IJBPAS, April, 2022, 11(4): 1999-2012

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

APPROACHES TO IMPROVE ORAL BIOAVAILABILITY AND SOLUBILITY OF CURCUMIN

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Received 19th April 2021; Revised 20th May 2021; Accepted 30th July 2021; Available online 1st April 2022

https://doi.org/10.31032/IJBPAS/2022/11.4.6039

ABSTRACT

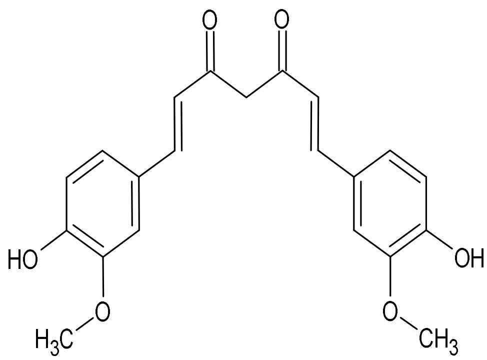
Curcumin is a hydrophobic polyphenol obtained from Turmeric. Two major components, namely desmethoxycurcumin (DMC, 2) (20 to 30 percent) and bisdemethoxycurcumin (BDMC, 3), are associated with curcumin, the major curcuminoid (50 to 60 percent).The main explanation for this is that curcumin has a low oral bioavailability in humans, which means it is scarcely absorbed. Curcumin oral bioavailability is low due to its limited water solubility, bio accessibility, fast digestion, tissue distribution, Poor liquid, and gastro-intestinal fluid solubility and excretion. Approaches to increasing the bioavailability and preparation of more bioavailable formulation such as Consuming curcumin with fatty materials, Addition of matrices, etc. are studied. Various types of nanocarriers have been developed to enhance oral curcumin bioavailability, including nanoparticles, phospholipid complexation, nanoemulsion, solid dispersion, liposome, piperine as penetration enhancer, and other adjuvants. Micro-carriers are larger than Nano-carriers. Reducing the size of the carrier enables it to carry the drug molecule across the cell membrane barriers. Pharmacokinetic data studies the AUC and Cmax of different formulations of curcumin, resulting in increased bioavailability of curcumin loaded with nanoparticles in comparison with unencapsulated curcumin powder.

Keywords: Curcumin, desmethoxycurcumin, bisdemethoxycurcumin, curcuminoid, bio accessibility, nanocarriers, etc.

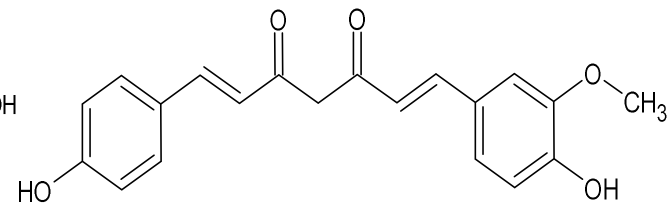
INTRODUCTION

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione], a low molecular weight hydrophobic polyphenol obtained from turmeric rhizomes (Curcuma longa Linn.), is used as a spice in many foods and as a coloring agent Curcumin, desmethoxycurcumin, and bisdemethoxycurcumin are three hydrophobic curcuminoids found in natural curcumin **[1]**. Turmeric, Linn's Curcuma longa. The main source of curcumin is turmeric (Zingiberaceae). This plant is native to South-East Asia and India. Turmeric is up to 1.0 m in height, is a perennial herb. Its main rhizome is ovate with a diameter of about 3 cm and a length of 4 cm and consists of orange flesh **[2]**. The largest producer of turmeric is India. Two other major components, namely desmethoxycurcumin (DMC, 2) (20 to 30 percent) and bisdemethoxycurcumin (BDMC, 3), are associated with curcumin, the major curcuminoid (50 to 60 percent). (7 to 20 percent). Of the three curcuminoids, curcumin has the strongest antidiabetic, cardioprotective, and neuroprotective impact. The mixture of curcuminoids, on the other hand, has higher nematocidal activity than the individual curcuminoids.For chronic disorders such as Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, atherosclerosis, and more, Cur has various pharmacological activities **[3-5]**. Response-1-gene product (EGR-1). The first inhibition of growth factor tyrosine kinase protein kinase, the mitogen kinase protein kinase (MAPK), is involved in Curcumin antitumor activity. Curcumin also has antioxidant properties due to the phenolic group's electron-donating property, which allows it to scavenge free radicals. Curcumin's ability to inhibit DNA-binding NFrB (Nuclear Factor B) is linked to its anti-inflammatory properties. **[6]**. The pro-inflammatory molecules MMP-3 (metalloprotease 3 matrices) and MMP-99 (metalloprotease 3 matrices) are repressed by inhibiting NFaB-DNA binding (matrix metalloprotease 9). The main explanation for this is that curcumin has a low oral bioavailability in humans, which means it is scarcely absorbed. At an oral dose of 12 g, curcumin plasma concentration was below the detection level in healthy male subjects. Every year, a slew of research studies is published in an attempt to solve the curcumin bioavailability problem **[7]**. Curcumin oral bioavailability is low due to its limited water solubility and fast digestion and excretion. Various types of nanocarriers have been developed to enhance oral curcumin bioavailability, including nanoparticles, phospholipid complexation, nanoemulsion, solid dispersion, liposome, piperine, and other adjuvants **[1]**.

