CYCLODEXTRIN NEWS
VOLUME 30. No. 5. MAY 2016 ISSN 0951-256X

Cyclodextrin for Prevention and Treatment of Atherosclerosis

Zimmer *et al.* have just published their comprehensive study on the antiatherosclerotic and anti-inflammatory effects of HPBCD [1]. Their paper is the result of 20 research groups applying the most sophisticated methods. It triggered us to review the literature of the field.

As early as in 1992 Pitha *et al.* have already observed that repeated administration of HPBCD to rabbits led to a gradual increase in total cholesterol in circulation and in urine and eventually to a slight relief of atherosclerotic lesions in the thoracic aorta [2]. Based on the effect on the cellular cholesterol efflux in three cell lines Kilsdonk *et al.* proposed in 1995 to use HPBCD as potential pharmacological agent that could modify *in vivo* cholesterol metabolism and influence the development of the atherosclerotic plaque [3]. As 7-ketocholesterol plays an important role in the atherogenesis and HPBCD enhances the removal of this oxysterol, HPBCD was suggested to be applied as potential oxysterol removing agent for preventing atherosclerosis [4]. HPBCD was found to be a cholesterol shuttle enhancing bidirectional efflux of cholesterol between cells and lipoproteins in serum which phenomenon was thought to be useful in treating unstable atherosclerotic plaques [5].

Dass and Jessup wrote a review in 2000 with the title "Apolipoprotein A-I, cyclodextrins and liposomes as potential drugs for the reversal of atherosclerosis. A review" [6]. Both Apolipoprotein A-I (apoA-I, the major protein of high density lipoproteins, HDL) and HPBCD remove cholesterol from membranes of various cells with a similar biphasic mechanism suggesting the presence of two kinetic pools of unesterified cholesterol. Cholesterol is removed first in a rapid efflux phase in a few minutes then in the second phase a slower efflux is observed after the fast pool is refilled with cholesterol. The first phase is significantly shorter with CDs than with apoA-I but the second phase is of similar rate. The mass of effluxed cholesterol is much higher with HPBCD than with apoA-I. On the other hand, apoA-I stimulates the hydrolysis of cholesteryl esters within foam cells, what HPBCD cannot do. Dass and Jessup suggested a combination of apoA-I and cyclodextrins to enhance cholesterol desorption into the bloodstream and stimulate reverse cholesterol transport in atherosclerotic-prone patients.

The cholesterol/sphingomyelin-enriched rafts in the membrane of cells and cell organelles seem serve as signaling platforms involved in many biological processes. Modulation of

cholesterol level might be used in the treatment of raft-related diseases such as atherosclerosis [7]. According to Irie & Uekama not only cholesterol but also phosphatidylcholine and sphingomyelin are removed by CDs [8]. Loosening the membrane structure in this way, some proteins anchored by lipids are also released.

Atherosclerosis is a chronic disease triggered by lipid disturbances, endothelial injury and sustained by inflammation. CD treatment inhibited the activation of proinflammatory cytokines such as interleukin-1 beta (IL-1β), the major cytokine linking inflammation and angiogenesis in pathological vascular processes, such as atherosclerosis [9]. Changes in cholesterol level (reduction with methyl BCDs or increase by cholesterol/methyl BCD complex) can modulate interleukin-8 (IL-8) synthesis in endothelial cells [10].

Decreasing the membrane cholesterol content by CDs and disrupting caveolae in intact rat arteries results in changed signaling steps, e.g. the localization of TRPC-1 (Transient receptor potential channel 1, an ion channel protein) and the vascular reactivity of Endothelin-1 (peptide constricting blood vessels and raising blood pressure) [11] and influx of Ca^{2+} [12]. Similarly, the p38 mitogen-activated protein kinase (MAPK), a stress-activated protein kinase potentially participating in the development of atherosclerosis can be activated [13] and the transforming growth factor (TGF-beta)-induced signaling can be facilitated [14].

