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Improvement of Curcumin Bioavailability for Medical Applications

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Abstract

Curcumin, a natural polyphenol isolated from the rhizomes of the turmeric plant (*Curcuma longa* Linn), is well known for its antioxidant and anti-inflammatory properties. Curcumin is currently marketed as a dietary supplement in several countries (United States, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan). Nevertheless, the use of curcumin has been limited due to its poor aqueous solubility, chemical instability, photodegradation, rapid metabolism, and short half-life. Moreover, orally administered curcumin shows poor bioavailability. Many strategies have been designed to overcome this limitation. In this review, we discuss the bioavailability of curcumin and the commercially available formulations.

Keywords: Curcumin; Bioavailability; Conventional formulation; Nanocarrier; Microcarrier

Introduction

Natural plant-based phytochemicals may be of interest for medical applications. Among them, curcumin is a natural polyphenol found in the rhizome of *Curcuma longa* L. (Zingiberaceae).

Natural products from plants, microorganisms and animals play a major role in drug discovery, particularly of anti-infective and anticancer agents [1]. Among them, herbal secondary metabolites have proved to be valuable sources for thousands of years [2]. Curcumin isolated from the rhizome of *Curcuma longa* L. (Zingiberaceae) is one of them. Recent reviews reported that more than 9,000 papers have been published on this natural polyphenol [3,4].

First isolated from the rhizomes of turmeric in 1815 by two German Scientists, Vogel and Pelletier [5], curcumin has gained considerable attention due to its pharmacological effects such as its antioxidant, anti-inflammatory, choleretic and cholagogue and also antimicrobial properties [6]. At the end of 2018, at least 183 clinical trials were reported by the database clinical.trials.gov [7] to evaluate the efficiency of curcumin in various chronic diseases including inflammatory (hepatobiliary diseases, gastritis, inflammatory bowel syndrome, osteoarthritis, psoriasis), several types of cancers, neurological (Alzheimer's disease) and infectious diseases or metabolic pathologies with cardiovascular issues (diabetes, obesity) [3,8-11]. Overall, curcumin is associated with a number of health claims, but its therapeutic use is limited due to its low bioavailability, poor aqueous solubility, instability at neutral and basic pH, poor absorption, rapid metabolism, and short half-life [12,13]. Curcumin is a class IV drug (low solubility and low permeability) based on the biopharmaceutics classification system (BCS) [14]. Many strategies have been developed to overcome these limitations, particularly for oral delivery systems [15,16]. In this review, we present the source of curcumin, its physicochemical properties, therapeutical potential, and the formulations that have been developed.

Curcumin

Sources of curcumin

Turmeric, *Curcuma longa* Linn. (Zingiberaceae) is the major source of curcumin. This plant native from India and South-East Asia [17,18]. Turmeric is a perennial herb, up to 1.0 m in height. Its main rhizome is ovate, approximately 3 cm in diameter and 4 cm long, and consists of an orange flesh. The lateral rhizome has, large leaves lanceolate, which are uniformly green. The flower is yellow and have a funnel-shape. Turmeric has an aromatic odor and a bitter taste [19]. It grows in tropical and subtropical regions throughout the world and is commonly found in India, China, South-East Asia (Cambodia, Indonesia, Thailand, Laos, Malaysia, Philippines, and Vietnam), Nepal, and tropical regions of Africa (Madagascar) [19-21]. The largest producer of turmeric is India [22]. In *C. longa* roots, curcuminoids constitute 1 to 6% of, depending on its origin and the soil conditions in which it has grown [23]. Curcumin (1), the major curcuminoid (50 to 60%) is associated to two other major components, i.e., demethoxycurcumin (DMC, 2) (20 to 30%), and bis-demethoxycurcumin (BDMC, 3) (7 to 20%) [24-37] (Figure 1). The purification of pure curcumin is difficult and time-consuming. Consequently, it is commercially available in the form of curcuminoids. The extraction of curcuminoids from turmeric has been carried-out using various procedures, such as conventional extraction using, for example Soxhlet apparatus but also ultra-sound-assisted and supercritical fluid extraction (SFE). Ethanol is commonly used to extract curcuminoids, as it allows the higher yield of extract and the best amount of curcuminoids. Ethanol added to CO_2 during the SFE process improves the yield of curcuminoids [24].

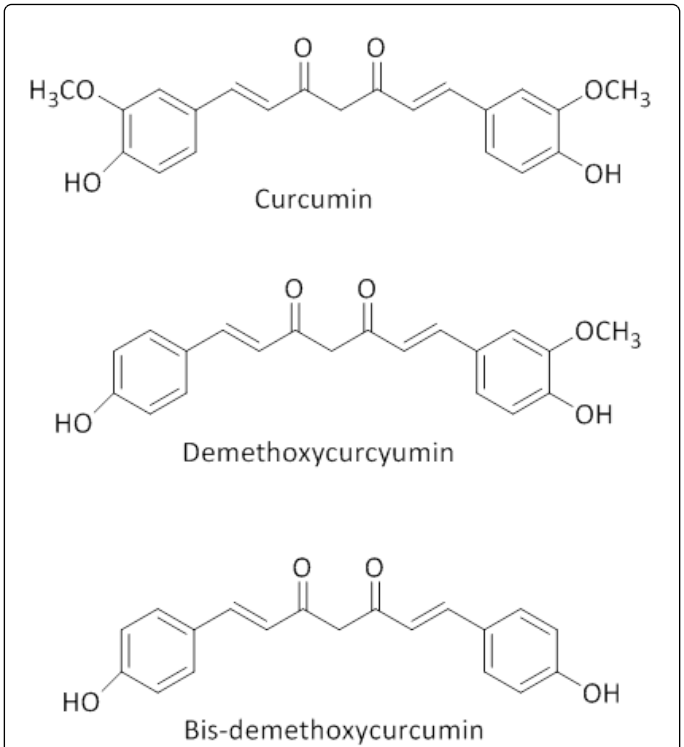

Figure 1: Chemical structure of curcumin (1), demethoxycurcumin (2), and bis-demethoxycurcumin (3) [38].

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Structure and physicochemical properties of curcumin

The IUPAC name of curcumin (1) is ([1,7-bis (4-hydroxy-3-methoxy- phenyl)-1,6-heptadiene-3,5-dione]). Its chemical formula is $C_{21}H_{20}O_6$, molecular weight 368.38 g/mol, and melting point 183°C. The chemical structure was identified in 1910 by Milobedzka. The di-ketone functionality of curcumin can undergo reversible tautomerization between keto and enol forms (Figure 2) in a pH-dependent manner, as the enol form exists in alkaline solutions and the keto form in acidic and neutral solutions [25,26]. The keto form dominates at pH 3 to 7 and the enol form predominates at pH>8 [27]. However, under physiological conditions, both the keto and enol forms of curcumin play important roles in its antioxidant activity by scavenging free radicals through H-atom donation and electronic transfer [28]. Curcumin exists mainly in the enol form in organic solvents [29,30]. The enol form is more stable than the keto form, due to the presence of strong intramolecular hydrogen bonds [31]. However, all functionalities present in the curcumin molecule play crucial roles in its biological activities. The solubility of curcumin in various media is presented in Table 1. Curcumin is poorly soluble in water (11 ng/mL) [32] and its log P value is 2.5-3.6 [33]. Nevertheless, it is soluble in polar solvents, such as acetone, 2-butanone, ethyl acetate, methanol, ethanol, 1,2-dichloroethane, 2-propanol, dimethyl sulfoxide, etc. [34-36]. Moreover, curcumin has been shown to be highly soluble in some oils, surfactants, and co-surfactants (Table 1).

