cAMP-dependent protein kinase ↓ |
| Acetylcholinesterase ↓ | CSN-associated kinase ↓ |
| Aldose reductase ↓ | EGF receptor-kinase ↓ |
| Arylamine N-acetyltransferases-1 ↓ | Extracellular receptor kinase ↓ |
| Beta-site APP-cleaving enzyme-1 ↓ | Focal adhesion kinase ↓ |
| CD13 ↓ | IL-1 receptor-associated kinase ↓ |
| DNA polymerase I ↓ | IκB kinase ↓ |
| DNA topoisomerase-II ↓ | Janus kinase ↓ |
| GTPase (microtubule assembly) ↓ | Mitogen-activated protein kinase ↓ |
| Glutathione reductase ↓ | pp60c-src tyrosine kinase ↓ |
| Glutathione-peroxidase ↓ | Phosphorylase kinase ↓ |
| Glutathione S-transferase ↑ | Protein kinase A ↓ |
| Hemeoxygenase-1 ↑ | PI3K-Akt ↓ |
| Ca2+-dependent ATPase ↓ | Protamine kinase ↓ |
| Inosine monophosphate dehydrogenase ↓ | |
| 17β-HSD3 ↓ | **Drug resistance proteins** |
| Ornithine decarboxylase ↓ | Multi-drug resistance protein-1 ↓ |
| Monoamine oxidase ↓ | Multi-drug resistance protein-2 ↓ |
| NADP(H):quinoneoxidoreductase -1 ↓ | |
| Phospholipase D ↓ | **Adhesion molecules** |
| Thioredoxinreductase 1 ↓ | Intracellular adhesion molecule-1 ↓ |
| Telomerase ↓ | Endothelial leukocyte adhesion molecule-1 ↓ |
| Ubiquitin isopeptidases ↓ | Vascular cell adhesion molecule-1 ↓ |
| **Growth factors** | **Cell-survival proteins** |
| Connective tissue growth factor ↓ | B-cell lymphoma protein-xL ↓ |
| Epidermal growth factor ↓ | Cellular FLICE-like inhibitory protein ↓ |
| Fibroblast growth factor ↓ | Inhibitory apoptosis protein ↓ |
| HER2 ↓ | X-linked IAP ↓ |
| Hepatocyte growth factor ↓ | |
| Platelet derived growth factor ↓ | **Chemokines and chemokine receptor** |
| Tissue factor ↓ | Chemokine ligand 1 ↓ |
| Transforming growth factor-β1 ↓ | Chemokine ligand 2 ↓ |
| | Chemokine receptors 4 ↓ |
| **Receptors** | **Invasion and angiogenesis biomarkers** |
| Androgen receptor ↓ | Matrix metalloproteinase-9 ↓ |
| Aryl hydrocarbon receptor ↓ | Urokinase-type plasminogen activator ↓ |
| Death receptor-5 ↓ | Vascular endothelial growth factor ↓ |
| EGF-receptor ↓ | |
| Endothelial protein C-receptor ↓ | **Others** |
| Estrogen receptor-α ↓ | cAMP response element binding protein ↓ |
| Fas ↑ | DNA fragmentation factor 40-kD subunit ↑ |
| Histamine 2- receptor ↓ | Fibrinogen ↓ |
| Interleukin 8-receptor ↓ | Ferritin H and L ↓ |
| Inositol 1,4,5-triphosphate receptor ↓ | Heat-shock protein 70 ↑ |
| Integrin receptor ↓ | Iron regulatory protein ↓ |
| Low density lipoprotein-receptor ↑ | Prion fibril ↓ |
| Transferrin receptor 1 ↓ | |
| **Cell-cycle regulatory proteins** | |
| Cyclin D1 ↓ | |
| Cyclin E ↓ | |
| c-Myc ↓ | |
| p21 ↓ | |