In this review, a detailed study of recent strategies for improving oral bioavailability and solubility is given to maximize the effect of curcumin **(Figure 1)**.



a)



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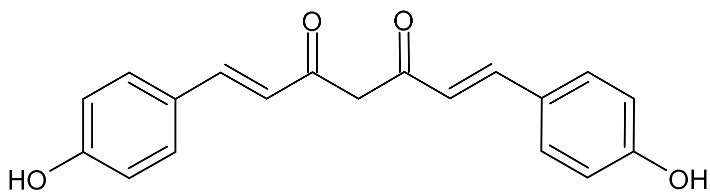

c)

Figure 1: The Chemical structure of a] curcumin b]desmethoxycurcumin and c] bisdemethoxycurcumin

REASONS FOR LOW SOLUBILITY AND BIOAVAILABILITY

Curcumin is also classified as a category IV drug by the Biopharmaceutics System (BCS) because of its low liquid solubility and limited permeability across enteric membranes **[8]**. Curcumin also has a low blood serum concentration, a weak pH-dependent aqueous stability, and a quick metabolism in both animals and humans, except for poor solubility and intestinal permeability, which are thought to be the primary causes of curcumin's poor oral bioavailability **[9]**.

1. **Bio accessibility:** To exercise biological activities, nutraceuticals, in this case, curcumin, need to be bio accessible to be absorbed into the GIT epithelium and then transferred into the systemic circulation. For that, it is important to solubilize the compounds in aqueous gastro-intestinal fluids. Curcumin is a strongly hydrophobic substance, and

there is low solubility in aqueous fluids that contributes to poor bio-accessibility **[10]**. Curcumin co-ingestion with lipids may help improve the solubility and bioaccessibility of curcumin through encapsulating curcumin through mixed micelles for GIT lipid hydrolysis medication. Not only does this combination help protect curcumin from decay, but it also increases the risk of being absorbed into the lining of the GIT epithelium. The solubility of nutraceuticals in the mixed micelles determines the length of the fatty acid chains and degree of saturation.

2. **Absorption:** Its poor absorption is one reason for the low bioavailability of curcumin. The primary source of curcumin absorption within the GIT is in the small intestine. The curcumin is a lipophilic phenolic agent, however, makes it impossible to deliver the curcumin to be ingested by the small intestine epithelium cells orally. Even if it were ingested into the epithelium, through the efflux mechanism, its hydrophobic property would allow it to be flushed back into the lumen. Previous research found that the primary route to curcumin removal was through feces after a dose of 10-400 mg curcumin in animals, indicating low curcumin absorption **[11]**. By modulating cell membrane dynamics and altering lipid fluidity due to it’s a polar existence, piperine, an active compound derived from peppers, was reported to be able to decrease efflux transport back to the lumen.
3. **Tissue Distribution:** How curcumin is transmitted in the tissues of the body is an essential consideration for its biological functions after being consumed and circulated. Few studies have been undertaken to tackle this issue, however. Ravindranath& Chandrasekhara (1980) demonstrated that after oral administration of 400 mg of curcumin, only traces of free-formed curcumin were present in the liver and kidneys of rats **[12]**. Further research using tritium-labeled curcumin found that radioactivity was detectable in the blood, liver, and kidney of the treated animal after a dose of 10-400 mg curcumin. To determine the tissue distribution of curcumin using various

administration methods, further studies are required.

