Cyclodextrins in the Battle against Antibiotic Resistant Microorganisms: Mimicking Cyclic Peptide Antibiotics

Introduction

Nowadays, antibiotics are among the most frequently prescribed medications worldwide [1]. However, their indiscriminate use, improper prescriptions and their misuse by consumers led to the development of antibiotic-resistant bacterial strains. The established antimicrobial therapies are becoming less effective due to increasing emergence and prevalence of resistant bacteria. Conventional antibiotics are no longer the ‘magic bullets’ they were once thought to be and therefore there is an urgent need for development of new antibiotics and/or other novel strategies to combat the infections caused by antibiotic-resistant organisms. As resistance to antibiotics becomes more common, a greater need for alternative treatments arises. However, despite a push for new antibiotic therapies, there has been a continued decline in the number of newly approved drugs. Because all of the so-called easily exploitable and already discovered bacterial binding sites for antibiotics have been exploited, drug development has become more complex than it was decades ago.

A World Health Organization report released April 2014 stated, "this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance –when bacteria change so antibiotics no longer work in people who need them to treat infections– is now a major threat to public health"[2].

Cyclodextrins (CDs) offer several innovative strategies against microbial infection including not only reducing the resistance of the known antibiotics via complexation [3] but also decreasing the cell-to-cell communication (quorum sensing) [4], inhibiting bacterial and viral infections via cholesterol depletion [5] and plugging the pores of the pathogens by CDs [6]. The present issue of Cyclodextrin News gives an overview on one of the new alternative strategies where cyclodextrins are successfully used against antibiotic resistant microorganisms.
Cyclodextrin Derivatives as Membrane Disrupting Agents

Antimicrobial peptides have been recognized as promising agents against multidrug-resistant bacteria [7]. Many of these peptides owe their antibacterial activity to the formation of trans-membrane ion-channels resulting in cell lysis. They have cyclic structure and contain positively charged hydrophilic moieties that interact with negatively charged bacterial cell membranes, while their hydrophobic groups interact with fatty acid moieties in the lipid membrane to trigger membrane disruption. Nearly all known natural cyclic peptides display high antibacterial activity.

CDs have been modified in order to mimic the effect of these naturally occurring channel-forming peptides. Their diameter is nearly identical as the diameter of the antibiotic oligopeptides (ca. 1 nm), their structure also contain a rigid channel available for pore forming and they can be further modified due to their numerous hydroxyl groups in order to enhance their interaction with a bacterial cell membrane. This strategy has been followed recently by two research groups, the group of Hatsuo Yamamura from the Nagoya Institute of Technology and by the group of Troels Skrydstrup from the Aarhus University. Their work led to new CD derivatives capable of causing bacterial cell membrane disruption. Since these derivatives do not act on a specific cellular enzyme or receptor, but on the bacterial membrane itself, they exhibit broad-spectrum antibacterial activity. Therefore, compared to that of conventional antibiotics, the development of resistance to these membrane disrupting agents is difficult.

Research group of Hatsuo Yamamura is interested in the synthesis of regioselectively modified γCD derivatives bearing polyalkylamino and polyarylamino derivatives, able to strongly interact with a bacterial cell membrane and cause cell lysis. The study of his research group relies on a structure—activity relationship study of Polymyxin B and Gramicidin S, which are membrane active cyclic polypeptides that strongly permeabilize both the outer and cytoplasmic membranes of Gram-negative bacteria. These polypeptides contain amino acid residues, whose side chain amino groups form a cationic region of an amphiphilic peptide structure (Fig. 1). Earlier studies demonstrated that the fatty acid chain in the molecule of polymyxin B has a high importance in the antimicrobial activity. The polymyxin B nonapeptide, a polymyxin B analogue lacking the fatty acid tail showed no significant antimicrobial activity, but it retained the high outer membrane-permeabilizing activity [8.]. These findings showed that the fatty acid portion is important in the antimicrobial activity because it dissolves in hydrophobic region of cytoplasmic membrane and disrupts membrane integrity. Binding of Polymyxin B causes leakage of cellular molecules and inhibition of cellular respiration. It also binds and inactivates endotoxins. It has bactericidal action only for Gram-negative bacteria species, since the cell wall in Gram-positive species is too thick to permit access to membrane.
Fig. 1: Schematic representation of the structural relationship between the naturally occurring Polymyxin B and its CD based analogue, octakis(6-deoxy-6-benzylamino)-γCD.

In order to prepare CD derivatives which are able to mimic the action of Polymyxin B, Yamamura and his coworkers prepared first a series of polyamino CDs where the amino groups were arranged on the primary side of the CD [9]. Activity of these derivatives to permeabilize bacterial membranes was examined by measuring the $K^+$ efflux from the bacteria. The measurement showed that the compound containing 8 amino groups, namely the octakis(6-deoxy-6-amino)-γCD caused the highest $K^+$ efflux from both the Gram-positive strains of *Staphylococcus aureus* and from the Gram-negative *Escherichia coli*. The heptaamino derivative (heptakis(6-deoxy-6-amino)-βCD) showed only moderate membrane activity while the αCD derivative (hexakis(6-deoxy-6-amino)-αCD) containing six amino groups had no significant activity on the studied strains. These results demonstrated the importance of the number of the amino groups and the size of the CD cavity on the membrane activity. The observed $K^+$ efflux value from *E. coli* was smaller than that from *S. aureus*, which may be due to the differences in membrane structure between the Gram-negative and Gram-positive bacteria.