**Table 1:** Molecular targets of curcumin [27].

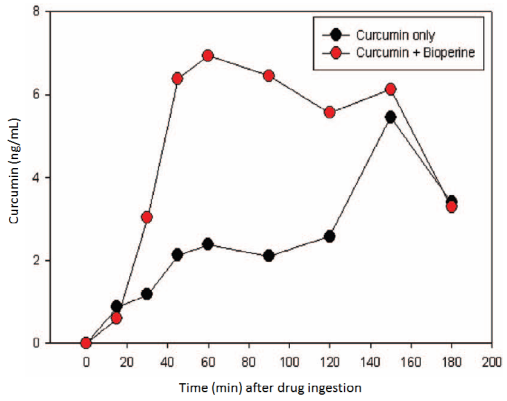



**Figure 2:** Bioavailability of curcumin in human with and without piperine [1].

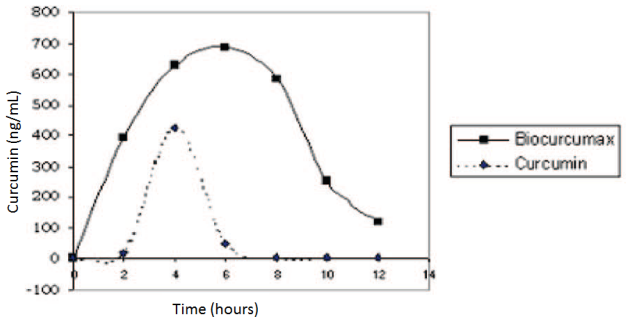



**Figure 3:** Bioavailability of curcumin in presence of Turmeric oil (Biocurcumax) [1].

the apical side of the cells. The results indicated asymmetrical transport properties of curcumin regardless of the pH applied to the apical side. In both cases, the BL-AP permeability was significantly higher than the absorptive one ($p < 0.05$). However, under slightly acidic conditions (pH 6.5) on the apical side, the absorptive permeability of curcumin significantly surpassed the one, determined at iso-pH conditions (apical and basolateral pH 7.4). However, AP-BL permeability value measured at pH 6.5 was not in the range of AP-BL permeabilities determined for highly permeable standards through Transwell grown Caco-2 monolayers [41,47], and therefore curcumin was classified as a low permeable compound. The authors did not observe any permeability decrease in BL-AP directions when specific Pgp and MRP inhibitors were added [41].

Berginc et al. [41] also assessed the participation of BCRP to curcumin efflux from Caco-2 cells. Fumitromorgin C is a specific BCRP inhibitor that increased the BL-AP permeability of curcumin significantly. The authors concluded that the permeability increase observed in the presence of 5 mM fumitromorgin C was not due to Caco-2 cell monolayer injuries, because TEER (transendothelial electrical resistance) values and the permeability of paracellular marker fluorescein (the marker of tight junction integrity) did not change.

Berginc et al. [41] also observed that the permeability of curcumin through rat intestine was even lower than through Caco-2 cell monolayers. There were also no significant differences between permeabilities in M-S (mucosal to serosal indicating absorptive) and S-M (serosal to mucosal indicating secretive) direction, indicating that efflux transporters did not participate in the intestinal absorption from rat jejunum. Considering the differences between both models, the authors anticipated that mucus could represent an additional barrier to curcumin absorption.

## Novel Drug Delivery Systems of Curcumin

In the past 8-10 years,nanopaticles (NPs) research has been focused in developing a suitable nanoparticle delivery system of the active form of curcumin to the target tissue. Different types of curcuminNPs, such as liposomes, nano- or micro- emulsions, polymeric NPs and solid lipid NPs, polymer conjugates, nanocrystals, polymeric micelles, nanogels, and self-assemblies continue to be developed in order to improve the stability and bioavailability of curcumin [23].

### Curcumin microemulsions and liposomes

Microemulsions are single phase optically isotropic nanostructures composed of surfactants, oil and water forming a thermodynamically stable system. Eucalyptol curcumin-microemulsionswas found to have high permeability and flux compared to oleic acid and esteem oil-based microemulsions [48]. Other microemulsions such as self-microemulsifying drug delivery system (SMEDDS) comprising 20% ethanol, 60% Cremophor RH40® and 20% isopropyl myristatehad curcumin encapsulation efficiency of 50 mg/mL and the drug was entirely released in 10 minutes. This was shown to increase dissolution and bioavailability *in vivo* [49].