Category	Solvent, oils, surfactant and co-surfactant		Cur. Solubility	Reference
	General name/Trade name	Chemical name		
Aqueous solvent	Water [Buffer pH 5.0]	/	11 ng/mL	[31]
	Water (pH 7)	/	0.6 µg/mL	[165]
	FaSSGF (pH 1.2)	/	0.5 µg/mL	[166]
	FaSSIF (pH 6.8)	/	5.4 µg/mL	[166]
	Phosphate buffer saline 0.2M, pH 6.8 (containing 0.05% Tween 80)	/	0.03 ± 0.01 mg/mL	[164]
Organic solvent	Propylene glycol	/	6.52 mg/mL	[167]
	Dimethylsulfoxide	/	~10 mg/mL	[14]
	Polyethylene glycol 400	/	~140 mg/g	[166]

	Ethyl oleate	/	<25 mg/g	[166]
	Acetone	/	50 mg/mL	[164]
	Ethanol	/	10 mg/mL	[166]
	Sesame oil	/	<25 mg/g	[166]
	Groundnut oil	/	<25 mg/g	[166]
	Peanut oil	/	0.17 ± 0.01 mg/mL	[167]
	Maisine® 35-1	Glyceryl monolinoleate	<25 mg/g	[166]
	Labrafil® M2125CS	LinoleoylPolyoxylglycerides	<25 mg/g	[166]
	Labrafil®M1944CS	OleoylPolyoxyl glycerides	<25 mg/g	[166]
Oil	Labrafac®lipophile WL 1349	Caprylic/capric triglyceride	18.87 ± 0.82 mg/mL	[168]
	Cremophor® EL	PEG-35 castor oil	<25 mg/g	[166]
	Cremophor® RH40	PEG-40 Hydrogenated castor oil	103.94 ± 14.12	[167]
			mg/mL	
	Labrasol®	Caprylocaproyl Polyoxylglycerides	85 mg/g	[166]
	Tween® 80	Polyoxyethylenesorbitanmonooleate	~50 mg/mL	[168]
	Tween® 20	Polyethylene glycol sorbitanmonolaurate	~40 mg/mL	[168]
	Span® 80	Sorbitanemonostearate	2.50 ± 0.09 mg/mL	[167]
Surfactant	Solutol® HS 15	Polyethylene glycol hydroxystearate	93.64 ± 2.92 mg/mL	[168]
	Transcutol® HP	Diethylene glycol monoethyl ether	~100 mg/g	[166]
Co-surfactant	Capryol® 90	Propylene glycol monocaprylate	9.89 ± 0.18 mg/mL	[167]

Table 1: Solubility of curcumin in various solvents, oils, surfactants, and co-surfactants.

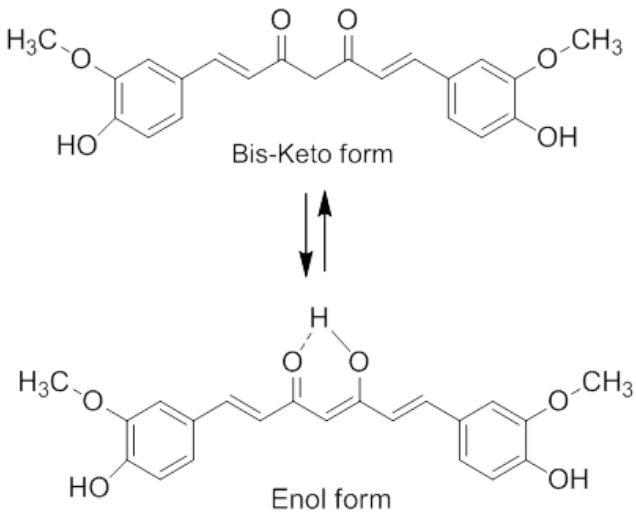

Figure 2: Tautomerism of curcumin under physiological conditions [24].

Curcumin is photo-sensitive. The maximum UV-vis absorption of curcumin in most organic solvents is in the range of 408 to 430 nm, whereas the maximum spectra emission is very sensitive to the surrounding solvent medium and ranges from 460 to 560 nm [26]. Curcumin absorbs strongly in the visible wavelengths and is consequently susceptible to photo-oxidative and/or oxidative degradation when exposed to light [37-39]. Furthermore, curcumin is unstable at neutral and basic pH [40]. Ninety percent of curcumin is degraded in 30 min in phosphate buffer pH 7.2-7.4 at 37°C [41]. The main degradation products obtained from the photo-degradation and alkaline degradation of curcumin are ferulic acid, ferulic aldehyde, feruloyl methane, vanillin, vanilic acid and trans-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal [41-43].

Applications of curcumin

Pharmacological properties and therapeutic potential: The use of curcumin roots has been documented in the traditional medicines of India (Ayurveda), Asia, and Africa for a large variety of diseases for at least 4,000 years [17]. Curcumin species such as *C. longa* have been used as a house remedy against biliary and hepatic disorders, anorexia, cough, hepatic disorders, rheumatism, sinusitis, and diabetic wounds [44,45]. In the ancient texts of India, turmeric (*C. longa*) was also described to be used to treat sprains, swelling, and abdominal problems and to promote wound healing [46], as well as to treat

respiratory problems (asthma, bronchial hyperactivity) and other disorders, such as like anorexia, coria, cough, and sinusitis [47]. In traditional Chinese medicine, it has been used for the treatment of diseases associated with abdominal pain [46]. In both traditional Indian and Chinese medicine, curcumin has been used to treat diabetes [48]. Most health applications of curcumin are based on its antioxidant, anti-inflammatory, antimicrobial properties.

Currently, many countries, including the United States, Europa, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan market curcumin as a dietary supplement [49] as capsules (e.g., Doctor's Best Curcumin-Phytosome®, Curcu-Gel Ultra®) [50] or medicinal ointments, creams, soaps, and food products, such as energy drinks [47].

Pharmacodynamics of curcumin: Extensive research has shown that curcumin mediates its anti-inflammatory effect by modulating several target molecules, such as deactivation of the transcription factor nuclear factor kappa B (NF-κB), inhibition of the expression of pro-inflammatory enzymes (cyclooxygenase-2, 5-lipoxygenase), and down-regulation of the expression of cytokines (e.g., TNF, IL-1, IL-6), growth factors, cell-surface adhesion molecules, and protein kinases [10,46,51]. Furthermore, curcumin can modulate multiple cellular pathways involved in carcinogenesis, mainly due to its ability to inhibit the cell cycle and induce apoptosis [52,53] (Figure 3).

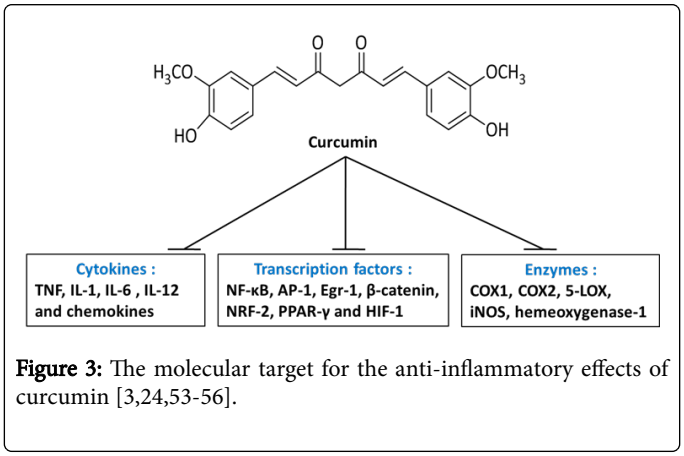

Figure 3: The molecular target for the anti-inflammatory effects of curcumin [3,24,53-56].