4. **Metabolic Transformation:** Curcumin undergoes rapid metabolic declines (Phase I metabolism) and conjugation (Phase II metabolism) in tissues such as the GIT and liver following oral consumption, due to its low systemic bioavailability. To produce a variety of reduction products, including dihydro curcumin, tetrahydro curcumin, hexahydro curcumin, and octa-hydro curcumin, curcumin could be metabolized by NADPH-reductase. Curcumin has two phenolic groups, making it ideal for Phase II detoxification enzymes such as glucuronosyltransferase and sulfotransferase to be metabolized, resulting in the production of conjugates of glucuronide and sulfate, respectively. A trial of oral administration of 0.1 g/kg of curcumin in mice yielded a peak free curcumin plasma concentration of just 2.25 μg/ml. Curcumin glucuronide and curcumin sulfate are less involved or inactive relative to curcumin. The metabolism in Step II also contributes to decreased curcumin biological activities. Curcumin has an alpha, β-unsaturated carbonyl moiety along with enzymatic phase I and phases II metabolisms, which can react with protein thiols in a Michael reaction to form covalently connected protein conjugates. Therefore, it is probable that a proportion of curcumin will invade intracellular space after ingestion of curcumin and react with protein thiols to form intracellular protein adducts. The low circulating concentration of free-form curcumin after ingestion of curcumin may also lead to this process. The biological importance of the development of curcumin-protein adducts needs more analysis. The previous study has demonstrated that in controlling certain important biological processes, cysteine residues (or protein thiols) play critical roles. Covalent modulation of cysteine residues of Keap1 proteins, for example, leads to the destruction of the Keap1-Nrf2 complex and activation of the signaling cascade for Nrf2-mediated Phase II detoxification. The latest research has demonstrated that curcumin can

covalently change a signaling protein in kinase I gamma, which plays a crucial role in the biological activity of curcumin. The development of curcumin-protein adducts could also lead to curcumin's biological effects **[6]**.

5. **Poor liquid and gastro-intestinal fluid solubility:** Curcumin is a hydrophobic compound, but its water solubility is very weak. Also, its aqueous solubility is dependent on pH. It is essentially insoluble at acidic or neutral pH. The overall aqueous solution solubility of curcumin at pH 5 was just 11 ng/ml. Solubility at pH 6.8 was stated to have increased to 0.1 µg/ml. However, when the pH was lifted to 7.4, it plummeted to 0.06 µg/ml. It must dissolve in gastrointestinal (GI) fluids for oral substances to be absorbed. This is not clear due to the higher solubility tested in the simulated gastrointestinal fluids, but it can be attributed to the presence of pepsin in the simulated gastrointestinal fluids. Studies have shown that pepsin can increase lipophilic drug solubility, but the mechanisms behind it have not yet been identified. And after offering a high oral dosage, curcumin has a poor plasma concentration. The plasma curcumin content was too low to be observed in a clinical trial performed in stable human males following an oral dosage of curcumin as high as 12 g.

   The results of this study clearly show that curcumin still has very low plasma levels, even after many doses in rats and humans. When administered at the same dose as mice, plasma showed that he had higher curcumin levels than humans **[13]**.

6. **Chemical stability of curcumin:** The chemical stability of curcumin in a liquid solution, like its aqueous solubility, is impaired by pH scale changes. once within the atmosphere of the stomach or small intestine, curcumin is most stable at pH 1–6. At this pH range, however, the aqueous solubility becomes passing low whereas the curcumin stability decreases dramatically when the pH is higher than 7. The findings of a stability check using 5 mm curcumin solution (dissolved in fuel and applied to 0.1 M phosphate solution at pH 7.2) incubated at 37 C for various

periods and analyzed by HPLC discovered that 90% of the curcumin was degraded to numerous degradation product as well as a compound, ferulic acid, and feruloyl gas among thirty minutes. during this assay, following first-order kinetics, vanillin was reported to be the most degradation agent. Overall, as a result of curcumin are often quickly degraded in alkaline solutions and is poorly soluble in acidic liquid solutions, the steadiness issue of curcumin affects oral bioavailability (even although additional stable).