The most interesting result of this study is the observed synergic effect of polyamino CDs with probe antibiotics, such as novobiocin and erythromycin. These probes dosed alone have no effect on the growth of *E. coli* strains because the outer membrane of the Gram-negative
bacteria cell acts as a barrier for them (MIC>120 µg/mL for novobiocin, MIC> 80 µg/mL for erythromycin). The polyamino CDs themselves have no antibiotic activity (MIC > 128 µg/mL) either, but the combination of the antibiotics with polyamino CDs showed surprisingly high antimicrobial activity (MIC < 10 µg/mL). Especially the octakis (6-deoxy-6-amino)-γCD showed high synergic effect with both antibiotics. These observed effects and the MIC values of the polyamino-γCD were comparable to those of polymyxin B nonapeptide.

After the successful demonstration of the fact that polyamino CDs can mimic the effect of the polymyxin B nonapeptide the researchers went further with altering the properties of the most promising derivative, the octakis(6-deoxy-6-amino)-γCD. Their aim was to increase the amphiphilicity of the polyamino CDs because, as it was proved for polymyxin B and polymyxin B nonapeptide, the appropriate amphiphilicity of the membrane disrupting molecule is important in antimicrobial activity [8].

First, the octakis(6-benzylamino)-γCD (6-BnAmγCD) derivative was prepared via the reaction of benzylamine as a nucleophile with a per-tosylated γCD. This reaction resulted in moderate isolated yield of the product (17.3 %) mainly because the purification required an inefficient gel filtration chromatography. The prepared 6-BnAmγCD however showed much higher disruption of the bacterial membrane than the polyamino derivatives and exhibited surpassing antibiotic activity against Gram-positive strains (MIC = 4–8 mg/mL). The observed MIC values are comparable to the activity of the gramicidin S. It is interesting that the introduction of hydrophobic benzyl groups to polymyxin B nonapeptide-like amino CDs led to Gramicidin S-like membrane activity.

The direct nucleophilic substitution methodology used for the preparation of octakis(6-benzylamino)-γCD was not effective in the synthesis of other alkylamino and arylamino γCDs. To solve this problem Yamamura and co-workers developed an effective polyfunctionalization of γCD via microwave-assisted Huisgen reaction [10]. Starting from octaazido γCD they prepared a library of compounds varying the type of the alkyl chain or aryl moiety on the primary side of the γCD (Fig. 2).

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**Fig. 2: Structure of polyalkylamino and polyarylamino γCDs [9, 10]**
Their bioactivity for the permeabilization of bacterial cell membranes depended on the substituents on the amino group. The results showed that the triazole ring in the structure did not decrease the membrane disrupting ability of these derivatives. The hemolysis of rabbit red blood cells by the prepared alkylamino and arylamino γCDs was also examined in order to determine whether they disrupt the membranes of animal cells. It is worth pointing out, that although the benzylamino derivative prepared via direct substitution on the C6 carbon (compound 1, Fig. 2) showed excellent membrane disrupting activity on bacteria cells, it also permeabilized the red blood cells, therefore its selectivity is low. On the other hand, the benzylamino derivative prepared via the Huisgein reaction (compound 2, Fig. 2) exhibited significantly less hemolysis at the experimental concentration (50 µM) while the MIC for the two compounds was found to be nearly the same (MIC = 4–8 µg/mL) for both the Gram-negative and Gram-positive strains. These results suggest, that the triazole moiety works very well not only for effective functionalization but also for selective membrane disruption.

Slightly different approach towards CD based membrane permeabilizers was followed by the research group of Troels Skrydstrup from the Aarhus University, Denmark. Their main idea was to use cyclodextrin as a cyclic template for alamethicin oligomers [11]. Alamethicin is a subclass of pore-forming proteins called peptaibols. It has a hydrophobic α-conformation which can form channels in biological membranes. Although the precise structure of these channels is unknown, NMR and molecular dynamics investigations suggest that they are highly dynamic and nonuniform by nature and the most stable and predominant channel structure is helical consisting of 6–8 helices [12, 13].

In order to prepare a stable ion channel from alamethicin subunits, Skrydstrup and co-workers covalently attached 6 and 7 alamethicin molecule to α- and βCD respectively. These conjugates were prepared via click reaction from per-6-azidated CDs and alkyne conjugated alamethicin (Fig. 3). The permeabilizing ability of the conjugates was tested with calcein-release assay, in which calcein was entrapped in dioleoyl-phosphatidylcholine (DOPC) vesicles at a concentration high enough to cause self-quenching of its fluorescence. When permeabilization of the vesicle occurs, the released calcein dilutes and gives detectable fluorescent signal [14]. The ion channel forming ability of the alamethicin:CD conjugates was examined with voltage-clamp studies. The free alamethicin did not produce any detectable conductance at peptide concentrations below $10^{-3}$ mg/mL. However, with the alamethicin:CD conjugates, conductance could be measured at concentrations as low as $10^{-5}$ mg/mL. The membrane permeabilizing properties of the conjugates proved to be highly effective also, and lysis experiments revealed a 100-fold increase in activity for the most active alamethicin:CD conjugate in comparison to the free peptide.

These results suggest, that alamethicin:CD constructs are able to perturb cell membranes through the formation of stable ion-channels therefore are promising new semi-synthetic antimicrobial agents.
Conclusions and future perspectives

Because of the worldwide spread of antibiotic-resistant microorganisms the infectious
diseases in the 21st century are again at the epicenter of a global dialogue capturing the
attention of academics, governments, public health officials, and the general public alike.
These diseases are evolving extremely fast, faster than the research in drug discovery. As Nobel
laureate Joshua Lederberg stated that technology will never win this war permanently and we
must be satisfied to merely stay one step ahead of the pathogens [15].

The works reviewed in the present issue of Cyclodextrin News show only a few of the many
alternative ways in the treatment of antibiotic-resistant bacteria and emphasizes that CDs can
be our very versatile weapons in this evolutionary battle between the host and the pathogen.