| Species | Route[a] | Dose | Plasma/Tissue | Levels |
|---|---|---|---|---|
| mice | i.p. | 100 mg/kg | plasma | 2.25 µg/mL |
| | | | intestine | 117 ± 6.9 µg/g |
| | | | spleen | 26.1 ± 1.1 µg/g |
| | | | liver | 26.9 ± 2.6 µg/g |
| | | | kidney | 7.5 ± 0.08 µg/g |
| | | | brain | 0.4 ± 0.01 µg/g |
| mice | oral | 100 mg/kg | plasma | 0.22 µg/mL |
| mice | i.p. | 100 mg/kg | plasma | 25 ± 2 nmol/mL |
| | | | intestinal mucosa | 200 ± 23 nmol/g |
| | | | liver | 73 ± 20 nmol/g |
| | | | brain | 2.9 ± 0.4 nmol/g |
| | | | heart | 9.1 ± 1.1 nmol/g |
| | | | lungs | 16 ± 3 nmol/g |
| | | | muscle | 8.4 ± 6 nmol/g |
| | | | kidney | 78 ± 3 nmol/g |
| rat | oral | 2 g/kg | stomach | 53.3 ± 5.1 (µg/g) |
| | | | small intestine | 58.6 ± 11.0 (µg/g) |
| | | | cecum | 51.5 ± 13.5 (µg/g) |
| | | | large intestine | 5.1 ± 2.5 (µg/g) |
| rat | oral | 340 mg/kg | serum | 6.5 ± 4.5 nM |
| rat | oral | 1g/kg | serum | 0.5 µg/mL |
| rat | oral | 2 g/kg | serum | 1.35 ± 0.23 µg/mL |
| rat | oral | 500 mg/kg | plasma | 0.06 ± 0.01 µg/mL |
| rat | i.v. | 10 mg/kg | plasma | 0.36 ± 0.05 µg/mL |
| human | oral | 2 g/kg | serum | 0.006 ± 0.005 µg/mL |
| human | oral | 4–8 g | serum | 0.4–3.6 µM |
| human | oral | 10 g | serum | 50.5 ng/mL |
| human | oral | 12 g | serum | 51.2 ng/mL |
| human | oral | 3.6 g | plasma | 11.1 ± 0.6 nmol/mL |
| human | oral | 0.4–3.6 g | colorectum | 7–20 nmol/g |

[a]Key: i.p: intreperitoneal; i.v.: intraveneous
**Table 2:** Serum and tissue levels of curcumin in rodents and humans after different routes of administration [1].