APPROACHES TO INCREASE ORAL BIOAVAILABILITY AND THERAPEUTIC EFFICACY OF CURCUMIN: (Table 1)

Curcumin is a yellow powder with the active ingredient curcuminoid of Curcumin Longa, remedy to treat many diseases and disorders such as- arthritis, wound healing, inflammatory bowel disease, pancreatic cancer, Parkinson's disease, psoriasis, ulcerative colitis, etc. First isolated in 1895, with low oral-systemic absorption with only traces found in liver and portal circulation. Thus, there arises a need to design formulations with increased bioavailability to enhance the therapeutic activity of the moiety. Approaches to increasing the bioavailability and preparation of a more bioavailable formulation **[6, 12, 14]**.

1) **Consuming curcumin with fatty materials:** Curcumin is a fat-soluble substance, taking it with a fatty meal can increase the absorption of curcumin. Certain fatty substances like turmeric oil are included in formulations of curcumin to enhance the activity. The market available products are BCM-95®; BioCurcumax®; Curcugreen a small amount of piperine (Curcumin C3 Complex®) to stimulate the gastrointestinal system, or as a turmeric oleoresin (Curcugen) which have resulted in a small incremental increase in curcumin absorption **[4]**.

2) **Addition of matrices:** Matrices system, also known as a monolithic delivery system is a dispersion of the chemical moiety in a matrices substance that forms an envelope to develop a viable orally-extended formulation, thereby releasing it at the targeted site. Natural matrices forming substances such as cellulose, starch, and glycogen are preferably engineered than synthetic matrices. Formulation of curcumin with

matrices like rice flour, whey protein is available as commercial products **[6, 15]**. Matrix of medium-chain triglycerides, glycol esters of fatty acids (GFA), HMC, and sodium alginate Micro Active Curcumin) **[3]**.

3) **Reducing the particle size of curcumin molecules:** Particle size reduction is inversely proportional to the rate of drug release. A decrease in the particle size proportionally increases the rate of release of a drug molecule. Various unit operations and techniques are performed to reduce the size, it includes the use of instruments for granule preparations or incorporation of curcumin in reducing agents like Tween 80, Polysorbate 80, and sodium alginate.

Preparing nano-micelles with lauryl poly oxy 32-glycerides and polysorbate 20. A proprietary mixture of solvents, surfactants, and polar lipids. Colloidal dispersions with glycerin

4) **Delivery systems:** Chemically-modified forms of curcumin incorporated in the number of the delivery system based on the target site can significantly increase the absorption in the small intestine, preventing degradation in the microenvironment. Micelles, phospholipid complexes, micro-emulsions, nano-emulsions, use of carriers, surface stabilizers show promising clinical application for curcumin. A study comparing the bioavailability studies of different curcumin formulations showed significantly higher cellular uptake when compared with a free-curcumin powder.

5) **Use of carrier for targeted-release:** Naturally-occurring substances do not show adverse effects, proving to be the best carriers like gelatin and chitosan. Gelatin is a widely used naturally occurring polymer obtained from animal skins and bones. The hydrophilic nature of gelatin repeals the aqueous ions and proportionally increasing the lipid solubility of a drug (curcumin).

Curcumin-loaded gelatin sponge is used in topical delivery for wound healing application **[16]**. Chitosan is obtained from chitin, a polysaccharide biopolymer is a unique polycationic molecule, with film-forming and chelating properties. It can be used to enhance the stability of curcumin resulting in increased accumulation at the site of infection, wound, and toxicity to cancer cells **[17]**.