The potential anti-inflammatory activity of curcumin (Figure 3) is attributed to its ability to inhibit cyclooxygenase (COX), and lipoxygenase (LOX) and induce nitric oxide synthase (iNOS) and the production of cytokines, all important mediators of inflammatory processes [3,25,54-57]. Curcumin inhibits COX-2 and iNOS expression through the suppression of NF-κB activation [58] and the inhibition of arachidonic acid metabolism [59-61], as the metabolites of arachidonic acid consist of COX-1, COX-2, LOX, and cytochromes P450. Moreover, arachidonic acid metabolism is highly involved in carcinogenesis. NF-κB is an important transcription factor that regulates cellular proliferation, cell transformation, the inflammatory response, and tumorigenesis [62,63]. Curcumin suppresses NF-κB activation by inhibiting the phosphorylation and degradation of the inhibitory factor I-kappa B kinase (IKK), consequently resulting in the suppression of cytokine-induced-NF-κB activation [64]. NF-κB inactivation is a mechanism used in the treatment of inflammatory diseases and tumors, resulting in the suppression of COX-2 and iNOS expression and reduced cytokine and chemokine production (e.g., TNF-α, interleukins) [65-67].

Pharmacokinetics studies: Numerous pharmacokinetics studies in humans and rodents have shown curcumin to have very low bioavailability, limiting its benefits. Such low bioavailability is probably due to its low absorption and rapid metabolism in the intestine and liver and rapid elimination [68-70]. Indeed, Ravindranath and Chandrasekhara showed that approximately 60% of a 400 mg dose of curcumin was absorbed following oral administration (PO) to rats as a water suspension containing polysorbate 20. But curcumin was not detected in the heart and negligible quantities were detected in the liver and kidneys (<20 μg/tissue). Nearly 40% of the dose was excreted, unchanged, in the feces, whereas it was not detected in the urine [71]. The pharmacokinetics of curcumin in mice have been investigated by PO and intraperitoneal (IP) routes. For oral administration, curcumin was given at a dose of 20 mL/kg (1000 mg/kg) as an emulsion. For the IP route, mice received curcumin at a dose of 4 mL/kg (100 mg/kg) as a solution by dissolving curcumin in dimethyl sulfoxide. After oral administration, the maximum concentration of curcumin in plasma was found to be below 0.22 μg/mL after 1 h and below the limit of detection after 6 h. After IP administration, the plasma level of curcumin was 2.25 μg/mL after 15 min but decreased rapidly within 1 h [72]. In addition, the quantity of curcumin in plasma after oral and intravenous (IV) administration was measured in rats for a dose of 500 mg/kg PO (curcumin incorporated in 0.5 mL of yoghurt) and 10 mg/kg by IV injection (16 mg/mL curcumin in DMSO). The maximum concentration (cmax) of curcumin in plasma after oral administration was lower than that after IV administration: 0.06 ± 0.01 μg/mL and 0.36 ± 0.05 μg/mL, respectively. The observed oral bioavailability of curcumin was only 1% [73]. Studies have been performed with the same dose of curcumin in diabetic rats. The maximum concentration of curcumin in plasma after oral administration was similar to that of the previous study (0.06 ± 0.01 μg/mL), whereas it was higher following IV administration 3.14 ± 0.90 μg/mL. The oral bioavailability obtained for curcumin in diabetic rats was 0.47 ± 0.12% [74]. Both studies showed curcumin to have a short half-life ($t_{1/2}$<30 min for IV and $t_{1/2}$<45 min for for oral administration). Despite the low quantity of curcumin detected in plasma, its potential therapeutic effect was significant [74]. Perkin et al. dispensed curcumin mixed in the diet to mice with intestinal tumors at a dose of 300 or 750 mg/kg/day for 21 days. Curcumin was detected in the plasma at levels near the limit of detection (5 pmol/mL) and a large amount was found in the feces. However, the intestinal tumor volume in mice decreased significantly by 39 and 40% for the two doses, respectively [75].

In a phase I dose escalation clinical study, curcuma extract in capsules containing 36 to 180 mg curcumin was administered PO daily in patients with advanced colorectal cancer for four months. Curcumin was not detected in the blood or urine, but curcumin sulfate was detected in the feces. There was no therapeutic effect. This is related to the low bioavailability of curcumin in humans, which may undergo intestinal metabolism before being excreted in the feces [76], whereas curcumin has been reported to be excreted in the bile following IV or IP administration [69,77]. A dose of 3.6 g given daily for up to four months was more recently studied in patients with advanced colorectal cancer and no toxicity was shown. Nevertheless, a low level of curcumin was detected in plasma (11.1 ± 0.6 nmol/L) and urine (between 0.1 and 1.3 μmol/L) after 1 h and its glucuronide and sulfate metabolites were also detected in plasma and urine. However, no therapeutic effect was observed in any of the patients [78]. Additionally, the maximum tolerable dose of curcumin was determined in a phase I clinical trial in healthy participants. They

received escalating doses of curcumin (0.5 to 12 g) PO. A very low level was detected in the serum at a dose of 10 or 12 g [79]. Vareed et al. examined curcumin metabolites for the same single doses of 10 or 12 g and showed that glucuronide and sulfate metabolites were detectable in the plasma of all subjects, whereas no curcumin was observed, indicating that curcumin was absorbed, but rapidly converted into its metabolites [80]. A phase II clinical trial of oral curcumin was performed to determine its biological activity. Patients with advanced pancreatic cancer (n=25) received 8 g curcumin daily PO for up to two months. The curcumin was poorly absorbed, with low circulating levels in the plasma (22-41 ng/mL). Nevertheless, cytokine levels in the serum of some patients was significantly reduced [81]. Carrol et al. tested the effect of curcumin in smoking subjects with aberrant crypt foci in the rectum, the precursor of colorectal polyps. Subjects received 2 or 4 g curcumin/day PO for one month. Curcumin, at a dose of 4 g, significantly reduced the aberrant crypt foci by 40%, whereas no effect was observed for the 2 g curcumin group [82]. A later study showed oral administration of curcumin at a dose of 4 g/day for 24 weeks to patients with Alzheimer's disease to be clinically ineffective. The mean plasma concentration of native curcumin was lower (7.76 ± 3.23 ng/mL) than its metabolites, curcumin-glucuronide and tetrahydrocurcumin (96.05 ± 26 ng/mL and 298.2 ± 140.04 ng/mL, respectively) [83].

Overall, preclinical and clinical studies have shown that only a very small fraction of curcumin reaches the systemic circulation after high-dose administration and that most is excreted in the feces. Despite its low bioavailability, clinical trials have shown curcumin to be well tolerated at high doses of up to 12 g/day in humans. However, the effective dose has not been defined.

Metabolism of curcumin: Curcumin is most often conjugated after its absorption. The predominant metabolites following curcumin hydrolysis in plasma after oral administration are glucuronide and/or sulfate conjugates [84]. Pan et al. characterized the metabolites of curcumin after IP injection and showed that 99% consisted of glucuronide conjugates [72]. An *in vivo* study examined curcumin metabolism in rats. They received curcumin either by oral gavage (500 mg/Kg) or IV (40 mg/kg; dose volume 1 mL/kg). The concentration of curcumin in plasma was near the limit of detection and it disappeared rapidly, whereas conjugated curcumin was more detectable. The major curcumin conjugates were curcumin glucuronide and curcumin sulfate. Nevertheless, the curcumin conjugates disappeared rapidly, particularly following IV administration [85]. Curcumin metabolism has also been examined in the intestinal and/or liver tissue of rats and human's *ex vivo*. The observed metabolites of curcumin were curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin [86]. However, the major metabolites of curcumin in rats and humans have been shown to be curcumin glucuronide, curcumin sulfate, and tetrahydrocurcumin, and the minor curcumin metabolites hexahydrocurcumin, hexahydrocurcuminol, octahydrocurcumin, and hexahydrocurcumin-glucuronide [87,88]. Curcumin metabolism following oral or IV administration is summarized in Figure 4. The metabolites of curcumin have less bioactivity than curcumin [89,90]. Shoji et al. investigated the bioactivity of curcumin glucuronide using human hepatocellular carcinoma (HepG2) cells. They demonstrated that curcumin glucuronide shows lower bioactivity and cellular absorption than curcumin [91]. Similarly, another study demonstrated that tetrahydrocurcumin and octahydrocurcumin have anti-inflammatory activity, as they inhibited the expression of COX-2 and suppressed the nuclear factor-kB pathway [92]. In addition, tetrahydrocurcumin was used as an antioxidant to alleviate hypertension and vascular dysfunction in iron-overloaded mice [93].