References:

1. Tansarli, G.S.; Rafailidis, P.I.; Kapaskelis, A.; Falagas, M.E. Expert Rev Anti Infect Ther. 2012, 10,
   1383–1392
   antibiotic resistance reveals serious, worldwide threat to public health" Retrieved 2015-02-27
   Pharmacol. 2003, 55, 291–300
   116, 175-179
   2005, 1746, 305–313
   Commun., 2011, 48, 892

The financial support of the CyclonHit project (FP7-PEOPLE-ITN-2013-608407) is greatly acknowledged.

Gabor Benkovics
CycloLab Cyclodextrin R&D Laboratory, Ltd.,
Budapest, HUNGARY
BIBLIOGRAPHY & KEYWORDS

1. CDs: Derivatives, Production, Enzymes, Toxicity


A CGTase with high coupling activity using γ-cyclodextrin isolated from a novel strain clustering under the genus Carboxydocella

*Gene isolation, Cyclization reaction, CODEHOP strategy*


Structural insights into the catalytic reaction that is involved in the reorientation of Trp238 at the substrate-binding site in GH13 dextran glucosidase

*Retaining glycosidase, Glycoside hydrolase family 13, Glucosyl-enzyme intermediate, transglucosylation, Acceptor specificity*
FEBS Letters, 2015, 589, 484-489; DOI:10.1016/j.febslet.2015.01.005


A γ-cyclodextrin duplex connected with two disulfide bonds: synthesis, structure and inclusion complexes

*Per(2,3,6-tri-O-benzyl)-γ-cyclodextrin, Steroid, Dimerization, Bile acid*
Organic & Biomolecular Chemistry, 2015, 13, 2980-2985; DOI: 10.1039/C4OB02464H

2. CD complexes: Preparation, Properties in solution and in solid phase, Specific guest

Chandrasekaran, S.; Sudha, N.; Premnath, D.; Enoch, I. V. M. V.

Binding of a chromen-4-one Schiff’s base with bovine serum albumin: capping with β-cyclodextrin influences the binding

*COSY, FRET, ROESY*


Theoretical investigation to characterize the inclusion complex of α-lipoic acid and β-cyclodextrin
PM6, DFT and ONIOM2 hybrid calculations, NBO, GIAO
Comptes Rendus Chimie, 2015, 18, 170-177; DOI:10.1016/j.crci.2014.05.003

Ji, R.; Cheng, J.; Song, C-C.; Du, F-S.; Liang, D-H.; Li, Z-C.
Acid-sensitive polyplexseudorotaxanes based on ortho ester-modified cyclodextrin and pluronic F-127
"Click" reaction, Hydrolysis, Biocompatibility, Water-insoluble CD derivatives, Inclusion complex, β-cyclodextrin
ACS Macro Letters, 2015, 4, 65-69; DOI: 10.1021/mz5007359

Kundu, P.; Ghosh, S.; Jana, B.; Chattopadhyay, N.
Binding interaction of differently charged fluorescent probes with egg yolk phosphatidylycholine and the effect of β-cyclodextrin on the lipidprobe complexes: A fluorometric investigation
Competitive binding
Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2015, 142, 15-24; DOI:10.1016/j.saa.2015.01.038

Li, S.; Zhang, L.; Wang, B.; Ma, M.; Xing, P.; Chu, X.; Zhang, Y.; Hao, A.
An easy approach for constructing vesicles by using aromatic molecules with β-cyclodextrin
β-CD/L-phenylalanine system, Self-assembly, Stimuli-responses, Nanocarriers

Li, Y.; Guo, H.; Zheng, J.; Gan, J.; Wu, K.; Lu, M.
Thermoresponsive and self-assembly behaviors of poly (oligo (ethylene glycol) methacrylate) based cyclodextrin cored star polymer and pseudo-graft polymer
Transition from micelle to nano-aggregates, CD-POEGMAs, CD-PNIPAMs
Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2015, 471, 178-189; DOI:10.1016/j.colsurfa.2015.01.024

Ma, M.; Xu, S.; Xing, P.; Li, S.; Chu, X.; Hao, A.
A multistimuli-responsive supramolecular vesicle constructed by cyclodextrins and tyrosine
Competitive guest molecules, Copper ions
Colloid and Polymer Science, 2015, 293, 891-900; DOI: 10.1007/s00396-014-3424-4

Riela, S.; Arcudi, F.; Lazzara, G.; Lo Meo, P.; Guernelli, S.; D'Anna, F.; Milloito, S.; Noto, R.
Binding abilities of new cyclodextrin-cucurbituril supramolecular hosts
Non-covalent interactions, N-(p-nitrophenyl)-1,8-diaminooctane
Supramolecular Chemistry, 2015, 27, 233-243; DOI: 10.1080/10610278.2014.975704

Siva, S.; Nayaki, S. K.; Rajendiran, N.
Fabrication of cyclodextrins-procainamide supramolecular self-assembly: Shapeshifting of nanosheet into microtubular structure
Rolling mechanism
Carbohydrate Polymers, 2015, 122, 123-134; DOI:10.1016/j.carbpol.2015.01.005

Textor, M.; Vargas, C.; Keller, S.
Calorimetric quantification of linked equilibria in cyclodextrin/lipid/detergent mixtures for membrane-protein reconstitution

Transition from micelles to bilayer membranes, 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, 2-Hydroxypropyl-β-cyclodextrin, Isothermal titration calorimetry, Detergent removal, Phase diagram, Vesicles, Micelles, Mistic