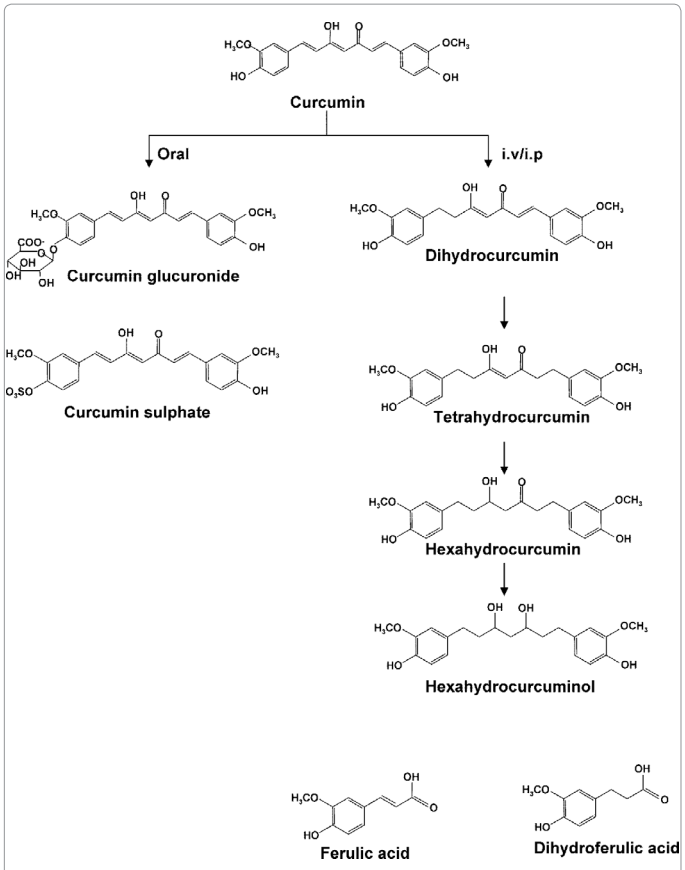



**Figure 4:** Metabolic pathway and possible metabolites of curcumin [1].

Phospholipid vesicles or liposomes and lipid- nanospheres embedded with curcumin can be formulated to be delivered through intravenous injection. Lipid based curcumin nanoparticles have successfully been prepared using 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and an anionic amphiphile, L-glutamic acid, N-(3-carboxy-1-oxopropyl)-, 1,5-dihexadecyl ester (SA) [50]. Nanodisk NPs comprising disk-shaped lipid bilayer complexes of curcumin, DMPC and stabilized by recombinant apolipoprotien A-I have also been reported. Nanodisk NP provided a broad platform for hydrophobic bioactive agent delivery [51]. Other curcumin loaded lipid formulations such as Eggphosphatidylcholine (EPC) liposomes have also shown to increase plasma concentration of curcumin [23,52].

Lin et al. [53] evaluated the potential of polycationic liposome complex of curcumin(LPPC) containing polyethylenimine (PEI) and polyethylene glycol (PEG). LPPC were prepared using 1,2-Dioleoyl-sn-Glycero-3-Phosphocholine (DOPC) and 1,2-Dilauroyl-sn-Glycero-3-Phosphocholine (DLPC). The lipid suspensions were extruded through a LiposoFast extruder with a 200 nm mesh to form unilamellar liposomes. LPPC were roughly spherical in shape with hair-like projections on the surface and the diameters ranged from 258 to 269 nm. The zeta potential was ~ 40 mV and the encapsulation efficiency of curcumin in LPPC was determined to be 45 ± 0.2%. It was foundthat the cytotoxic activity of curcumin/LPPC was 3.9 to 20 foldhigher in a variety of cancer celllines (Table 3), including curcumin sensitiveand -resistant cells, as compared to nonencapsulatedcurcumin. Curcumin/LPPC liposomes were also able toarrest the cell cycle at the G2/M phase and induce apoptosis at alower dose than noncapsulatedcurcumin by facilitating a rapid delivery of thedrug into the cells. Additionally,curcumin/LPPC liposomes significantly increased caspase-3 activity in CT-26 and B16F10 cells. *In vivo*, curcumin/LPPC liposomes also resultedin a significantinhibition of tumor growth, which may be due to the higher delivery and accumulationof the drug in the tumor area [53].

## Curcumin encapsulated polymer NPs

Figure 5 shows the various representative PLGA-based nanoparticle dosage forms possible with a drug. Poly(lactic-co-glycolic acid) (PLGA) has been used as a safe carrier molecule for curcumin encapsulation due to its biodegradability and biocompatibility characteristics. Solvent evaporation method had been used to prepare curcumin-encapsulated PLGA NPs [54]. Alternatives such as curcumin-encapsulated dextran-sulfate chitosan NPs [52,55] and acurcumin analog encapsulated in polycaprolactone (PCL) NPs can be used in oral, intravenous and controlled delivery systems [52,56].

## Polymer conjugates

Curcumin-polymer conjugates are alternative delivery systems in order to improve bioavailability of the compound. Curcumin has interesting structure with two phenolic rings and active methylene function, which are potential site for attaching biomolecules [57]. This can increase oral bioavailability of curcumin in GI tract. Nucleoside-curcuminbioconjugates have been designed to obtain high levels of glucuronide and sulfate curcumin conjugates [23,58].

Polyethylene glycosylated (PEGylated) curcumin analogs are also known to increase curcumin solubility by increasing prolonged internalization time in a cell and resisting cellular efflux [23,59]. Polycatocol-curcumin conjugates were synthesized by condensation polymerization of curcumin and anhydrides. These polycurcumins, also called curcumin polymers, were found to have high drug loading efficiency, fixed drug loading contents, and stabilized curcumin in their backbones [23,60].