Table 1: Approaches to increase oral bioavailability and therapeutic efficacy of curcumin

Addition of Lipid substance		
Lipid substance	***Commercially Available Products***	***Description***
Piperine	**Curcumin C3 complex**	**Supports healthy cholesterol levels and prevents tissue damage**
Turmeric Oleoresin	**Curcugen®**	**50% curcuminoid concentration, optimized by SELFD™ technology**
Turmeric oil	**BioCurcumax® BCM-95® Curcugreen®**	**Bioavailability of 8 hours. 700% more potent than free curcumin powder.**
Dispersion on matrixes		
Cellulose derivative	**CurcuWIN®**	**Higher plasma levels of curcuminoid than LongVida or Mervica**
SiO_2/ Triacetin	**Micronized curcumin® Panodan®**	**Available in capsule forms with maximum potency**
Whey protein	**Curcumin Pro™**	**Maintenance of good health and to relieve joint inflammation**
Rice flour/ silica/ magnesium stearate	**Curcufresh®**	**Prepared from fresh turmeric rhizome, never extracted using solvents or dried.**
Microcrystalline cellulose/ Lecithin	**Meriva®**	**Sustained-release curcumin phytosome supplement**
Y-cyclodextrin	**Cavacurmin®**	**Improved dispersibility in water with gamma dextrin complex**
Reducing Agents		
Polysorbate 20	**Biocurc®**	**Triple-acting supplement for mind, skin, and body with pure omega3 fatty acids.**
Galactomannan Fiber	**CurQfen®**	**New generation powder, therapeutically used for heart, liver, brain, and joints**
Acacia	**TurmiPure®**	**World's first bioequivalent turmeric at low dose by Naturex company**
Docosahexaenoic Acid	**LongVida®**	**Optimized curcumin designed by neuroscientist using SLCP technology to deliver free curcumin to the brain**
Delivery system		
Micelle formation	**Gelicure®**	**SMEEDS for ulcerative colitis**
Adsorption technique	**Theracurmin®**	**Gum ghatti is used as an adsorbent along with size reducing technology**
Phospholipid-complex	**Hydrocur®**	**Cold and water dispersible**
Nanoparticles	**Biocure®**	**Omax turmeric supplement**
Use of carriers		
Gelatin	**Turmipure®**	**Highly bioequivalent at low dose extended use in the food industry**
Chitosan	**Gelicure®**	**Under clinical trials**
Sodium alginate	**Microactive® curcumin**	**Well-tolerated without adverse effect.**

NANO-CARRIERS AND MICRO-CARRIERS OF CURCUMIN: (Table 2)

Nano and microcarriers differ only in their size. Micro-carriers are larger than Nano-carriers. Reducing the size of the carrier enables it to carry the drug molecule across the cell membrane barriers. Pharmacokinetic data studies the AUC and Cmax of different formulations of curcumin, resulting in increased bioavailability of curcumin loaded with nanoparticles in comparison with unencapsulated curcumin powder.

Nanoparticles carry and release the curcumin in the targeted site, causing a proportionally increase in the site accumulation of bioactive curcumin to the therapeutic effect of it **[18]**.

Nano-carrier and micro-carrier formulations include-

1. **Nano-emulsions:** Emulsions are formed by the incorporation of two immiscible liquids, stabilized by the addition of emulsifying agents like tween80 along with the gelling agent, thickening agents which depend upon the route of administration of the formulation. Nano-emulsions have a structural diameter below or equal to 200nm. The color of the curcumin depends upon pH, generally is yellow to orange with a clear or milky appearance.
2. **Nanostructured lipid carriers:** Liposomes are lipid nanocarriers used for targeted drug delivery. Curcumin-loaded PEG 400 tends to show enhanced stability and increased accumulation at the targeted site. Liposomes form a shell-like structure that sustains the first-pass metabolism by releasing the embedded curcumin molecule at the intended site, resulting in increased pharmacological activity. PEG is composed of polyethylene glycol that is bound to each other by covalent linking. The process is called as PEGlyation.
3. **Microemulsions:** Curcumin is used in the treatment of Parkinson's as neuroprotective. Curcumin being low lipid soluble cannot cross the blood-brain barrier due to overexpression of p-glycoprotein. To improve the therapeutic effect of curcumin at the targeted site of the brain, it is loaded with sodium hyaluronate (mucoadhesive) microemulsion. The pre-clinical study showed an increase in drug concentration at the brain site **[15, 17]**.
4. **Micro-encapsulation:** Encapsulation means enclosing the curcumin in a sac- to control its release at the site. The incorporation of colloidal particles in curcumin increases the ability of water dispersing. Structurally, having a hydrophobic interior and hydrophilic exterior. Curcumin is prone to chemical instability. Interestingly, chemical stability, as well as bioavailability of curcumin, is shown to increase with

the size of hydrophobic colloid particles **[19]**.