Methods, 2015, In Press; DOI:10.1016/j.ymeth.2015.01.002

3. CDs in Drug Formulation

A "green" strategy to construct non-covalent, stable and bioactive coatings on porous MOF nanoparticles

Phosphates, Cyclodextrin-based coating, Targeting

Scientific reports, 2015, 5, 7925; DOI:10.1038/srep07925

Ali, M. S.; Rub, M. A.; Khan, F.; Al-Lohedan, H. A.; Kabir-ud-Din
β-Cyclodextrin-promazine hydrochloride interaction: Conductometric and viscometric studies

Critical micelle concentration, Viscosity


Bilensoy, E.
Amphiphilic cyclodextrin nanoparticles for effective and safe delivery of anticancer drugs

Advances in experimental medicine and biology, 2015, 822, 201; DOI:10.1007/978-3-319-08927-0_24

Chen, Y.; Li, N.; Yang, Y.; Liu, Y.
A dual targeting cyclodextrin/gold nanoparticle conjugate as a scaffold for solubilization and delivery of paclitaxel

Gold nanoparticles (AuNPs) bearing adamantane moieties, Cyclodextrin dimers, Biotin-modified cyclodextrin

RSC Advances, 2015, 5, 8938-8941; DOI: 10.1039/C4RA13135E

Corciova, A.; Ciobanu, C.; Poiata, A.; Mircea, C.; Nicolescu, A.; Drobota, M.; Varganici, C-D.; Pinteala, T.; Marangoci, N.
Antibacterial and antioxidant properties of hesperidin:β-cyclodextrin complexes
obtained by different techniques

Kneading, Co-evaporation, Lyophilization

Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2015, 81, 71-84; DOI: 10.1007/s10847-014-0434-2

Dan, Z.; Cao, H.; He, X.; Zeng, L.; Zou, L.; Shen, Q.; Zhang, Z.

Biological stimuli-responsive cyclodextrin-based host–guest nanosystems for cancer therapy

Controlled rug delivery

International Journal of Pharmaceutics, 2015, 483, 63-68; DOI:10.1016/j.ijpharm.2015.01.035

Epifano, F.; Fiorito, S.; Taddeo, V. A.; Genovese, S.

4'-Geranyloxyferulic acid: an overview of its potentialities as an anti-cancer and anti-inflammatory agent

Azoxymethane as an inclusion complex in cyclodextrins, Acronychia, Colon cancer

Phytochemistry Reviews, 2014, In Press; DOI: 10.1007/s11101-014-9377-x

Ferreira, M. J. G.; García, A.; Leonardi, D.; Salomon, C. J.; Lamas, M. C.; Nunes, T. G.

$^{13}$C and $^{15}$N solid-state NMR studies on albendazole and cyclodextrin albendazole complexes

Methyl-β-cyclodextrin, Hydroxypropyl-β-cyclodextrin, Citrate-β-cyclodextrin

Carbohydrate Polymers, 2015, 123, 130-135; DOI:10.1016/j.carbpol.2015.01.031

Goodchild, C. S.; Serrao, J. M.; Kolosov, A.; Boyd, B. J.

Alphaxalone reformulated: A water-soluble intravenous anesthetic preparation in sulfobutyl-ether-β-cyclodextrin

Fast-onset anesthesia, Therapeutic index, Safety margin

Anesthesia and analgesia, 2014, In Press; DOI:10.1213/ANE.0000000000000559

Iordache, F.; Grumezescu, V.; Grumezescu, A. M.; Curuți, C.; Dițu, L. M.; Socol, G.; Ficai, A.; Trușcă, R.; Holban, A. M.

Gamma-cyclodextrin/usnic acid thin film fabricated by MAPLE for improving the resistance of medical surfaces to Staphylococcus aureus colonization

Matrix Assisted Pulsed Laser Evaporation (MAPLE) as anti-adherent coating on medical surfaces

Applied Surface Science, 2015, In Press; DOI:10.1016/j.apsusc.2015.01.081

Lin, W.; Ma, G.; Ji, F.; Zhang, J.; Wang, L.; Sun, H.; Chen, S.

Biocompatible long-circulating star carboxybetsaine polymers

β-cyclodextrin initiator, Circulation half-life, Internalization, Biocompatibility, Drug delivery

Journal of Materials Chemistry B: Materials for Biology and Medicine, 2015, 3, 440-448; DOI: 10.1039/C4TB01477D
Ma, X.; Zhao, Y.
Biomedical applications of supramolecular systems based on host-guest interactions
  Calixarene, Cyclodextrin, Cucurbituril, Drug and gene delivery, Photodynamic therapy, Imaging, Review
Chemical Reviews (Washington, DC, United States), 2014, In Press; DOI: 10.1021/cr500392w

Ma, G-N.; Yu, F-L.; Wang, S.; Li, Z-P.; Xie, X-Y.; Mei, X-G.
A novel oral preparation of hydroxysafflor yellow a base on a chitosan complex: A strategy to enhance the oral bioavailability
  β-CD, Pharmaceutical excipients
AAPS PharmSciTech, 2015, In Press; DOI: 10.1208/s12249-014-0255-z

Nagai, N.; Yoshioka, C.; Mano, Y.; Tnabe, W.; Ito, Y.; Okamoto, N.; Shimomura, Y.
A nanoparticle formulation of disulfiram prolongs corneal residence time of the drug and reduces intraocular pressure
  HP-β-CD, Glaucoma, Eye drops, Drug delivery system
Experimental Eye Research, 2015, 132, 115-123; DOI:10.1016/j.exer.2015.01.022

Bioactive soy isoflavones: extraction and purification procedures, potential dermal use and nanotechnology-based delivery systems
  Topical systems, Anti-aging action, Estrogenic activity, Wound healing properties, Antiphotocarcinogenic effects
Phytochemistry Reviews, 2014, In Press; DOI: 10.1007/s11101-014-9382-0