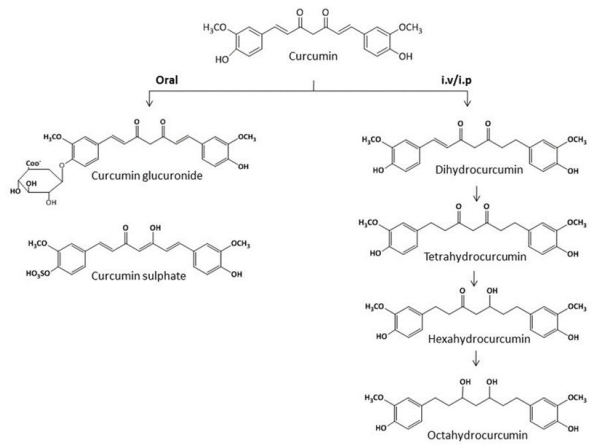

Figure 4: Curcumin metabolism through oral and other routes of administration [83].

Formulations of Curcumin

Classic dosage form of curcumin

Here, we describe some of the classic formulations which are currently available, with improved oral bioavailability and demonstrated to be of therapeutic interest.

Combined with adjuvants: The combination of curcumin with an adjuvant could increase its bioavailability in both rodents and humans. The most highly recommended adjuvant is piperine. Piperine enhances bioavailability by inhibiting drug metabolism. It modulates enzymatic metabolism of the drug in the liver and intestine and promotes intestinal absorption [94]. The mechanism of piperine is based on the inhibition of the cytochrome P450-mediated pathway and/or P-glycoprotein substrates [95,96]. The molecular structure consists of a conjugated aliphatic chain that acts as a bridge between the piperidine heterocycle and 5-(3,4-methylenedioxypenyl) group. Thus, piperine provides optimal electronic features for its propensity to bind to cytochrome P450 enzymes. The combination of piperine and curcumin, through an intermolecular hydrogen bond, aids curcumin transport and inhibits the enzymes CYP3A4, UDP-glucose dehydrogenase (UDP-GDH), and UDP glucuronosyltransferase (UGT). Glucuronosylation of curcumin is reduced and the curcumin stays longer at the site of absorption, increasing its oral bioavailability [97]. Shoba et al. showed oral administration of curcumin with piperine to rats (2 g curcumin/kg and 20 mg/kg piperine) and humans (2 g curcumin and 20 mg piperine) to significantly increase the serum concentration of curcumin in both cases and bioavailability by 154 and 2,000%, respectively [98]. Concomitant administration of piperine (10 mg/day) and curcuminoids (1 g/day) for eight weeks to patients with cardiovascular disease significantly reduced the plasma C-reactive protein concentration (CRP), considered to be a marker and risk factor of cardiovascular disease [99]. Nevertheless, piperine in combinate therapy should be used with caution to avoid drug interactions [94,100]. A study to assess curcumin associated with phytochemicals

(sesamin, ferulic acid, naringenin, and xanthohumol), with a single dose of 98 mg curcuminoids, was carried out in healthy humans. The bioavailability of the curcuminoids was eight-fold higher than that of the native curcuminoids [101], showing that this adjuvant can increase curcumin bioavailability.

Curcumin-phospholipid complexes: There are several dietary supplements based on a turmeric extract called Meriva®. It is a formulation that combines curcuminoids and phosphatidylcholine, well known as curcumin-phtytosom, and has been patented by Indena SpA. Meriva® contains 20% of a standardized mixture of natural curcuminoids and 40% lecithin (phosphatidylcholine), at a 1:2 weight ratio, and 40% microcrystalline cellulose used to improve the physical state of the powder. The composition of the curcuminoids includes 70 to 75% curcumin, 15 to 20% demethoxycurcumin, and 5 to 10% bis-demethoxycurcumin [102,103]. Within the phytosome formulation, the curcumin polar group interacts with the polar head of phosphatidylcholine through hydrogen bonding and polar interactions, while the non-polar tail of the phosphatidylcholine wraps over. This complex provides a lipophilic character which allows curcumin to cross the intestinal membrane and access the systemic circulation. Preclinical and clinical studies have demonstrated that Meriva® can improve diabetes-related complications, such as microangiopathy and chorioretinopathy, and decrease inflammation due to osteoarthritis, leading to better disease control [102,104,105]. The area under the curve (AUC1-120 min) for curcumin for rats receiving Meriva® at 340 mg/kg was five-fold higher than that for rats that received standard curcuminoids. Nevertheless, the maximum plasma concentration of curcumin achieved after oral administration of Meriva® in rats is lower (33.4 ± 7.1 nM) than that required for its pharmacological effects (10 to 20 μM) [106]. In humans receiving a dose of 209 to 376 mg curcuminoids (165 to 297 mg curcumin), the average relative absorption of curcuminoids was 29-fold and curcumin 18.3-fold higher than that for participants receiving standard curcuminoids. Furthermore, it has been noted that the absorption of demethoxycurcumin from Meriva® was greater than that of curcumin: 61.9-fold higher [103].

Combination with turmeric volatile oils: Turmeric volatile oils are amongst the active components of turmeric root and are composed of aromatic turmerone (ar-turmerone), turmerone, and curlone [107], which act as dispersing agents in aqueous media and interfere with curcumin metabolism, similarly to piperine [108]. The curcumin and turmeric oils formulation, containing 376 mg curcuminoids, was orally administered to healthy human subjects. The absorption of curcuminoids was 1.3-fold higher than that of unformulated curcuminoids [109]. Cureit® is a novel curcuminoid formulation developed by Aurea Bio-labs to improve its bioavailability. Cureit® was prepared by polar-nonpolar sandwich (PNS) technology using a completely natural turmeric matrix. Cureit® is composed of three different extracted compounds: curcuminoid (50%), turmeric essential oil (3%), and water-extracted turmeric (40% carbohydrate, 5% dietary fiber, and 2% turmerin-protein) [110]. The bioavailability of the completely natural turmeric matrix formulation (Cureit®) was compared to that of two other commercial formulations, a curcumin with volatile oils formulation (Curcu-Gel Ultra®) and a curcumin with phospholipids formulation (Doctor's Best Curcumin-Phytosome®). A dose of 500 mg of each formulation in capsule form was administered PO to healthy human subjects, corresponding to 180 mg curcumin for the turmeric matrix formulation, 351 mg for the curcumin-volatile oils formulation, and 80.5 mg for the curcumin-phospholipids formulation. The bioavailability of the turmeric-matrix formulation was significantly higher than that of the two other formulations, based on pharmacokinetic parameters: 7.3-fold higher than the curcumin-volatile oils formulation and 5.6-fold higher than curcumin-phospholipids formulation [50], as well as 10-fold higher than unformulated curcuminoids [110].

Curcumin with a hydrophilic carrier: Solid dispersion of the curcumin formulation using a hydrophilic carrier, such as polyvinylpyrrolidone, has been shown to improve curcumin solubility and therefore its bioavailability [109,111]. Curcumin in combination with a hydrophilic carrier was prepared by dispersing curcuminoids (20 to 28%) and antioxidants, including tocopherol and ascorbic palmitate (1 to 3%) in an aqueous solution of polyvinylpyrrolidone and cellulose derivatives (63 to 75%). This formulation was then orally administered to healthy humans and compared to a curcumin-phytosome formulation, a curcumin-turmeric volatile oils formulation, and standardized curcuminoids [109]. The participants received 376 mg curcuminoids of each formulation or 1.8 g standardized curcuminoids. The relative absorption of curcuminoids combined with a hydrophilic carrier was 45.9-fold higher than that of standardized curcuminoids and significantly higher than that of the curcumin-phytosome and curcumin-volatile oils formulations [109]. Furthermore, the solid dispersion of curcumin prepared with the surfactant Solutol® as a hydrophilic carrier, at a 1:10 ratio, was studied. Rats received a solid dispersion of curcumin PO at a dose of 50 mg/kg. The AUC0-12 h for bioavailability of this formulation was approximately five-fold higher than that of pure curcumin [112].