5. **Micelles:** Micelles are relatively thermodynamically stable, spontaneously formed, and smaller in size that allows them to form optically transparent solutions. The viscosity of the micellar systems can be impaired depending upon the amount of addition of surfactants, low volume addition results in low viscosities whereas higher concentrations form semi-solids or gel. They can be formed from synthetic or natural surfactants like tweens and casein. It was shown to have 185 times fold in AUC and Cmax of pharmacokinetic data calculations than free curcumin.

6. **Nanoparticle complex:** Sodium alginate is used as a carrier of curcumin for preparing extended-release dosage forms. Montmorillonite (MMT) can also be used as an alternative to preparing microbeads to increase the rate of bioavailability. Microbeads possess porous nature and the incorporation of multivalent ions like Ba^{2+}, Al^{3+}, Mg^{2+} in the calcium alginate matrix can enhance the swelling property as well as promote the rate of release of biochemically active molecules **[20]**.

Table 2: Nano-carrier and micro-carrier formulations of curcumin

Type of nanoparticle	Form	Models	Results
Liposome	Globular	Renal ischemia malaria	Increased solubility, tissue distribution, anti-tumor, and anti-angiogenesis effect
Micelle	Spherical	Breast cancer	Improved anti-oxidative and anti-tumor effects.
Noisome	Lamellar	Albino rat skin	Enhanced fluorescence effect.
Cyclodextrin	Cyclic	Bowel disease	Developed proliferative effect
Dendrimer	Globular polymer	Colon cancer	Increased proliferative effect
Nanogel	Cross-linked	Melanoma	Controlled release, better half-life
Chitosan	Linear polysaccharide complex	Wound melanoma	Prolonged blood circulation, antioxidant and anti-tumor effect

IMPROVING SOLUBILITY

Nano-sponges: The lipophilic nature of curcumin leads to lower water retention and lower absorption, leading to higher digestion and faster excretion in the body. CDNS has been used to increase the solubility and availability of curcumin drugs through hydrophobic interactions between proteins and liposomes. Above all, CDNS offers significant advantages over alternatives due to its high drug-carrying capacity, longevity, and cost-effectiveness. The next section of the study showing the usefulness of CDN. we studied the image effects of curcumin loading curcumin CDNS complex extraction features, promoted by the promising features of curcumin integrated CDNS. , The three curcumin CDNS properties were repaired by lyophilization, dehydration, and body mixing, and their radiation and properties were studied and compared. In vitro release tests have shown that curcumin can be released in three companies for a longer period. The release rate behavior observed in the three samples showed that nanosponge formation and complex dosing techniques influence the formation of curcumin release that is affected by the nanosponge synthesis process. Curcumin-loaded nanosponges through freeze-drying approach as a beneficial provider for the discharge of curcumin in an aqueous media **[21]**.

CONCLUSION

Curcumin is a popularly known therapeutic agent for its various activity such as nematocidal activity, chronic disorders such as Alzheimer's disease, multiple sclerosis, rheumatoid arthritis, atherosclerosis, and more. Because of its low bioavailability and low solubility, it is readily absorbed and therefore there is no result as expected. By studying various approaches and the formulation there is an increase in bioavailability and solubility and it is beneficial for the use of curcumin.

CONFLICT OF INTEREST

The authors of this article declare that there is no conflict of interest for publishing this article.

ACKNOWLEDGMENT

The authors are incredibly thankful to Management, Dr. Vishwanath Karad MIT World Peace University, Dean and HoS, School of Pharmacy for providing all necessary facilities in the publication of this paper. The authors are also thankful for various sources of internet, google, and various newspapers, magazines for giving fruitful information for the publication of this paper.

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