Solid-state characterization of sertraline base–β-cyclodextrin inclusion complex
  NMR, Computational interpretation

Rassu, G.; Soddu, E.; Cossu, M.; Brundu, A.; Cerri, G.; Marchetti, N.; Ferraro, L.; Regan, R. F.; Giunchedi, P.; Gavini, E.; Dalpiaz, A.
Solid microparticles based on chitosan or methyl-β-cyclodextrin: A first formulative approach to increase the nose-to-brain transport of deferoxamine mesylate
  Cerebospinal fluid, System absolute bioavailabilities, Nasal formulations, Pharmacokinetic studies
Journal of Controlled Release, 2015, 201, 68-77; DOI:10.1016/j.jconrel.2015.01.025

Influence of the preparation method on the physicochemical properties of indomethacin and methyl-β-cyclodextrin complexes
  Method of preparation, Spray drying, Supercritical carbon dioxide
International Journal of Pharmaceutics, 2015, 479, 381-390; DOI:10.1016/j.ijpharm.2015.01.010
Simões, S. M. N.; Rey-Rico, A.; Concheiro, A.; Alvarez-Lorenzo, C.

**Supramolecular cyclodextrin-based drug nanocarriers**

*Grafting, Poly(pseudo)rotaxane-based networks, Zipper-like assemblies, Depot-like formations*


Sudha, N.; Sameena, Y.; Chandrasekaran, S.; Enoch, I. V. M. V.; Premnath, D.

**Alteration of the binding strength of dronedarone with bovine serum albumin by β-cyclodextrin: A spectroscopic study**

*Fluorescence quenching, Forster resonance transfer*


Tian, G.; Li, Y.; Yuan, Q.; Cheng, L.; Kuang, P.; Tang, P.

**The stability and degradation kinetics of Sulforaphene in microcapsules based on several biopolymers via spray drying**

*Hydroxypropyl-β-cyclodextrin*

Carbohydrate Polymers, 2015, 122, 5-10; DOI:10.1016/j.carbpol.2015.01.003


**Preparation of hydrophilic C_{60}(OH)_{10}/2-hydroxypropyl-β-cyclodextrin nanoparticles for the treatment of a liver injury induced by an overdose of acetaminophen**

*Prolonged survival rate of liver injured mice, Polyhydroxylated fullerene, Antioxidant*

Biomaterials, 2015, 45, 115-123; DOI:10.1016/j.biomaterials.2014.12.032

Wallin, K. G.; Wood, R. I.

**Anabolic–androgenic steroids impair set-shifting and reversal learning in male rats**

*Cognition, Operant behavior, Food reward, Testosterone*


Yang, C-H.; Ting, W-J.; Shen, C-Y.; Hsu, H-H.; Lin, Y-M.; Kuo, C-H.; Tsai, F-J.; Tsai, C-H.; Tsai, Y.; Huang, C-Y.

**Anti-apoptotic effect of San Huang Shel Shin Tang cyclodextrin complex (SHSSTc) on CCl₄-induced hepatotoxicity in rats**

*Liver protection effects, Serum cholesterol level suppression*


Zhang, D.; Wei, Y.; Chen, K.; Zhang, X.; Xu, X.; Shi, Q.; Han, S.; Chen, X.; Gong, H.; Li, X.; Zhang, J.

**Biocompatible reactive oxygen species (ROS)-responsive nanoparticles as superior drug delivery vehicles**

*ROS-triggerable β-cyclodextrin material, Nanomedicine, Tumor targeting*

Advanced healthcare materials, 2015, 4, 69-76; DOI:10.1002/adhm.201400299

Preparation, spectroscopy and molecular modelling studies of the inclusion complex of cordycepin with cyclodextrins

ESI-MS experiment
Carbohydrate Research, 2015, 406, 55-64; DOI:10.1016/j.carres.2015.01.005

4. CDs in Cell Biology

Bhamidimarri, S. P.; Lu, J.; Prajapati, J. D.; Uribarri, I. B.; van den Berg, B.; Kleinekathoefer, U.; Winterhalter, M.

Cyclodextrin interaction with specific channel CymA from K. Oxytoca
Biophysical Journal, 2015, 108, 442a -443a; DOI:10.1016/j.bpj.2014.11.2417


Rapid kinetics of β-cyclodextrin entering and exiting cells: Implication of its mechanism on reduction of cholesterol accumulation in Niemann–Pick disease type C cells
Molecular Genetics and Metabolism, 2015, 114, S35; DOI:10.1016/j.ymgme.2014.12.061

Neirynck, P.; Schimer, J.; Jonkheijm, P.; Milroy, L-G.; Cigler, P.;Brunsveld, L.

Carborane-β-cyclodextrin complexes as a supramolecular connector for bioactive surfaces

Cell adhesion and spreading properties, Supramolecular immobilization strategy
Journal of Materials Chemistry B: Materials for Biology and Medicine, 2015, 3, 539-545; DOI: 10.1039/C4TB01489H

Nicolas, V.; Liévin-Le Moal, V.

Antisecretory factor peptide AF-16 inhibits the secreted autotransporter toxin-stimulated transcellular and paracellular passages of fluid in cultured human enterocyte-like cells

Cultured cellular model of human intestinal epithelial barrier, Lipid rafts, Methyl-β-cyclodextrin
Infection and immunity, 2015, 83, 907-922; DOI:10.1128/IAI.02759-14

Ochi, R.; Gupte, S. A.