Niemann-Pick type C1 (NPC1), an integral membrane protein on the limiting membrane of late endosome/lysosome (LE/LY), is known to accept cholesterol from NPC2 and then mediate cholesterol transport from LE/LY to endoplasmic reticulum and plasma membrane. Its role in regulating intracellular cholesterol trafficking and atherosclerosis has been recently reviewed [15]. HPBCD has been approved by both the US FDA and European Medicinal Agency (EMA) for the treatment of NPC1-deficient patients. HPBCD acts as a cholesterol shuttle enhancing the cholesterol esterification, suppressing the cholesterol synthesis, increased the expression of liver X receptor (LXR) genes, stimulates the cholesterol transport from LE/LY [16].

It was shown that methyl BCD can cause lipid depletion of LDL and impairs LDL susceptibility to oxidation, an effect inhibiting atherogenesis [17]. *In vitro* studies showed that treatment with CRYSMEB can block atheroprogression by reducing atherosclerotic plaque size via improving triglyceride serum levels and T helper cells (Th1)-mediated response in Apoe $^{(-/-)}$ mice on high-cholesterol diet [18].

Hyperlipidemic mice treated with HPBCD demonstrated a shift in intracellular distribution of cholesterol towards cytoplasmic cholesteryl ester storage and a decrease in cholesterol crystallization inside Kupfer cells suggesting that HPBCD could be a useful tool to improve intracellular cholesterol levels in the context of the metabolic syndrome, such as atherosclerosis and non-alcoholic fatty liver disease (NAFLD) [19].

In vitro studies demonstrated the potential benefits of HPBCD treatment in peripheral artery disease (PAD). This disease is caused by atherosclerosis and results in progressive narrowing

and occlusion of the peripheral arteries thus inhibits blood flow to the lower extremities [20].

The comprehensive study of Zimmer *et al.* recently published in *Science of Translational Medicine* ascertened that HPBCD treatment not only impairs the atherogenesis but also mediates the regression of the existing atherosclerotic plaques [1]. The atherosclerotic lesions with aortic roots were profoundly reduced in apolipoprotein E ($ApoE^{-/-}$) deficient mice and the amount of crystalline cholesterol (CC) was decreased in atherosclerotic plaques. The treatment did not influence weight gain, blood pressure and heart rate. Interestingly there was no change in plasma concentration of cholestanol and cholesterol precursors showing that treatment had no impact on the endogenous biosynthesis. On the other hand, the secretion of proinflammatory cytokines as well as the production of reactive oxygen species was reduced suggesting anti-inflammatory effect of HPBCD.

Several *in vitro* tests were performed to clarify the mechanism. Rhodamine-labeled HPBCD was found to be bound to the cholesterol crystals and started to dissolve them. As macrophages rapidly internalized the fluorescent CD derivative the dissolution of both intra- and extracellular CC was demonstrated by confocal microscopy. The mechanism of the metabolism of CC derived from D_6-cholesterol after HPBCD treatment was studied by GC-MS. The analysis evidenced that the treatment promoted both the esterification and oxidation of cholesterol resulting in cholesteryl esters and oxysterols, which are water soluble and not cytotoxic. Gene set enrichment analysis showed that the genes involved in driving cholesterol efflux (LXR genes) were enriched upon HPBCD treatment.

Ex vivo experiments on human atherosclerotic plaques derived from biopsy specimens obtained from carotid endarterectomies showed similar effects of HPBCD to those obtained in murine: HPBCD helped the transfer of cholesterol from plaques to supernatants. The oxysterol production was increased and the genes involved in lipid transport, storage, metabolism and efflux were up-regulated. The urinary cholesterol excretion was studied by monitoring NPC patients receiving HPBCD treatment. Enhanced cholesterol concentration was measured in the urine of these patients in a time-dependent manner showing that in addition to changing the cholesterol metabolism HPBCD can also directly extract and transport cholesterol for excretion.