Curcumin-cyclodextrin complexes: Cyclodextrins are cyclic oligosaccharides that can interact with appropriate-sized molecules, forming inclusion complexes. Such inclusion complexes are obtained by non-covalent interactions (van der Waals forces). Hence, inclusion complexes with lipophilic drugs can increase their aqueous solubility, dispersity, and absorption [113]. The bioavailability of curcumin combined with a cyclodextrin formulation (CW8) was investigated and compared to that of curcumin-phytosome and curcumin-turmeric volatile oils formulations and standardized curcumin. Each formulation was orally administered to healthy human subjects at a dose of 376 mg curcuminoids and 1.8 g standard curcuminoids, as in the previous study. The oral bioavailability of curcuminoid in the cyclodextrin formulation was 39-fold higher than that of the standard curcuminoids [114].

Furthermore, many studies have shown that the use of emulsion-based systems can increase the solubility of curcumin and enhance its absorption [115-117]. Curcumin microemulsions were prepared using food-grade components, composed of tocopherol as an oil phase, polysorbate 20 as a surfactant, and ethanol and water as an aqueous phase. The *in vitro* study was performed using the parallel artificial membrane permeability assay (PAMPA), a method used to determine the ability of a drug to permeate and/or be absorbed through an artificial membrane by passive diffusion. For the curcumin microemulsion, 120.12 g curcumin crossed the membrane after 24 h, higher than the amount of free curcuminoids [118]. Jaisamut et al. developed and optimized the curcumin self-microemulsion process, called supersaturated self-microemulsion (curcumin S-SMEDDS), which consists of 55% surfactant (Cremophor®EL:Labrasol®, 1:1 w/w), 40% oils (Capryol® 90:Labrafac® PG, 1:1 w/w), and 5% Eudragit® E PO, with a curcumin content of 44.4 mg/g in the formulation. The droplet size obtained for the curcumin S-SMEDDS was 21.6 ± 0.1 nm. The *in vitro* permeability of curcumin S-SMEDDS across $CaCO_2^-$ cells was five-fold higher than that of curcumin solubilized in DMSO, but the

trans-epithelial electrical resistance (TEER) did not differ between the two formulations, indicating that the curcumin traversed the $CaCO_2$ cells without interacting with the cellular efflux pump systems. In an *in vivo* absorption study, curcumin S-SMEDDS was diluted with distilled water and orally administered to rabbits at a dose equivalent to 50 mg/kg. Pharmacokinetics showed that the maximum concentration of curcumin obtained for S-SMEDDS was 31-fold higher than that for an aqueous suspension of curcumin [119].

Most of the commercially available formulations of curcumin are curcuminoids which contain 70-75% curcumin. These products have been demonstrated to have potential health benefits and improved curcumin bioavailability (Table 2). Nonetheless, to achieve a greater therapeutic effect and improve sales, curcumin has been developed using innovative formulations, such as nano-microcarriers.

Curcumin Formulation	Dose of curcuminoids [mg]	Equivalent dose of curcumin [mg]	Pharmacokinetic parameter of curcumin				Trade name and Company	References
			Cmax [ng/mL]	AUC [ng mL/h]	Tmax [h]	Relative absorption		
Phytosome	376 209	297 165	50.3 ± 12.7 24.2 ± 5.9	538.0 ± 130.7 272.6 ± 68.52	3.8 4.2	19.2-fold 17.5-fold	Meriva®; Indena, Milan, Italy.	[102]
Phytosome	376	297	2.8 ± 0.3	28.7 ± 2.6	1.7	12.7-fold	Curcumin Phytosome®, Indena, USA Inc., Seattle, WA, USA.	[108]
Phytosome	376	297	4.7 ± 1.8		1	9-fold	N/A	[113]
Phospholipids	500	80.5	69.63 ± 51.1	187.3 ± 190.9	2.63	#	Doctor's Best Curcumin-Phytosome®	[49]
Turmeric volatile oil	376	297	0.5 ± 0.0	5.8 ± 0.1	3.2	2.6-fold	DolCas Biotech, LLC, Landing, NJ, USA.	[108]
Turmeric volatile oil	376	297	0.9 ± 0.3		6	1.7-fold	Not reported	[113]
Turmeric volatile oil	500	351	47.54 ± 26.4	117.3 ± 56.8	3	#	Curcu-Gel Ultra®	[49]
PNS technology [turmeric matric]	500	180	170.14 ± 104.6	824.9 ± 466.5	4	#	CureitTM; Aurea Biolabs [P] Ltd, Cochin, India.	[49]
Curcumin combined with hydrophilic carrier	376	297	27.3 ± 6.4	307.6 ± 44.6	1.4	136.3-fold	Omni Active Health Technologies, Inc., Morristown, NJ, USA	[108]
Cyclodextrin complex	376	297	73.2 ± 17.5		1	85-fold	N/A	[113]

Notes: []: The bioavailability was significantly increased but its value was not mentioned. The relative absorption compared to that of standard curcuminoids at a dose of 1.8 g curcuminoids. N/A: data not available.

Table 2: The pharmacokinetics of curcumin in humans for different commercial formulations [oral dosage form].

Nanocarriers for curcumin delivery

Polymer-based nanoparticle formulations: Curcumin-loaded nanoparticles have been widely studied and shown to improve the bioavailability of curcumin (Table 3). Polymeric nanoparticle formulations are generally prepared using various polymers by the nanoprecipitation method or emulsion-diffusion-evaporation methods. Nanoprecipitation is a solvent displacement technique. The process to prepare polymeric nanoparticles by the nanoprecipitation method involves the precipitation of dissolved materials as nanoscale particles, after exposure to non-solvent that is miscible with the solvent [120]. The emulsion-diffusion-evaporation method consists of dissolving the polymer and/or active ingredient in the organic solvent. The organic phase is emulsified with the aqueous phase under stirring and subsequently diluted with water to evaporate-diffuse the solvent [121]. PLGA is the most widely used polymer to prepare curcumin-loaded nanoparticles, due to its biocompatibility and biodegradability. Curcumin-loaded PLGA nanoparticles (Cur-PLGA NPs) prepared by the emulsion-diffusion-evaporation-method are spherical, with a diameter of 264 nm, PdI of 0.31, 76.9% entrapment efficiency, and 15% drug-loading capacity [122]. In this study, *in vitro* drug release showed a biphasic release profile with an initial release of 24% at 24 h and 43% sustained drug release over 20 days. An *in vivo* study in rats showed that the oral bioavailability of curcumin-loaded PLGA nanoparticles was up to nine-fold higher than that of curcumin with piperine [122]. Joseph et al. prepared curcumin-loaded PLGA and poly (lactic-co-