Pegylated cholesterol and methyl-Beta-cyclodextrin are modulators of L-type calcium channel current and decrease membrane capacitance in vascular smooth muscle cells


A novel trigger for cholesterol-dependent smooth muscle contraction mediated by the
sphingosylphosphorylcholine-Rho-kinase pathway in the rat basilar artery: a mechanistic role for lipid rafts

Depletion of cholesterol

Journal of Cerebral Blood Flow & Metabolism, 2015, In Press; DOI: 10.1038/jcbfm.2014.260


Intracisternal cyclodextrin ameliorates neurological dysfunction, increases survival time, and stops Purkinje cell death in feline Niemann–Pick type C1 disease

Molecular Genetics and Metabolism, 2015, 114, S122; DOI:10.1016/j.ymgme.2014.12.280


Vasopressin-induced mouse urethral contraction is modulated by caveolin-1

Cholesterol, Caveolae, Arginine-vasopressin (AVP), V1a receptor, Methyl-β-cyclodextrin

European Journal of Pharmacology, 2015, 750, 59-65; DOI:10.1016/j.ejphar.2015.01.029

5. CDs in Food, Cosmetics and Agrochemicals


Antifungal effect of essential oil components against Aspergillus niger when loaded into silica mesoporous supports

β-CD, Natural preservatives


Chun, J-Y.; Jo, Y-J.; Bjrapha, P.; Choi, M-J.; Min, S-G.

Antimicrobial effect of α- or β-cyclodextrin complexes with trans-cinnamaldehyde against Staphylococcus aureus and Escherichia coli

Particle sizes, Polydispersity index

Drying Technology, 2015, 33, 377-383; DOI:10.1080/07373937.2014.957388

Heghes, A.; Hadaruga, N. G.; Fulias, A-V.; Bandur, G. N.; Hadaruga, D. I.; Dehelean, C-A.

Capsicum annum extracts/β-cyclodextrin complexes - Thermal analyses-Karl Fischer water titration correlations and antioxidant activity

Capsaicin, "Strongly-retained" water molecules


Hymas, R. V.; Ho, N. F. H.; Higuchi, W. I.

Capric acid absorption in the presence of hydroxypropyl-β-cyclodextrin in the rat ileum using the in situ single-pass perfusion technique

Edited and produced by: CYCLOLAB – page: 15
Increase in the accessible area for absorption, Absorption enhancer, Bioavailability, Epithelial delivery/permeability, Passive diffusion/transport, Solubility


Ngemakwe, P. N.; Jideani, V.; Le Roes-Hill, M.

**Advances in gluten-free bread technology**

* Cyclodextinase, Viscoelasticity, Gluten-free products, Enzymes, Functional properties, Hydrocolloids

Food science and technology international, 2014, In Press, DOI:10.1177/1082013214531425

### 6. CDs for other Industrial Applications

Castro-Silva, C.; Ruiz-Valdiviezo, V. M.; Rivas-Rivera, S. G.; Sosa-Trinidad, A. R.; Luna-Guido, M.; Delgado-Balbuena, L.; Marsch, R.; Dendooven, L.

**Bioavailability and dissipation of anthracene from soil with different alkalinity and salinity**

* Extractability, Hydroxypropyl-β-cyclodextrin*

Journal of Environmental Biology, 2015, 36, 229-234

Das, D.; Varghese, L. R.; Das, N.

**Enhanced TDS removal using cyclodextrinated, sulfonated and aminated forms of bead–membrane duo nanobiocomposite via sophorolipid mediated complexation**

* CNTs, Chitosan, Gum Arabic, Total dissolved solids (TDS), Tap water*

Desalination, 2015, 360, 35-44; DOI:10.1016/j.desal.2015.01.011


**Strategies for controlled synthesis of nanoparticles derived from a group of uniform materials based on organic salts**

* Cyclodextrin-assisted syntheses, Ionic liquids, GUMBOS, NanoGUMBOS, Size-Control*

Journal of Colloid and Interface Science, 2015, 446, 163-169; DOI:10.1016/j.jcis.2015.01.023

Jurecska, L.; Dobosy, P.; Barkács, K.; Fenyvesi, É.; Záravv, G.

**Reprint of “Characterization of cyclodextrin containing nanofilters for removal of pharmaceutical residues”**

* Micro-pollutants, Nanofiltration, β-Cyclodextrin, Sorption, Ibuprofen*

Journal of Pharmaceutical and Biomedical Analysis, 2015, 106, 124-128; DOI:10.1016/j.jpba.2015.01.024

Mokashe, N.; Chaudhari, A.; Patil, U.;

**Optimal production and characterization of alkaline protease from newly isolated halotolerant *Jeotgalicoccus* sp.**

* Activity in the presence of rhamnolipid and cyclodextrin, Purification*

Biocatalysis and Agricultural Biotechnology, 2015, In Press; DOI:10.1016/j.bcab.2015.01.003
Qi, M.; Tan, P. Z.; Xue, F.; Malhi, H. S.; Zhang, Z-X.; Young, D. J.; Hor, T. S. A.

A supramolecular recyclable catalyst for aqueous Suzuki-Miyaura coupling

Palladium(II)-dipyrazole, Adamantyl moiety, β-CD, Heptakis(2,6-di-O-methyl)-β-CD

RSC Advances, 2015, 5, 3590-3596; DOI:10.1039/C4RA13953D

Ramanujam, K.; Sundrarajan, M.

Biocidal activities of monochlorotriazine-β-cyclodextrine with MgO modified cellulosic fabrics

Citric acid as cross linker, Kid's clothes, Sportswear, Staphylococcus, Escherichia, Candida


Romero-Zerón, L. B.; Kittisrisawai, S.