The authors conclude that HPBCD exerts its potent effect mainly by reprogramming the cells in atherosclerotic plaques. By enhancing cholesterol solubility, LXR activity becomes higher and as a consequence the cholesterol efflux is increased restoring the cholesterol and immune homeostasis. Unlike to HDL HPBCD can also mobilize cholesterol for direct excretion into urine and feces.

The authors are optimistic as HPBCD is a drug (it has received the orphan drug status against NPC disease). Its development for a new indication after the necessary clinical trials might be a less rocky road.

References

1. Zimmer, S.; Grebe, A.; Bakke, S. S.; Bode, N.; Halvorsen, B.; Ulas, T.; Skjelland, M.; De Nardo, D.; Labzin, L. I.; Kerksiek, A.; Hempel, C.; Heneka, M. T.; Hawxhurst, V.; Fitzgerald, M. L.; Trebicka, J.; Björkhem, I.; Gustafsson, J.-Å.; Westerterp, M.; Tall, A. R.; Wright, S.D.; Espevik, T.; Schultze, J. L.; Nickenig, G.; Lütjohann D. and Latz, E.: Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming. Sci. Transl. Med. (2016), 8, 333-350

2. Irie, T.; Fukunaga, K.; Garwood, M. K.; Carpenter, T. O.; Pitha, J.: Hydroxypropyl cyclodextrins in parenteral use. II: Effects on transport and disposition of lipids in rabbit and humans. J. Pharm. Sci., (1992), 81(6), 524-528

3. Kilsdonk, E. P. C.; Yancey, P. G.; Stoudt, G. W.; Bangerter, F. W.; Johnson, W. J.; Phillips, M. C.; Rothblat, G. H.: Cellular cholesterol efflux mediated by cyclodextrins. J. Biol. Chem. (1995), 270(29), 17250-17256

4. Kritharides, L.; Kus, M.; Brown, A. J.; Jessup, W.; Dean, R. T.: Hydroxypropyl-β-cyclodextrin-mediated efflux of 7-ketocholesterol from macrophage foam cells. J. Biol. Chem. (1996), 271(44), 27450-27455

5. Atger, V. M.; de la Llera Moya, M.; Stoudt, G. W.; Rodrigueza, W. V.; Phillips, M. C.; Rothblat, G. H.: Cyclodextrins as catalysts for the removal of cholesterol from macrophage foam cells. J. Clin. Invest. (1997), 99(4), 773-780

6. Dass, C. R.; Jessup, W.: Apolipoprotein A-I, cyclodextrins and liposomes as potential drugs for the reversal of atherosclerosis. A review. J. Pharm. Pharmacol. (2000), 52(7), 731-761

7. Barenholz, Y.: Chapter 5 - Sphingomyelin and cholesterol: From membrane biophysics and rafts to potential medical applications. In: Subcellular Biochemistry; Kluwer Academic/Plenum Publishers (2004), Vol. 37(Membrane Dynamics and Domains), pp. 167- 215

8. Irie, T.; Uekama, K.: Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J. Pharm. Sci. (1997), 86(2), 147-162

9. Jagielska, J.; Kapopara, P. R.; Salguero, G.; Scherr, M.; Schutt, H.; Grote, K.; Schieffer, B.; Bavendiek, U.: Interleukin-1 beta assembles a proangiogenic signaling module consisting of caveolin-1, tumor necrosis factor receptor-associated factor 6, p38-mitogen-activated protein kinase (MAPK), and MAPK-activated protein kinase 2 in endothelial cells. Arterioscler. Thromb. Vasc. Biol. (2012), 32(5), 1280-1288

10. Yeh, M.; Cole, A. L.; Choi, J.; Liu, Y.; Tulchinsky, D.; Qiao, J.-H.; Fishbein, M. C.; Dooley, A. N.; Hovnanian, T.; Mouilleseaux, K.; Vora, D. K.; Yang, W.-P.; Gargalovic, P.; Kirchgessner, T.; Shyy, Y.-J., Berliner, J. A.: Role for sterol regulatory element-binding protein in activation of endothelial cells by phospholipid oxidation products. Circ. Res. (2004), 95(8), 780-788