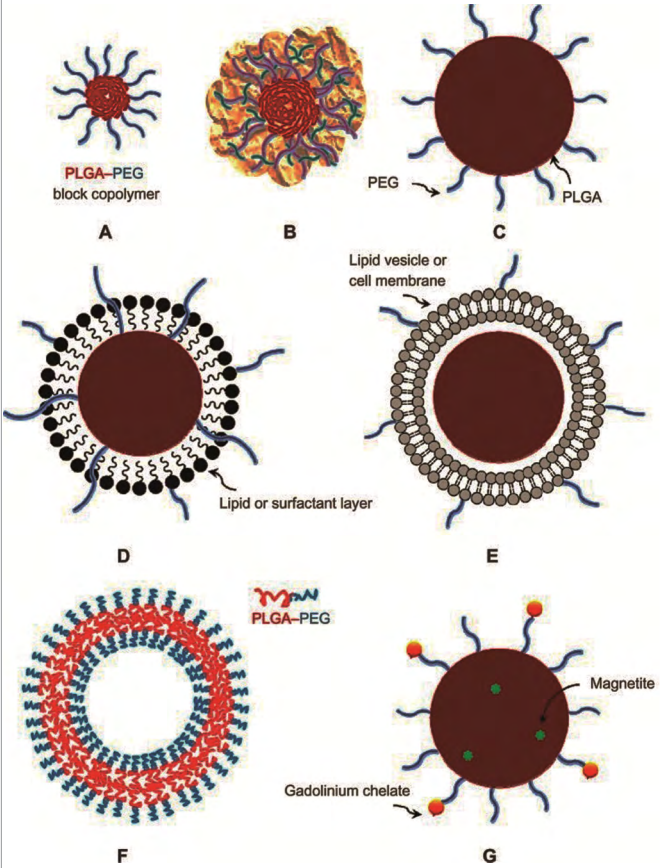
## Curcuminnanocrystals

These are nano-sized drug particles have large surface area therefore

| Cell lines | Curcumin (μM) | Curcumin liposome (μM) | Curcumin/LPPC (μM) |
|---|---|---|---|
| Mouse | | | |
| B16/F10 | 8.2 ± 1.0† | 7.8 ± 1.3 | 1.1 ± 0.1 |
| LL-2 | 10.8 ± 2.3 | 9.9 ± 0.1 | 1.4 ± 0.2 |
| CT-26 | 7.9 ± 0.8 | 6.8 ± 0.8 | 1.2 ± 0.1 |
| JC | 11.0 ± 1.5 | 9.3 ± 0.1 | 1.3 ± 0.1 |
| Human | | | |
| HepG2 | 12.2 ± 1.1 | 10.0 ± 0.4 | 1.7 ± 0.2 |
| HT-29 | 12.9 ± 1.2 | 10.9 ± 1.0 | 1.5 ± 0.1 |
| HeLa | 17.7 ± 7.0 | 10.0 ± 0.2 | 1.2 ± 0.2 |
| Curcumin-resistant cells | | | |
| A549 | 30.0 ± 9.5 | 12.5 ± 0.4 | 1.4 ± 0.1 |
| CT26/cur-r | 27.3 ± 4.6 | ND | 1.3 ± 0.1 |
| B16F10/cur-r | 24.0 ± 8.5 | ND | 1.3 ± 0.2 |
| Normal cells | | | |
| PBMC | 15.2 ± 4.1 | ND | 9.9 ± 1.1 |
| MS1 | 21.1 ± 6.4 | ND | 11.7 ± 1.5 |
| SVEC4-10 | 15.7 ± 3.7 | ND | 9.0 ± 0.5 |

*Inhibition of cells exposed to $IC_{50}$ levels of curcumin
ND: non-detection
†: All values are mean ± SD of 3 independent experiments (n=6)

**Table 3:** Effects of curcumin-LPPC liposomes on proliferation in different cell lines* [53].




**Note:** All of these nanoparticulate carriers can be further derivatized by cell-recognizable ligands

**Figure 5:** Representative PLGA-based nanoparticulate dosage forms. (**A**) PEGylated micelle (eg, PEG-PLGA block copolymeric micelle), (**B**) polyplex (eg, DNA-PEI-PLGA), (**C**) PEGylated PLGA nanoparticle, (**D**) core-shell type nanoparticle (eg, PEGylated lipid-PLGA hybrid nanoparticle), (**E**) cell membrane-PLGA hybrid nanoparticle (eg, PLGA nanoparticles encased by red blood cell), (**F**) polymersome (eg, PEG-PLGA block copolymeric vesicle), and (**G**) magnetic PLGA particle either conjugated with gadolinium-chelate or laden with magnetite (e.g.theranostics) [54].

increasing their dissolution rate. High pressure homogenization at a pressure of 150 MPa applied in ten cycles and a temperature of 2°C is suitable in reducing bulk curcumin into NPs [23,61].

