

Enhanced Bioavailability of Curcumins

Curcuminoids (curcumin and related compounds, such as desmethylcurcumin and bis-desmethylcurcumin) are the main components of rhizomes of turmeric (*Curcuma longa*) used as spice and as yellow colorant mainly in South Asia. In addition to the food application, the beneficial effects on health have been traditionally utilized in India. The mechanism of the antioxidant, antibacterial, antifungal, anticancer and antiinflammatory effects of curcumin have been explored and recently also the benefits in cystic fibrosis and Alzheimer disease have been proved in cellular and animal models [1].

Curcumin is an oil-soluble polyphenol pigment, practically insoluble in water at acidic and neutral pH, soluble in alkali. It has low bioavailability owing to the poor aqueous solubility. It was obvious to try cyclodextrins (CDs) for enhancing the solubility as the two phenyl moieties might fit well into the CD cavity (Figure 1). For β CD a stoichiometry of 2:1 (host:guest) was established with an association constant of $5.53 \times 10^5 \text{ mol}^{-2} \text{ L}^2$ [2]. Later studies suggested 1:1 stoichiometry with most of the CDs.

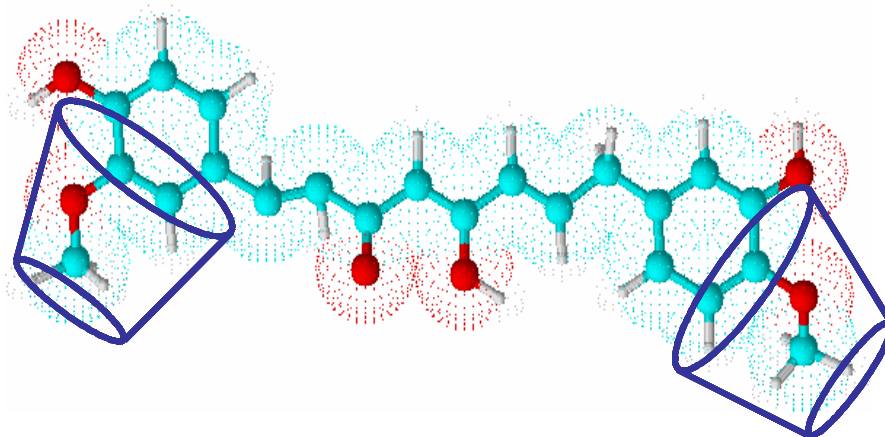


Figure 1. Scheme of curcumin/CD complexes

Aggregation of curcumin/ β CD complex resulting in spherical nanoparticles of approx. 500 nm was illustrated by transmission electron microscopic (TEM) images by Yallapu *et al.* [3]. This aggregation helps the cell penetration.

The phase solubility studies showed that all the three natural CDs enhance the solubility of curcumin with α CD giving the highest solubility (Figure 2) [4].

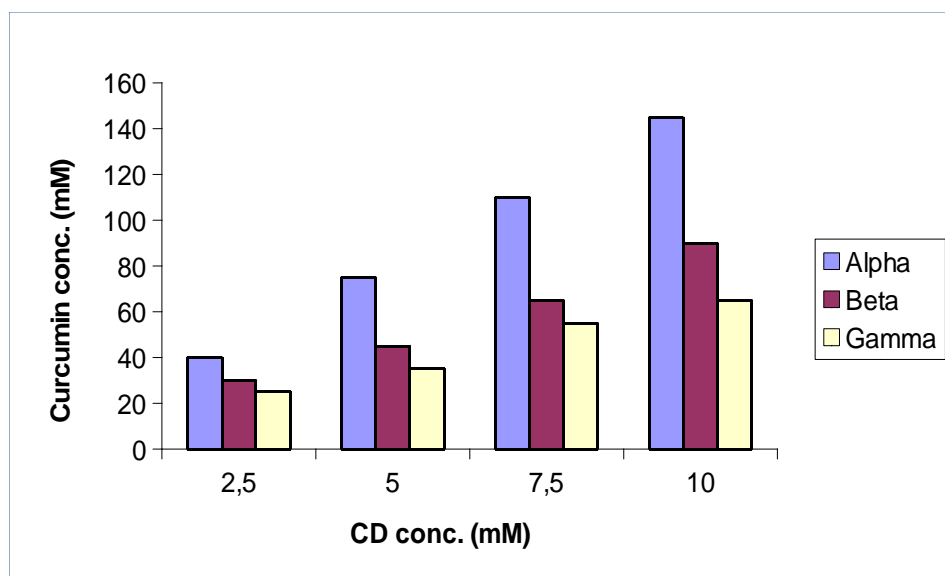


Figure 2. Comparison of the curcumin-solubilizing effect of α CD, β CD and γ CD [4]

According to Szente *et al.* RAMEB enhanced the solubility of curcuma oleoresin (curcuminoids obtained by extraction of turmeric with ethanol) by 3 orders of magnitude (Figure 3) [5]. On the other hand, solubility and phase-distribution studies showed that curcuminoids with side groups on the phenyl moiety have higher affinity for the HPGCD than for the β CDs and that the relative affinity of the larger HPGCD cavity increases with the curcuminoid molecular size [6]. Curcumin was found to have a more than 30-fold higher association constant with HPGCD compared to HPBCD in buffer containing 0.5% ethanol [6].