11. Bergdahl, A.; Gomez, M. F.; Dreja, K.; Xu, S.-Z.; Adner, M.; Beech, D. J.; Broman, J.; Hellstrand, P.; Swaerd, K.: Cholesterol depletion impairs vascular reactivity to endothelin-1 by reducing store-operated Ca^{2+} entry dependent on TRPC1. Circ. Res. (2003), 93(9), 839-847

12. Shiraishi, M.; Tani, E.; Miyamoto, A.: Modulation of rabbit platelet aggregation and calcium mobilization by platelet cholesterol content. J. Vet. Med. Sci. (2010), 72(3), 285-292

13. Dobreva, I.; Zschornig, O.; Waeber, G.; James, R. W.; Widmann, C.: Cholesterol is the major component of native lipoproteins activating the p38 mitogen-activated protein kinases. Biol. Chem. (2005), 386(9), 909-918

14. Chen, C.-L.; Liu, I.-H.; Fliesler, S. J.; Han, X.; Huang, S. S.; Huang, J. S.: Cholesterol suppresses cellular TGF-beta-responsiveness: Implications in atherogenesis. J. Cell Sci. (2007), 120(20), 3509-3621

15. Yu, X.-H.; Jiang, N.; Yao, P.-B.; Zheng, X.-L.; Cayabyab, F. S.; Tang, C.-K.: NPC1, intracellular cholesterol trafficking and atherosclerosis. Clin. Chim. Acta (2014), 429, 69-75

16. Liu, B.: Therapeutic potential of cyclodextrins in the treatment of Niemann Pick type C disease. Clin. Lipidol. (2012), 7, 289-301

17. Ao, M.; Gan, C.; Shao, W.; Zhou, X.; Chen, Y.: Effects of cyclodextrins on the structure of LDL and its susceptibility to copper-induced oxidation. Eur. J. Pharm. Sci., published online (2015)

18. Montecucco, F.; Lenglet, S.; Carbone, F.; Boero, S.; Pelli, G.; Burger, F.; Roth, A.; Bertolotto, M.; Nencioni, A.; Cea, M.; Dallegri, F.; Fraga-Silva, R. A.; Fougère, L.; Elfakir, C.; Gassner, A.-L.; Rudaz, S.; Parissaux, X.; Wils, D.; Salomé, M.; Vuilleumier, N.; Poggi, A.; Mach, F.: Treatment with KLEPTOSE® CRYSMEB reduces mouse atherogenesis by impacting on lipid profile and Th1 lymphocyte response. Vasc. Pharmacol. (2015), 72, 197-208

19. Walenbergh, S. M. A.; Houben, T.; Hendrikx, T.; Jeurissen, M. L. J.; van Gorp, P. J.; Vaes, N.; Damink, S. W. M. O.; Verheyen, F.; Koek, G. H.; Lütjohann, D.; Grebe, A.; Latz, E.; Shiri-Sverdlov, R.: Weekly treatment of 2-hydroxypropyl-β-cyclodextrin improves intracellular cholesterol levels in LDL receptor knockout mice. Intern. J. Mol. Sci. (2015), 16, 21056-21069

20. Qi, X.; Yuan, Y.; Xu, K.; Zhong, H.; Zhang, Z.; Zhai, H.; Guan, G.; Yu, G.: (2-Hydroxypropyl)-β-cyclodextrin is a new angiogenic molecule for therapeutic angiogenesis. PLoS ONE (2015), 10, e0125323

Éva Fenyvesi

CycloLab Cyclodextrin R&D Laboratory, Ltd.

Budapest, HUNGARY

BIBLIOGRAPHY & KEYWORDS

1. CDs: Derivatives, Production, Enzymes, Toxicity

Champagne, P.-L.; Ester, D.; Williams, V.; Ling, C.-C.