## Polymeric micelles of curcumin

Surfactants that form cationic micelles help stabilize curcumin better at high pH improving stability and absorption [23]. In addition plasma proteins can also be used as carriers of curcumin since they have the ability to stabilize it [62].

## Curcumin self-assemblies

Yallapu et al. [23] formulated self-assembly of β-CD and curcumin that improved intracellular uptake of the drug by cancer cells as compare to free curcumin. The self-assemblies were prepared by solvent evaporation technique and characterized using spectral, thermal, X-ray diffraction and electron microscopy. In another study, Yallapuet al. used nano poly (β-cyclodextrin)-curcumin (PCD/CUR) self-assembly to improve curcumin's water solubility, stability and bioavailability for enhancing its anti-cancer efficacy to treat prostate cancer. PCD/CUR complexes, prepared by supramolecular encapsulation or self-assembly (inclusion complexation), showed an improved intracellular uptake in cancer cells compared to free curcumin. Additionally, the optimized curcumin formulation (PCD30) showed superior anti-cancer efficacy in prostate cancer cells compared to free curcumin [63].

## Curcumin nanogel

Bisht et al. [64] tested the effects of nanocurcumin hydrogel on pancreatic cancer cell lines. Nanocurcumin efficiently blocked the activation of NF-kB, downregulated steady-state transcripts of multiple pro-inflammatory cytokines and inhibited interleukin (IL)-6 synthesis. The parenteral administration of the hydrogel nanocurcumin formulation also significantly inhibited tumor growth in both subcutaneous and orthotopic settings in xenograft models of human pancreatic cancer in athymic mice [65].

Various hydrogels and nanocomposites were subsequently investigated to improve the therapeutic effects of curcumin, such as curcumin- loaded dextran-modified hydrogel NPs [66], curcumin-encapsulated chitosan–PVA silver nanocomposite, poly(acrylamide)–poly(vinyl sulfonic acid) silver nanocomposite, and poly(acrylamide)–carboxymethyl cellulose magnetic nanocomposites [67], and curcumin loaded hydrogel NPs using PVP and hydroxyl propyl methyl cellulose in the presence of pluronic F68 [68].

## Curcumin-cyclodextrininclusion complexes

Cyclodextrins(CD) are known for their solubilizing and

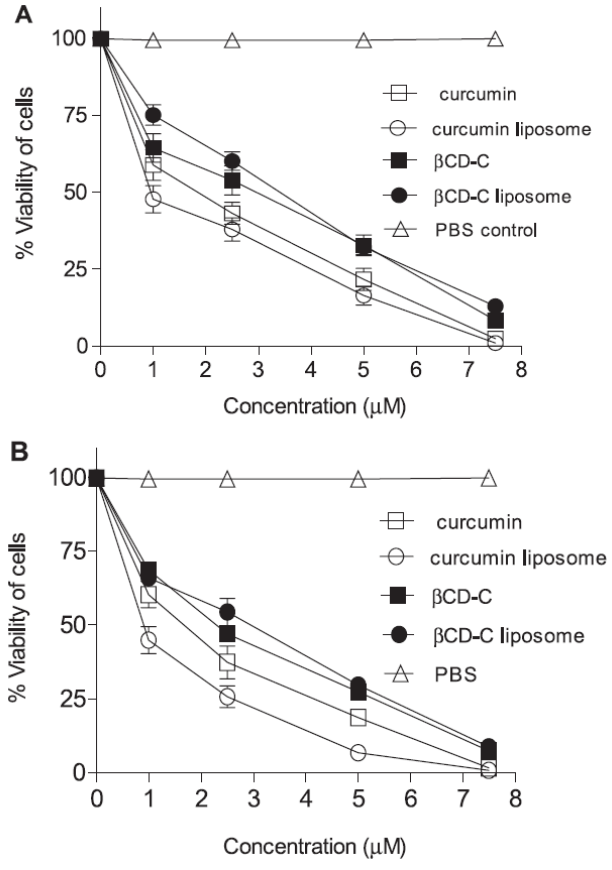



**Figure 6:** Cytotoxicity of curcumin formulations in SW-620 colon cancer cells (A) and A-549 lung cancer cells (B) Bars indicate SEM of three replicates [71].