glycolic acid)-poly (ethylene glycol) (PLGA-PEG) diblock copolymers using the nanoprecipitation method. The curcumin nanoparticle size was approximately 60 nm with a capacity of curcumin loading of 5.3 and 6% for curcumin-PLGA NPs and curcumin-PLGA-PEG NPs, respectively. An initial *in vitro* burst release was observed at 4 h for both curcumin-PLGA NPs and curcumin-PLGA-PEG NPs with 40 and 49% curcumin release, respectively, followed by sustained drug release of up to 59 and 99% at 4 h. Moreover, an *in vivo* study in rats showed that PLGA-PEG NPs increased curcumin diffusion through the brain parenchyma more highly than PLGA NPs and that curcumin PLGA-PEG NPs showed greater absorption at the site of injury [123]. In addition, curcumin-loaded poly (ethylene glycol)-poly (lactic acid) (PEG-PLA) nanospheres (cur-PEG-PLA NS) were prepared by the simple emulsion method. The nanoparticle size was 150 nm with an encapsulation efficiency of 56.1%. PEG-PLA is biodegradable and comprised of biocompatible amphiphilic copolymers to enhance curcumin solubility, increase its absorption, and protect it against hydrolysis. Indeed, PEG-PLA presents a hydrophilic surface of the PEG-polymer chain, which covers the hydrophobic core of PLA. The *in vitro* release of cur-PEG-PLA NS showed a biphasic release pattern, with the rapid release of approximately 24.3% curcumin in 1 h and sustained release of approximately 93% over five days. Curcumin-loaded PEG-PLA NS has been demonstrated to be taken up by Hela and MDA-MB-231 cancer cells [124]. Mayol et al. prepared curcumin-loaded PLGA poloxamer nanoparticles with a diameter of 160 nm and 90% encapsulation efficiency. Poloxamer is a tri-block copolymer made from poly (ethylene oxide), poly (propylene oxide), and poly (ethylene oxide) (PEO-PPO-PEO) which have amphiphilic properties. A hydrophilic coat of nanoparticles forms spontaneously, providing high stability and conferring stealth features to the NPs to take advantage of enhanced permeability and retention (EPR) [125]. However, curcumin in PLGA-poloxamer NPs showed rapid *in vitro* release, approximately 60% at 24 h and complete after four days. However, curcumin PLGA-poloxamer NPs were rapidly absorbed into mesothelioma cells after treatment, inducing significant cell cycle arrest for up to 72 h [125]. Curcumin encapsulation into polymeric pH-sensitive PLGA-Eudragit® S100 nanoparticles has been performed using a modified spontaneous emulsification-solvent-diffusion method. A particle size of 166 ± 3 nm and encapsulation efficiency of 67% were obtained. Eudragit® S100 is a pH-sensitive polymer. In this study, it was combined with PLGA for selective and specific delivery of curcumin to the inflamed mucosa in IBD disease. Thus Cur-NPs were not released at acidic pH (pH<1.2) but were rapidly released at neutral pH. *In vitro* experiments demonstrated a significant enhancement in the permeability of curcumin NPs across a $CaCO_2$ cell monolayer over that of a curcumin suspension [126]. In a recent study, curcumin-loaded polymeric nanoparticles were prepared with Eudragit® RLPO, PLGA, and polycaprolactone by the emulsion-solvent-evaporation method. Curcumin-loaded Eudragit® RLPO NPs were found to have the smallest particle diameters, with 245 ± 2 nm, and better re-dispersibility after lyophilization than the other formulations. Nonetheless, the encapsulation efficiency of curcumin- Eudragit® RLPO NPs was the lowest, 62%, whereas that of curcumin-PLGA NPs and curcumin- polycaprolactone NPs were 90 and 99%, respectively. *In vitro* experiments demonstrated that curcumin-loaded Eudragit® RLPO NPs release 91 ± 5% of their curcumin over 1 h, whereas PLGA NPs and polycaprolactone NPs released only 55 ± 2% and 47 ± 2%, respectively, after 24 h. The authors point out that the polycationic Eudragit® RLPO NPs could improve the oral bioavailability of curcumin due to its mucoadhesive properties and rapid curcumin release [127]. Additionally, curcumin has also been encapsulated in natural polymers, such as chitosan and gelatin. Farnia et al. prepared curcumin-loaded chitosan-gelatin nanoparticles by dissolving curcumin in polyethylene glycol (PEG). PEG is used as a co-solvent system to improve the solubility of curcumin. CUR-PEG was added dropwise to a chitosan-gelatin solution under constant magnetic stirring and nanoparticles were obtained. The nanoparticles were 300-400 nm in diameter, with 69.29% entrapment and a 17.11% drug payload [128].

Formulation	Size [nm]	Drug loading	Model *in vitro*	Model	Remarked	References
PLGA NPs	264 ± 2 nm	15% [w/w dry matter]	/	Rats	Bioavailability increased 9 folds	[121]
PLGA NPs	166 ± 3	7.4 ± 0.9% [w/w dry matter]	$CaCO_2$	/	Enhance the permeability of curcumin NPs cross a monolayer of $CaCO_2$ cells.	[125]
Eurdragit E 100 NPs	248.40 ± 4	N/A	/	Rats	Bioavailability increased 95-folds	[169]
Lipopoly-saccharide nanocarriers	108 ± 3.4	0.149 ± 0.07% [w/w suspension]	/	Rats	Bioavalability increased 130- fold	[170]
NE	67 ± 6	64.29% [w/w dry matter]	/	Rats	Bioavailability increased 11,88- fold	[168]
NE	121	N/A	/	Rats	Bioavailability increased 734%	[171]
SLN	134.6	10% [w/w suspension]	/	Rats	Bioavailability increased 155-fold for orally administered at 1 mg/kg of SLN	[142]

Table 3: Curcumin nanoparticle formulations improve its absorption and/or bioavailability.

Lipid-based nanocarriers: In recent years, attention has focused on lipid-based nanocarriers as a potential drug delivery system to improve the solubility of hydrophobic drugs in the gastrointestinal tract, enhance intestinal permeability, and protect against enzyme and/or chemical hydrolysis. The advantage of hydrophobic drug encapsulation in lipid-based formulations is that the drug is first dissolved in the lipid ingredients, surfactant, or a mixture of lipids and surfactants, to improve drug solubility and limit the dissolution step in the GI tract, a

factor that affects the rate of drug absorption [129,130]. For parental drug administration, lipid-based nanocarriers are also useful for prolonging the circulation time of the drug and targeting tissues [131].

Liposomes: the first closed bilayer phospholipid system to be studied was liposomes. They are spherical vesicles consisting of one or more phospholipid bilayers. Liposomes can be loaded with both lipophilic and hydrophilic drugs/substances, as lipophilic drugs partially localize within the phospholipid bilayers and hydrophilic drugs are entrapped in the aqueous core [132-134]. The encapsulation of curcumin in liposomes can enhance its absorption, as well as its bioavailability. Takahashi et al. prepared curcumin-loaded liposomes from commercial soybean lecithin (SLP-PC70) using the microfluidification method. The liposomes were composed of small unilamellar vesicles with a diameter of approximately 263 nm and 68% encapsulation efficiency. The bioavailability of curcumin after oral administration of 100 mg/kg curcumin loaded liposomes to rats was significantly higher than that of free curcumin [135]. Additionally, an *in vitro* study in MCF-7 cancer cells showed that cell cytotoxicity increased significantly after treatment with curcumin-loaded liposomes [136]. Saengkrit et al. prepared curcumin-loaded liposomes by modifying the liposome surface with the cationic surfactant didecyldimethylammonium bromide (DDAB), cholesterol, and non-ionic surfactant (Montanov® 82) as cur/liposome/cholesterol/DDAB and cur/liposome/Montanov®82/ DDAB formulations. These liposome formulations were prepared by the conventional thin film hydration method. The presence of DDAB in the liposomes resulted in a large particle size (> 200 nm) with a PdI in the range of 0.2 to 0.3. Both particle diameter and the zeta potential increased significantly after three months of storage, indicating instability of this formulation. Moreover, the presence of both surfactant and DDAB led to reduced entrapment efficiency of the curcumin in the liposomes, which may be related to their hydrophobic chains in the lipid bilayers of the liposome, resulting in repulsion of the curcumin and a consequent decrease in the efficiency of entrapment. *In vitro* release experiments of curcumin-liposomes showed sustained release of curcumin over 48 h, with approximately 80.3% for cur/liposome/cholesterol/DDAB and 64.6% for cur/liposome/Montanov®82/DDAB. The addition of the cationic surfactant DDAB to liposomes resulted in an increase in the uptake of cur-liposomes into human cervical cancer cell lines (Hela and SiHa cells) [137]. In another study, chitosan was used to coat liposomes. Liposomes were prepared using the reversed-phase evaporation-method. The diameter of the curcumin-loaded anionic liposomes (without chitosan) was 129 nm with a PdI of 0.095 and zeta potential of -49 mV. The diameter and PdI were not altered after chitosan coating, whereas the surface charge became positive [138]. Both formulations were tested in the *in vitro* digestion model, including simulated saliva fluid, simulated gastric fluid, and simulated intestinal fluid, and showed that liposomes without chitosan were digested slightly more in simulated saliva fluid and simulated gastric fluid, whereas chitosan-coated liposomes were more highly digested in simulated intestinal fluid. The presence of a positive charge on the chitosan-coated liposome surface results in an interaction with the negatively charged glycoproteins of mucin. This may result in their being covered by a layer of mucin and protection of the curcumin during the other phases of digestion, thus allowing greater curcumin absorption [138].