Synthesis and mesogenic properties of a novel family of amphiphilic cyclodextrins

Pre-2,3-O-propargylated intermediate, Perfunctionalization at the secondary face with azidoPEG groups

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 120

García-Fandiño, R.; Piñeiro, C.; Rosende, R.; Mixcoha, E.; Piñeiro, Á.

Fantastic voyage to the world of the cyclodextrins: Computational MD simulations and VR technologies to see how they move and interact from inside

Molecular Dynamics simulations, Virtual Reality visualization technologies, Aggregation, Encapsulation, Adsorption, Cyclolib (http://mduse.com/es/products/cyclo-lib/)

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 131

Ito, S.; Kida, T.

Synthesis and inclusion ability of cyclodextrin cage dimers in nonpolar solvents

Heptakis(6-O-tert-butyldimethylsilyl)-BCD, Connected with seven m- or p-xylylene linkers, Inclusion complexes with phenol and aniline in cyclohexane

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 140

Malanga, M.; Benkovics, G.; Darcsi, A.; Béni, S.; Szemán, J.; Szente, L.

Syntheses of 6-monosubstituted HPβCDs

Key intermediates 6-monoazido-, 6-monoamino- and 6-monocarboxymethyl-HPβCD were reacted with propargyl α-D-mannopyranoside, fluorescein isothiocyanate and L-glutamic acid

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 153

Sonnendecker, C.; Zimmermann, W.

Engineering of cyclodextrin glucanotransferases for the specific production of gamma-cyclodextrin in high yields

CGTases, Highly specific gamma-CD-producing variants, Large ring CDs

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 172

Strattan, C. R.

Why are cyclodextrins so unloved?

GRAS, Activities or excipients

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 107

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

Champagne, P.-L.; Ling, C.-C.; Ester, D.; Williams, V.

Novel smectic a mesophases driven by first family of β-cyclodextrin liquid crystals promoted by dipole-dipole interactions

14 Oligoethylene glycol moieties, 7 Octadecylthio groups at the primary face, Self-assembly

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 119

García-Fandiño, R.; Volkov, N. A.; Calvelo, M.; Rosende, R.; Piñeiro, Á.

How to distinguish the quality of computational molecular dynamics simulations of cyclodextrins, are they reliable?

Simulation of the behaviour of CD complexes

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 133

Guo, K.; Chen, J.; Li, B.-J.; Zhang, S.

Supramolecular conductive materials with self-healing properties

Crosslinking poly (2-hydroxyethyl methacrylate), Nanotubes

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 135

Hilschmann, J.; Kali, G.; Wenz, G.

Synthesis of hydrophilic polyisoprene polyrotaxanes by radical polymerization

Rotaxa-polymerization, Non-ionic stopper poly(ethylene glycol) methylether methacrylate, Randomly methylated β-CD, Water soluble polyrotaxanes

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 138

Kato, K.; Ito, K.

Dynamics of polyrotaxane glass

Slide-ring gels, Phase separation, Unmoldable, Interlocked structures, PEG, Methoxyethylation, Relaxation

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 142

Kida, T.; Teragaki, A.; Akashi, M.

Organogel formation through the self-assembly of α-cyclodextrin nanostructures

Hexagonal nanostructures, PCB binding from oil, 1,1,1,3,3,3-Hexafluoro-isopropanol (HFIP)

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 143

Liang, X.; Wang, L.; Li, B.-J.; Zhang, S.

TiO_2-based coatings with self-healing capacity

β-CD, Adamantane derivative (guest) which has vinyl at the terminal, Vinyl-TiO_2,

Polymerized into P (2-Hydroxyethyl methacrylate/butyl acrylate)

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 147

Nakahata, M.; Takashima, Y.; Harada, A.

Highly flexible, tough, and self-healable supramolecular polymeric materials using host–guest interaction

Terpolymerization of acrylamide (AAm) carrying βCD, AAm carrying adamantane, Self-healable coating film

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 160

Piñeiro, Á.; Garrido, P. F.; García, E.; Rial, J.; Pérez, D.; Sabín, J.; Muñoz, E.