Evaluation of a surfactant carrier for the effective propagation and target release of surfactants within porous media during enhanced oil recovery. Part I: Dynamic adsorption study

Sand/kaolin blend, Surfactant delivery and carrier system, Surfactant adsorption inhibition, Surfactant/β-cyclodextrin complexations, EOR surfactant:β-cyclodextrin inclusion complexes

Fuel, 2015, 148, 238-245; DOI:10.1016/j.fuel.2015.01.034

Rostamnia, S.; Doustkhah, E.; Hassankhani, A.

Application of the β-cyclodextrin supramolecules as a green accelerator hosts in one-step preparation of highly functionalised rhodanine scaffolds

Catalyst, One-pot synthesis, Multicomponent reaction

Supramolecular Chemistry, 2015, 27, 1-3; DOI:10.1080/10610278.2014.890200

Thombal, R. S.; Jadhav, A. R.; Jadhav, V. H.

Biomass derived β-cyclodextrin-SO\textsubscript{3}H as a solid acid catalyst for esterification of carboxylic acids with alcohols

Esterification of various carboxylic acids and alcohols

RSC Advances, 2015, 5, 12981-12986; DOI:10.1039/C4RA16699J

Wang, S-X.; Chen, S.; Wei, Q.; Zhang, X.; Wong, S. Y.; Sun, S., Li, X.

Bioinspired synthesis of hierarchical porous graphitic carbon spheres with outstanding high-rate performance in lithium-ion batteries

Pluronic F127 micelle cluster induced self-assembly of α-cyclodextrin, Hydrothermal treatment, Pyrolysis, Graphitization

Chemistry of Materials, 2015, 27, 336-342; DOI:10.1021/cm504042s


Core-shell superparamagnetic Fe\textsubscript{3}O\textsubscript{4}@β-CD composites for host-guest adsorption of polychlorinated biphenyls (PCBs)

Scatchard equation, Density functional theory (DFT) calculations, Sol-gel

Journal of Colloid and Interface Science, 2015, 447, 1-7; DOI:10.1016/j.jcis.2015.01.061
7. CDs in Sensing and Analysis

Application of a C6-OH of chitosan immobilized cyclodextrin derivates on an electrochemical $\text{H}_2\text{O}_2$ biosensor

*Ferrocene, Crosslinking catalase*
Journal of Applied Polymer Science, 2015, 132, 41499; DOI:10.1002/app.41499

Chen, S.; Zhang, J.; Gan, N.; Hu, F.; Li, T.; Cao, Y.; Pan, D.
An on-site immunosensor for ractopamine based on a personal glucose meter and using magnetic $\beta$-cyclodextrin-coated nanoparticles for enrichment, and an invertase-labeled nanogold probe for signal amplification

*Sandwich immunoassay, Hydrolysis of sucrose to form glucose*
Microchimica Acta, 2015, 182, 815-822; DOI:10.1007/s00604-014-1392-5

A QCM immunosensor to rapidly detect ractopamine using bio-polymer conjugate and magnetic $\beta$-cyclodextrins

*Quartz crystal microbalance, Ractopamine, Immobilizing $\beta$-cyclodextrin on $\text{Fe}_3\text{O}_4$ nanoparticles*
Sensors and Actuators B: Chemical, 2015, 211, 523-530; DOI:10.1016/j.snb.2015.01.082

Gong, Z-S.; Duan, L-P.; Tang, A-N.
Amino-functionalized silica nanoparticles for improved enantiomeric separation in capillary electrophoresis using carboxymethyl-$\beta$-cyclodextrin (CM-$\beta$-CD) as a chiral selector

*Chiral selectivity, Racemates*

Li, X-J.; Wang, X-J.; Ji, Y-Z.
Applications of chemical factors in steroid bioconversion

*Review, Microbial enzymic bioconversion*
Advanced Materials Research (Durnten-Zurich, Switzerland), 2015, 1073-1076, 159-164; DOI:10.4028/www.scientific.net/AMR.1073-1076.159

The use of a sulfonated capillary on chiral capillary electrophoresis/mass spectrometry of amphetamine-type stimulants for methamphetamine impurity profiling

*Highly sulfated $\gamma$-cyclodextrin, chemically modified capillary*
Forensic Science International, 2015, 249, 59-65; DOI:10.1016/j.forsciint.2015.01.015
Müllerová, L.; Dubský, P.; Gaš, B.

**Generalized model of electromigration with 1:1 (analyte: selector) complexation stoichiometry: Part II. Application to dual systems and experimental verification**

6-monodeoxy-6-monoamino-β-cyclodextrin, model of electromigration, partly dissociated analyte

Journal of Chromatography A, 2015, 1384, 147-154; DOI:10.1016/j.chroma.2015.01.055


**An ultrafast molecular rotor based ternary complex in a nanocavity: a potential "turn on" fluorescence sensor for the hydrocarbon chain**

Benzothiazole, Thioflavin-T, γ-cyclodextrin

Physical Chemistry Chemical Physics, 2015, 17, 5691-5703; DOI:10.1039/c4cp04636f

Qi, Y.; Wang, X.; Chen, H.; Tang, J.; Yang, F.; He, P.

**A family of metallocyclodextrins: synthesis, absorption and luminescence characteristic studies based on host-guest recognition**

4-Dimethylamino-4’-carboxy-azobenzene, Methylene blue, β-cyclodextrin, Ruthenium bipyridine derivatives, Optical sensor

Supramolecular Chemistry, 2015, 27, 44-51; DOI:10.1080/10610278.2014.904867

Serio, N.; Chanthalyma, C.; Peters, S.; Levine, D.; Levine, M.