stabilizing characteristics.Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and lipophilic central cavity [69]. Drug-cyclodextrininclusion complexes are formed by binding of lipophilic drug moieties in the lipophilic cavity of thecyclodextrin [69]. The lipophilic cavity thus protects the lipophilic guest molecule from aqueous environment, while the polar outer surface of the CD molecule provides the solubilizing effect [69]. The polarity inside the cavity is suggested to be similar to that of a 40% solution of ethanol in water [69,70]. Commonly used cyclodextrins are α, β and γ-CD, and their derivatives such as hydroxypropyl-β-CD (HPβCD) and methyl β-CD (MβCD) [69]. It was observed that curcumin formed an $A_L$ type of phase solubility plots with βCD, γCD, MβCD and HPβCD, forming 1:1 inclusion complexes in the solution state [69]. The ability to increase the solubility of curcumin by CD increased in the order HPβCD>MβCD>γCD>βCD [69]. Curcumin molecules with bulky side groups on the phenyl moiety seemed to fitbetter into the HPβCD cavity than into the cavities of MβCD, and thus a significant increase in solubility was observed as compared to the pure drug [69]. Yadav et al. [69] also prepared solid inclusion complexes with HPβCD and MβCD complexes by kneading and solvent evaporation methods in the ratio of 1:1 and 1:2 molar concentrations, and characterized the solid complexes using dissolution studies, Fourier Transformed Infrared spectroscopy (FTIR), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRPD) studies. At 12 hrs, 97.82% of curcumin was released with HPβCD complex as compared to 68.75% release with MβCD and 16.12% release with the pure drug [69]. Higher dissolution/release rate should directly correlate with higher *in vivo* bioavailability of curcumin-HPBCD complexes as compared to curcumin alone.

Rahman et al. [71] reported the preparation of β-CD-curcumin inclusion complexesand their entrapment within liposomes followedby subsequent assessment of *in vitro* cytotoxicity usingmodel lung and colon cancer cell lines. Liposomes were prepared using film hydration method thatcan entrap both hydrophobic as well as βCD-complexedhydrophobic compounds, according to Maestrelli et al. [72]. Around 90% entrapment were achieved for both curcumin or βCD-curcumin complexes into thePEGylated liposomes prepared with EggPC, cholesteroland 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)-PEG. However, these liposomes graduallyincreased in particle size and polydispersity when stored at 2-8°C for 4 weeks, indicating poor stability on storage.

All the formulations including liposomalcurcumin and liposomal βCD-C complexes retain their anti-cancer activity and hadrelativelylow median effective dose ($EC_{50}$) values in both colon cancer and lung cancer cell lines tested. The $EC_{50}$ of the formulationson colon cancer cells were calculated to be 0.96 μM forcurcumin-entrappedliposomes, 1.9 μM for curcumin, 2.95 μM for βCD-C complexes and 3.25 μM for liposomescontaining βCD-curcumin (Figure 6A). The $EC_{50}$ of the formulationson lung cancer cells followed the same pattern,being 0.90 μM for curcumin-entrapped liposomes, 1.5μM for curcumin, 2.4 μM for βCD-C and 2.9 μM for liposomescontaining βCD-C (Figure 6B) [71].

## Conclusions

Curcumin which is derived from the common food spice, turmeric, possesses therapeutic efficacy against a variety of diseases, and also found to be safe at high doses. Owing to its poor solubility, stability and rapid metabolism, the bioavailability of curcumin has been of major concern. In this review, several novel drug delivery strategies such as liposomes, nano- or micro- emulsions, polymeric NPs and solid lipid NPs, polymer conjugates, polymeric micelles, nanocrystals, nanogels, self-assemblies and cyclodextrin inclusion complexes have been described to increase solubility, bioavailability and delivery of curcumin. However, much work is needed to further investigate the pharmacokinetics, enhance the delivery at the target tissues, the bioavailability and medicinal value of curcumin.

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