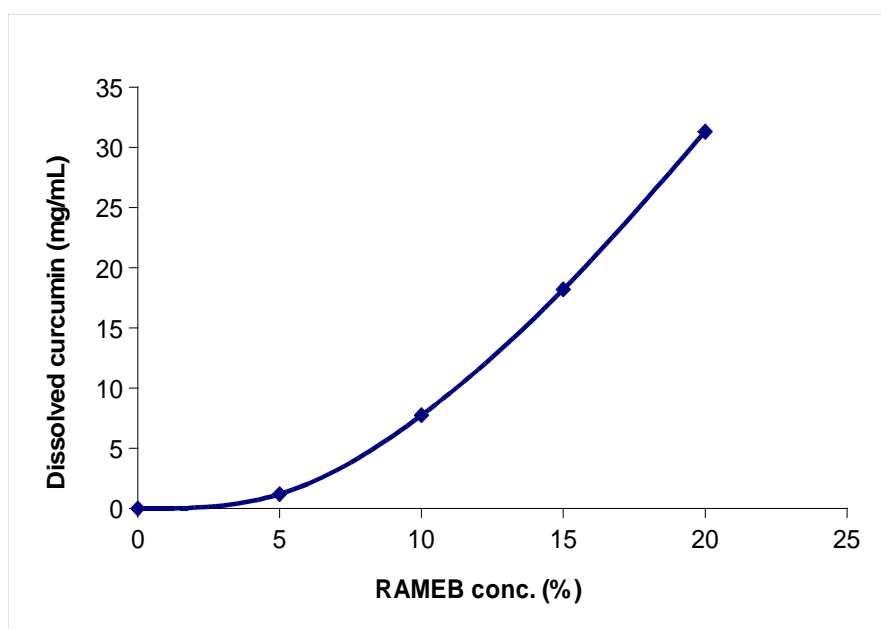


Figure 3. Solubility of curcuma oleoresin in deionised water at 25 °C after 48 h equilibration [5].

Complexation with β CD protects from decomposition upon UV-exposure: curcumin itself is fast decomposed while approx. 80% of residual curcumin content of the β CD complex was measured after 14 years of UV exposure [5]. CDs protect against hydrolytic decomposition in



the order of HPBCD > MeBCD » HPGCD [7].

The enhanced solubility results in enhanced bioavailability and improved clinical effects. Some results are listed in Table 1.

Table 1. Effects of CD-complexation on the biological activity of curcumin

Effect	CD	Ref
Enhanced relative bioavailability (plasma level) after oral administration	α -, β - and γ CDs	[4]
Enhanced bioavailability and controlled release against stomach cancer	β CD	[8]
Improved bioavailability in prostate cancer cell line	β CD	[3]
Enhanced oral bioavailability compared to commercial formulations	γ CD	[9]
Improved antimicrobial effect in photodynamic therapy of superficial infections	HPBCD, HPGCD	[10, 11]
Higher efficacy against inflammatory bowel disease (IBD) in colitis-induced rat model	HPBCD	[12]
Enhanced cellular uptake and effect against cell proliferation and angiogenesis	HPGCD	[13]
Enhanced apoptotic effect in human lung and ovarian carcinoma cells	CD polymer	[14]

Most recently curcumin/CD complexes formulated in liposomes, magnetic nanoparticles, nanosponges, nanosuspensions, hydrogels etc. have been also studied.

Some of the research results have been translated to the market: the highly bioavailable curcumin/Cawamax W8 (γ CD) formulation for application as food supplement is on the product list of Wacker Chemie [9].

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Gene Delivery, Nanovector, pH-Sensitive, siRNA Therapy, Smooth Muscle Cell, Polyethylenimine, Ac- α CD, poly(Lactic-co-Glycolic Acid), Apoptosis

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Apolipoprotein-E Knockout Mice, Calcium Signalling., Endothelium, Hypercholesterolemia, Methyl- β -cyclodextrin, RAMEB

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Angiogenesis, Cardiac Tissue Engineering, Cell Encapsulation, Injectable Biomaterials, Mesenchymal Stem Cell

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Cold Storage and Transport, Epididymides, In Vitro Fertilization, Motility, Sperm, Sphingosine-1-Phosphate

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Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Autophagy, Huntington's Disease, Lysosomal Storage Disorders, Parkinson's Disease

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Lipid Kinase, Lipid Transfer Proteins, Phosphatidylinositol 4-Phosphate, Viral Replication

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Cell Blebbing, Cell Fixation, Human Umbilical Vein Endothelial Cells (HUVECs), Lipid Rafts, Phosphatidylinositol 4,5-Bisphosphate (PIP2), THP-1-Derived Macrophages

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Cyclodextrin, Daucus Carota, Methyl Jasmonate, Pathogenesis-Related Proteins, Cell-Wall-Degrading Enzymes

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Achromobacter xylosoxidans, Bioremediation, Microcosm, Triton X-100, Chrysene, Glucose as a Co-Substrate

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Curcuma Longa Rhizomes, Curcuminoids, Herbal Products, Method Development, NACE

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Graphene, Picric Acid, Reduced Graphene Oxide, Sensor, β -Cyclodextrin, 1-Pyrenebutyl-amino- β -cyclodextrin
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