**2-Hydroxypropyl beta-cyclodextrin for the enhanced performance of dual function extraction and detection systems in complex oil environments**

Extraction of PAHs from oil samples, Fluorescent signal

Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2015, 81, 341-346; DOI:10.1007/s10847-014-0460-0

Shen, W-J.; Zhuo, Y.; Chai, Y.; Yang, Z-H.; Han, J.; Yuan, R.

**An enzyme-free electrochemical immunosensor based on host-guest nanonets catalyzing amplification for procalcitonin detection**

N,N-Bis (ferrocenoyl)-diaminoethane/β-cyclodextrins/polyamidoamine dendrimers-encapsulated Au nanoparticles, Synergetic catalysis

ACS Applied Materials & Interfaces, 2015, 7, 4127-4134; DOI:10.1021/am508137t


**Separating four diastereomeric pairs of dihydroflavonol glycosides from Engelhardia roxburghiana using high performance counter-current chromatography**

Two-phase solvent system, Hydroxypropyl-β-cyclodextrin, Dihydroflavonol glycosides

Journal of Chromatography A, 2015, 1383, 79-87; DOI:10.1016/j.chroma.2015.01.024

Singh, V.; Zhu, J.; Nand, A.; Cheng, Z.; Mo, Y.

**3D Small molecule microarray with enhanced sensitivity and immobilization capacity monitored by surface plasmon resonance imaging**

α-cyclodextrin as an alternative surface chemical, α-cyclodextrin photo-crosslinking surface, High throughput screening

RSC Advances, 2014, In Press; DOI:10.1039/C4RA07306A
A sensitive detection of T4 polynucleotide kinase activity based on β-cyclodextrin polymer enhanced fluorescence combined with an exonuclease reaction

Fluorescence of pyrene

Chemical Communications (Cambridge, United Kingdom), 2015, 51, 1815-1818; DOI:10.1039/C4CC08991J

Wang, L-Y.; Dong, L-Y.; Chen, L.; Fan, Y-B.; Wu, J.; Wang, X-F.; Xie, M-X.
A novel water-soluble quantum dot-neutral red fluorescence resonance energy transfer probe for the selective detection of megestrol acetate

Fluorescence resonance energy transfer (FRET) probe, Steroid hormones, Biosensor


Wang, L.; Dong, S.; Han, F.; Zhao, Y.; Zhang, X.; Zhang X.; Qiu, H.; Zhao, L.
Spherical β-cyclodextrin-silica hybrid materials for multifunctional chiral stationary phases

Mesoporous materials, Multiple chromatographic separation functions, Chiral resolution, Liquid chromatography

Journal of Chromatography A, 2015, 1383, 70-78; DOI:10.1016/j.chroma.2015.01.023

Xie, S.; Zhang, J.; Yuan, Y.; Chai, Y.; Yuan, R.
An electrochemical peptide cleavage-based biosensor for prostate specific antigen detection via host-guest interaction between ferrocene and β-cyclodextrin

Electrochemical signals

Chemical Communications (Cambridge, United Kingdom), 2015, 51, 3387-3390; DOI:10.1039/C4CC10363G

Xue, Q.; Liu, Z.; Guo, Y.; Guo, S.
Cyclodextrin functionalized graphene–gold nanoparticle hybrids with strong supramolecular capability for electrochemical thrombin aptasensor

Ferrocene, Electron transfer, Human serum albumin, Lysozyme, Insulin, Thio-β-cyclodextrin

Biosensors and Bioelectronics, 2015, 68, 429-436; DOI:10.1016/j.bios.2015.01.025

Yang, L.; Fan, S.; Deng, G.; Li, Y.; Ran, X.; Zhao, H.; Li, C-P.
Bridged β-cyclodextrin-functionalized MWCNT with Higher supramolecular recognition capability: The simultaneous electrochemical determination of three phenols

4-aminophenol, 4-chlorophenol, 4-nitrophenol, Tap-water, Sensor, Disulfides bridged β-cyclodextrin dimer

Biosensors and Bioelectronics, 2015, 68, 617-625; DOI:10.1016/j.bios.2015.01.059

Vortex-assisted magnetic β-cyclodextrin/attapulgite-linked ionic liquid dispersive liquid–liquid microextraction coupled with high-performance liquid chromatography
for the fast determination of four fungicides in water samples

**Magnetic solid-phase microextraction**

Journal of Chromatography A, 2015, 1381, 37-47; DOI:10.1016/j.chroma.2015.01.016

Zhang, T.; Zhao, H.; Quan, X.; Chen, S.

**An electrochemiluminescence sensing for DNA glycosylase assay with enhanced host-guest recognition technique based on α-cyclodextrin functionalized gold/silica cell-shell nanoparticles**

**Nanoparticle-modified electrode, High sensitivity**

Electrochimica Acta, 2015, 157, 54-61; DOI:10.1016/j.electacta.2015.01.075

Zhao, J.; Lu, X.; Wang, Y.; Lv, J.

**’Click’ preparation of a novel ‘native-phenylcarbamoylated’ bilayer cyclodextrin stationary phase for enhanced chiral differentiation**

**Immobilized onto silica surface, Multiple interaction sites, Enantiorecognition, Reversed phase high performance liquid chromatography (RP-HPLC)**

Journal of Chromatography A, 2015, 1381, 253-259; DOI:10.1016/j.chroma.2015.01.008

Zor, Erhan and Bingol, Haluk and Ramanaviciene, Almira and Ramanavicius, Arunas and Ersoz, Mustafa.

**An electrochemical and computational study for discrimination of D- and L-cystine by reduced graphene oxide/β-cyclodextrin**

**Biosensor, Modified electrode**

Analyst (Cambridge, United Kingdom), 2015, 140, 313-321; DOI: 10.1039/C4AN01751J