Solid lipid nanoparticles: solid lipid nanoparticles (SLNs) are another type of lipid-based nanocarrier. They have an average size of 40 to 1000 nm and are composed of approximately 0.1 to 30% w/w solid lipid dispersed in an aqueous phase and 0.5 to 5% w/w of surfactant to enhance stability. SLNs can encapsulate both hydrophilic and lipophilic drugs, providing drug stability during administration, prolonged release, and biocompatibility, due to their lipid matrix. Nevertheless, the common disadvantage of SLNs are low drug-loading capacity and an initial burst effect [139,140]. Wang et al. prepared SLNs to encapsulate curcumin using solvent-diffusion and hot emulsification techniques. This formulation was composed of 20 mg of the lipid compritol ATO 888® and sodium caseinate (0.15%, w/v) as emulsifier, pectin (0.5%, w/v) for coating, and a small amount of polysorbate 80 (0.15% w/v) as surfactant and two cross-linkers for polymeric coating with glutaraldehyde and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxy-succinimide (EDC:NHS, 1:1 w/w). These two cross-linkers were used to chemically bridge the sodium caseinate and pectin. The particle size was greater than 200 nm. The drug-loading capacity was 5% w/w curcumin per total lipid in the formulation. Furthermore, the stability in simulated gastrointestinal fluids demonstrated that the SLNs were stabilize in an acidic environment, due to the protective coating of pectin. *In vitro* experiments showed the slow release of curcumin under simulated gastrointestinal conditions: approximately 20 to 40% in simulated gastric fluid after 2 h and 10 to 20% in simulated intestinal fluid after 4 h [141]. In another study, curcumin-loaded SLNs (Cur-SLN) were prepared using high-pressure homogenization with the liquid lipid Sefsol-218® (propylene glycol mono-caprylic ester). The mean particle size was above 153 nm with 90% entrapment efficiency. The high entrapment efficiency of the drug is explained by the use of Sefsol-218®, which may redistribute on the nanoparticle surface due to its hydrophilic free hydroxyl group, improving its stability. *In vitro* release of curcumin from the SLN showed a biphasic release profile with curcumin release of 70% after 72 h. Moreover, the absorption of curcumin-SLN by MCF-7 cells was slower than that of a curcumin solution. The pharmacokinetics of Cur-SLN has been studied. The half-life and area under the curve (AUC0-∞) were significantly higher after administration of 2 mg/kg Cur-SLN to rats than that of free curcumin [142]. Kakkar et al. prepared curcumin-loaded SLNs by the micro-emulsification technique with Compritol®888 ATO as the lipid component and Pluronic® F68 as surfactant. They obtained nanoparticles with an average particle size of 134.6 nm, efficiency of drug entrapment of 82%, and 10% drug-loading capacity. *In vitro* release experiments showed rapid initial drug release via diffusion from the shell of the SLNs and prolonged release of approximately 86% of the curcumin over seven days. *In vivo* pharmacokinetics were assessed in rats after oral administration of Cur-SLNs with a dose of 50, 25, 12.5 and 1 mg/kg in comparison to 50 mg/kg of free curcumin. The bioavailability of curcumin after oral administration of Cur-SLNs to rats was 39, 32, 59, and 155-fold higher, respectively, than that of free curcumin. However, this study used much high concentrations of polysorbate 80 (45.45%) than of the lipid component (7.27%), which may have played an important role in enhancing Cur-SLN penetration [143]. Furthermore, these SLNs showed a significant increase in curcumin permeability and the presence of Pluronic® F68 on the surface of the nanoparticles may have led to bio-adhesion to the intestinal membrane [144].

Lipid-core nanocapsules: this formulation consists of an oily core surrounded by a polymeric shell. Curcumin encapsulation in lipid-core nanocapsules has been shown to protect it from degradation and increase its solubility and cellular absorption. Curcumin-loaded lipid-core poly (ε-caprolactone) nanocapsules coated with polysorbate 80 were prepared by interfacial deposition of the preformed polymer. Particle size was 196 nm and the drug-loading capacity 0.50 mg/mL,

corresponding to 100% entrapment efficiency. *In vitro* release experiments demonstrated that the curcumin was slowly released from the lipid-core nanocapsules, approximately 35% after 72 h. An *in vivo* study in rats with glioma brain tumors showed smaller tumors and less malignancy and a higher survival rate after treatment with curcumin lipid-core nanocapsules for 14 days with a dose of 1.5 mg/kg/day by IP administration than those treated with unloaded nanocapsules [145]. Moreover, curcumin-loaded lipid-core poly (ε-caprolactone) nanocapsules were more toxic for glioma cells (C_6 and U125 MG), whereas unloaded nanocapsules did not alter cell viability [145]. Another study prepared curcumin-loaded lipid-core poly (ε-caprolactone) nanocapsules using the same method, obtaining a nanoparticle size of 192 nm. The nanoparticles were evaluated in an animal model of Alzheimer's disease with a low dose of 2.5 mg/kg/day, administered by intracerebroventricular injection into rats. The curcumin-loaded lipid-core poly (ε-caprolactone) nanocapsules had a neuroprotective effect similar to that of the effective dose of free curcumin (50 mg/kg/day). This data suggests that lipid-core nanocapsules have the potential to enhance brain bioavailability [146]. Moreover, less than 10% of the curcumin loaded in the lipid-core poly (ε-caprolactone) nanocapsules was degraded in PBS pH 7.4 after 8 h. Thus, lipid-core nanocapsules can significantly protect curcumin from degradation at neutral and basic pH [147]. Curcumin-loaded lipid shell core nanocapsules containing a combination of surfactant and surrounding protamine were also prepared. Protamine is a polypeptide which improves cell penetration. These nanocapsules were prepared by the solvent displacement technique. Particles size was 188 nm with a positive zeta potential and 68% drug encapsulation efficiency. *In vitro* experiments showed that curcumin-loaded nanocapsule shell core protamine improved curcumin permeability across $CaCo_2$ cells 30-fold over that of the curcumin-loaded self-nanoemulsifying drug-delivery system and lipid-loaded nanostructure lipid-carrier formulation [148].

