Enhanced Bioavailability of Curcumins

Curcumionoids (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 βCD a stoichiometry of 2:1 (host:guest) was established with an association constant of 5.53 x 10⁵ mol⁻² L² [2]. Later studies suggested 1:1 stoichiometry with most of the CDs.

Aggregation of curcumin/βCD 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 αCD giving the highest solubility (Figure 2) [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 βCDs 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].

Complexation with βCD protects from decomposition upon UV-exposure: curcumin itself is fast decomposed while approx. 80% of residual curcumin content of the βCD 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

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

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

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

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


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*Mild Steel, AES, Acid Corrosion, Anodic Film, 1H NMR, FT-IR, XRD, DSC*


Gaich, T.

**Chapter 5.15 The Arene–Alkene Photocycloaddition**

*Exciplex, Meta Photocycloaddition, Photocycloaddition, Polycyclic Structures*


Griesbeck, A.G.; Franke, M.

**Chapter 5.04 Photochemical Cycloadditions**

*Intermolecular and Intramolecular Photochemistry, Selectivity, Sensitization*


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**Compatibilizing effect of β-cyclodextrin in RDP/phosphorus-containing polyacrylate composite emulsion and its synergism on the flame retardancy of the latex film**

*Compatibility, Flame Retardancy, Phosphorus-Containing Polyacrylate, Resorcinol Bis(diphenyl phosphate), β-Cyclodextrin, β-CD was Used as a Compatibilizer, Quality of the Char Formation*


Hu, J.; Lu, J.

**Chapter 14 - Smart polymers for textile applications**

*Moisture-Responsive Polymer, pH-Responsive Hydrogel, Smart Textiles, Thermal-Responsive Hydrogel, Thermal-Responsive Polymer*

Iwasawa, N.

Chapter 5.08 Thermal and Metal-Induced [3+2] Cycloadditions

1,3-Dipole, Allylsilane, C-H Activation, Fischer Carbene Complex, Lu Reaction, Meta-Cycloaddition Of Benzene, Methylene cyclopropane, Reductive Coupling, Trimethylenemethane, Vinylcyclopropane


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*Capillary Zone Electrophoresis, Cyclodextrins, Design Of Experiments, Edible Oil, Polycyclic Aromatic Hydrocarbons, Sulfobutylether-β-CD, Methyl-β-CD*


Haginaka, J.

**Chiral separations: liquid chromatography**

*Chiral Derivatization, Chiral Ligand Exchange, Chiral Mobile-Phase Additive, Chiral Stationary Phase, Crown Ethers, Donor–Acceptor Phases, Enantioseparation, Liquid Chromatography, Macrocyclic Antibiotics, Polysaccharides, Proteins*

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**The development of a highly sensitive urea sensor due to the formation of an inclusion complex between urea and sulfonated-β-cyclodextrin**

*Cyclodextrin, Inclusion Complexation, Polypyrrole, Urea Sensor, Urease, Electropolymerisation, Cyclic Voltammetry*

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**Chapter 10 – Chiral methods**

*Analytical Method Development, Chiral Column Screen, Chirality, Chromatography, Circular Dichroism, Electrophoresis, Enantiomer, Polarimetry, Stereoisomer, Validation*


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**Selective detection of picric acid using functionalized reduced graphene oxide sensor device**

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


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**Detecting Ni(II) in aqueous solution by 3-(2-pyridyl)-[1,2,3]triazolo[1,5-a]pyridine and dimethyl-β-cyclodextrin**

*Fluorescence, Pyridyltriazolopyridine, Sensor, Supramolecular Sensitizer, DIMEB*

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**Enantioseparation performance of novel benzimido-β-cyclodextrins derivatized by ionic liquids as chiral stationary phases**

*Chiral Stationary Phase, Enantioseparation, HPLC, Ionic Liquid, Mono-6-deoxy-6-(p-N,N,N-trimethylaminobenzimide)-β-CD Nitrate and Tosylate, Mono-6-deoxy-6-(p-N-methylimidazolemethylbenzimide)-β-CD Nitrate and Tosylate*


Prakash, S.; Yeom, J.

**Chapter 6 - Energy and environmental applications**


Savina, I.N.; Galaev, I. Yu.; Mikhalovsky, S.V.

**Chapter 13 - Smart polymers for bioseparation and other biotechnological applications**

*Adsorbents, Affinity Precipitation, Bioseparation, Catalysts, Chromatography, Membranes, Smart Polymer, Two-Phase Systems;*

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*Cyclodextrin-Based Stationary Phase, Cyclofructan-based Stationary Phase, Enantiomer, Functionalized Ethano-Tröger Base, Principal Component Analysis*


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**Mild and novel electrochemical preparation of β-cyclodextrin/graphene nanocomposite film for super-sensitive sensing of quercetin**

*Differential Pulse Voltammetry, Electro-Deposited Grapheme, Nanocomposite Film, Polymerized β-Cyclodextrin, Quercetin*

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