Lipid nanocapsules: among lipid-based nanocarrier formulations, lipid nanocapsules have been proposed as a promising new formulation to enhance the oral bioavailability of lipophilic drugs/substrates [149]. Lipid nanocapsules were first described by Heurtault et al. They were prepared by the phase-inversion temperature method, which is an organic solvent-free process that uses low energy [150]. Mazzarino et al. prepared curcumin-loaded lipid nanocapsules (Cur-LNC) and polymeric nanocapsules stabilized using the nonionic surfactants Pluronic®F68 and/or Solutol®HS15. These formulations were prepared by phase-inversion methods and nano-precipitation, respectively. The sizes of the nanoparticles were 34.7, 137.7, and 143.3 nm for the Cur-LNCs, Cur-Pluronic® NCs, and Cur-Solutol® NCs, respectively. The encapsulation efficiency obtained for all formulations was 99%. They determined curcumin uptake by macrophages by fluorescence microscopy and demonstrated that the fluorescence in cells treated with Cur-Pluronic® NCs was higher than in those treated with Cur-Solutol® NCs or Cur-LNCs. This result could be explained by the presence of the PEG chains of solutol®HS15, located on the surface of cur-LNCs and cur-PLA-Solutol® NCs, which reduced the interaction between the particles and the cells [151]. They evaluated the effect of free curcumin, Cur-Pluronic® NCs, and Cur-LNCs on tumor growth in mice by IP injection of 6 mg/kg, twice a week, for 21 days. Free curcumin and both formulations significantly reduced the tumor growth rate and there was no significant difference in the antitumor activity displayed by lipid and polymeric nanocapsules [151]. Furthermore, this group showed that more curcumin is released from LNCs than polymeric NCs at two days; approximately 77% of the curcumin was released from the Cur-LNCs and 51% from both the Cur-PLA-Pluronic® NCs and Cur PLA-Solutol® NCs However, the nanocapsule formulations could have protected the curcumin from hydrolytic and photochemical degradation, improving its biological activity [152]. The hydrolytic degradation of curcumin loaded in polymeric and lipid nanocapsules was investigated by dispersing these colloid suspensions in a buffer solution at pH 5.0 or 7.4 and storing them for 30 days. At pH 5.0, the curcumin content was found to be 97.9%, 92.1%, and 87.1% for LNCs, Cur-PLA-Pluronic® NCs, and Cur PLA-Solutol® NCs, respectively; whereas at pH 7.4, the curcumin content decreased significantly for all formulations down to less than 30% of the initial level [153].

Microcarriers for curcumin delivery

Microcarriers have been considered as potential drug delivery systems to control drug release, protect drugs from degradation, and increase drug bioavailability [154,155]. Recently, extensive research has led to the development of microcarriers to deliver curcumin, demonstrating that this carrier could improve its bioavailability and solubility. Paolino et al. developed two formulations of curcumin-loaded microparticles using different drug/polymer ratios (1:5 and 1:10 w/w). These microparticles were prepared by the solvent-evaporation method using a blend of Eudragit® RL100 and Eudragit® RS100 at a ratio of 30:70 w/w. The bioavailability of curcumin in rats after oral administration of microparticles at 100 mg/kg curcumin was seven-fold higher than that of unformulated curcumin in PBS. This increase in bioavailability may be due to the amorphous state of curcumin in the Eudragit® matrix, resulting in an increase in the speed of dissolution and curcumin absorption [156]. Xiao et al. prepared curcumin-loaded microparticles made with Eudragit®S100 mixed with PLGA (ratios of 2:1, 1:1, and 1:2 w/w) using the emulsion-solvent-evaporation process. The average diameter was 1.52 to 1.92 μm with a PdI above 0.3 and over 80% encapsulation efficiency with an approximately 6% loading capacity for curcumin. *In vitro* release experiments showed that the Eudragit®S100-PLGA (1:2, w/w) microparticles were able to maintain sustained release of curcumin at pH 7.2-7.4 for 20 h, with curcumin release of ~48%. However, curcumin was rapidly released from this matrix at pH 1.2 and 6.8. Thus, curcumin-Eudragit®S100-PLGA microparticles (1:2, w/w) were studied *in vivo* in mice with ulcerative colitis at a dose of 50 mg/kg OP for six days. Histological examination showed that the colon tissue of mice with ulcerative colitis showed no inflammation after treatment with curcumin Eudragit®S100-PLGA microparticles, in contrast to the control groups [157]. Magnetic microgels were developed based on the composition of pectin maleate, N-isopropyl acrylamide, and Fe_3O_4 by the inverse-polymerization technique. The N-isopropyl acrylamide, a thermo-responsive polymer, was grafted onto the pectin maleate, whereas Fe_3O_4 nanoparticles were associated with the microgels using an oil/water emulsion technique and poly (vinyl alcohol) as a stabilizing agent. The smallest average diameter of the microgels obtained was 10 μm. *In vitro* experiments showed that the curcumin was slowly released from the magnetic microgels. Approximately 90% of the curcumin was released after 80 h in simulated intestinal fluid pH 6.8. The magnetic microgels protected the curcumin from degradation under pH 6 [158]. Curcumin-loaded PLGA microparticles were prepared using the emulsion-solvent-evaporation technique and investigated for treating breast cancer in mice. The average diameter of the obtained microparticles was 22 ± 9 μm with 38% w/w drug loading. *In vitro* drug release experiments showed 100% curcumin release over six weeks. Mice received curcumin PLGA microparticles

at a dose equivalent to 29.1 mg curcumin through IP injection. The concentration of curcumin in blood, lung, and brain was higher and the tumor volume 49% lower in mice receiving curcumin-PLGA microparticles than those receiving blank PLGA microparticles [159]. Curcumin-loaded gelatin microparticles were developed to enhance the aqueous solubility of curcumin. The microparticles were prepared by electrohydrodynamic atomization. The obtained particles were 1.2 µm in diameter. SEM images showed the particles to be non-spherical, with a rough surface, and partially collapsed. However, the solubility of curcumin-gelatin microparticles in aqueous medium was 38.6-fold higher than that of free curcumin. This may be due to the encapsulation of curcumin in the microparticles in an amorphous state and its association with gelatin, a hydrophilic polymer, as this carrier can improve its solubility in aqueous media [160]. Another study assessed curcumin-loaded whey-protein microparticles obtained by spray drying. The hydrophobic interaction between curcumin and proteins increased the solubility of curcumin 11-fold over that of curcumin alone [161]. Gómez-Estaca et al. prepared curcumin-loaded liposomes and then encapsulated them within whey-protein microparticles using the spray-drying technique. The microparticles obtained were spherical with a diameter of nearly 1 µm. This study showed that whey-protein microparticles can protect curcumin from degradation in PBS buffer (pH 7.4) and curcumin-liposome digestion in the gastrointestinal environment [162]. Jyoti et al. synthesized curcumin complexed with 2-hydroxylpropyl-β-cyclodextrin loaded in chitosan microspheres by the emulsion-polymerization technique. The mean particle size was 6.8 ± 2.6 µm, with a surface charge of +39.2 ± 4.1 mV. *In vitro* experiments demonstrated that the curcumin complex-chitosan microspheres released 95.7% of their curcumin after 24 h in simulated colonic fluid. The concentration of curcumin in colon tissue was significantly higher (44.32 g/g) in mice that received 100 mg/kg of curcumin complex loaded chitosan microspheres by oral gavage than those that received unformulated curcumin (5.3 g/g) [163]. Microparticles containing a curcumin solid dispersion were prepared by the spray drying technique using Gelucire®50/13 (stearoyl macrogol-32 EP) and the colloidal silicon dioxide Aerosil® as a carrier for curcumin delivery. Their characterization showed a mean diameter of 550 m and porosity. These microparticles increased the solubility of curcumin in water by up to 3,600-fold over that of unformulated curcumin. This high solubility is due to Gelucire®50/13, a non-ionic surfactant that can form an aqueous "microemulsion" and improve the solubility of drugs. *In vitro* release experiments showed rapid release at pH 1.2 and 5.8: approximately 90% of curcumin release in 10 min. This may have been related to its porous surface. Pharmacokinetic experiments showed that the plasma concentration of 17.6 ± 9.4 ng/mL detected after 1 h following oral administration of 500 mg/kg curcumin solid dispersion microparticles was five-fold higher than that after oral administration of unformulated curcumin [164].

Conclusion

Curcumin has been proven to have a variety of biological activities, particularly antioxidant and anti-inflammatory properties, which are beneficial for the treatment of various diseases. Moreover, the therapeutic effect of curcumin has been investigated in preclinical and clinical studies, showing that it is safe, even when used at high doses. However, the drawbacks of curcumin are its low aqueous solubility, instability, and poor bioavailability. Thus, as summarized in this review, several formulations, including classic formulations and innovative formulations using nano- and microcarriers have been developed. Among these formulations, those based on nanoparticles have shown greater bioavailability after oral administration.

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