Squeezing information from isothermal titration calorimetry measurements of cyclodextrin-based systems

Multitemperature analysis, Competitive binding or/and higher order complexes, Freeware software AFFINImeter, Species distribution as a function of the concentration, Kinetic information

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 165

Puskás, I.; Szente, L.

Highly ordered architectures built from cyclodextrin complexes

Supra-colloidal structures, Stimuli-responsible characteristics, Gamma-cyclodextrin, Hyaluronic acid, Amiodarone, Bovine serum albumin

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 167

Schibilla, F.; Voskuhl, J.; Fokina, N. A.; Schreiner, P. R.; Ravoo, B. J.

Host-guest complexes of cyclodextrins and nanodiamonds as strong binding motif for self assembled nanomaterials

β-CD, Adamantane, Supramolecular hydrogel, Lectin ConA

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 169

Takahashi, K.; Watanabe, T.; Morimoto, S.; Narusawa, T.

Molecular peeling from the colloidal congo red aggregate with β-cyclodextrin forming asymmetric pseud[2]rotaxane

π-π Stacking interactions, Temperature

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 173

Takashima, Y.; Harada, A.

Stimuli responsive supramolecular materials formed from cyclodextrin and guest molecules on polymers

Azobenzene, Photosesponsive supramolecular hydrogel, UV or Vis light irradiation, Adamantane, Ferrocene, Self-healing, Redox-responsive actuation

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 174

Tate, J. L.

Pulse drying of cyclodextrin complexes for commercial applications

Atomization, Processing solutions and pastes, Energy efficiency, Lost efficiency

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 105

Wang, B.; Bols, M.

C-H activation using artificial metalloenzymes based on cyclodextrins

Carboxylate-cyclodextrins, Cumene, Selectivity

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 180

Wenz, G.

Cyclodextrin polyrotaxanes - From design to application

Polycationic CD, DNA delivery, si-RNA delivery, Polyethyleneimine, Protein delivery, Luciferase, Sequential threading

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 182

Yildiz, Z. I.; Celebioglu, A.; Uyar, T.

Electrospinning of polymer free nanofiber by cyclodextrin inclusion complexes of menthol: Their formation, characterization and enhanced properties

Self-assembly, Self-aggregation, Antimicrobal, Anticancer, Anti-inflammatory activities, HPBCD, HPGCD, Common additive in food and pharmaceutical industry, Polymer free IC nanofibers, Antioxidant and antibacterial properties

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 183

Zhang, P.; Wang, A.; Dune, L. E.; Klassen, J.; Ling, C.-C.

The inclusion properties of a class of polyanionic cyclodextrins

Polysulfates, Polycarbonates

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 149

3. CDs in Drug Formulation

Arima, H.; Hirotsu, T.; Higashi, T.; Hashim, I. I. A.; Motoyama, K.; Wada, K.

Design and evaluation of self-assembly pegylation retaining activity of protein drugs based on supramolecular complexation with cyclodextrins

Self-assembly PEGylation retaining the activity, Adamantane, Adamanane-insulin conjugate, Adamantane-lysozyme conjugate, PEG-beta-CD, Thermal stability, Enzymatic stability, Flat blood glucose profile

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 111

Aytaca, Z.; Yildiza, Z. I.; Kayaci-Senirmaka, F.; Keskinc, N. O. S.; Tekinayd, T.; Uyara, T.

Electrospinning of polymer-free cyclodextrin/geraniol-inclusion complex nanofibers: Enhanced shelf-life of geraniol with antibacterial and antioxidant properties

Polymer-free nanofibers, Slow release of geraniol, Uniform and bead-free morphology, HPBCD, MBCD, HPGCD

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 113

Botros, Y. Y.; Limketkai, B.; Stoddart, J. F.

Cyclodextrin-based metal-organic frameworks as nano-carriers for pharmaceutical and cosmetic applications

CD-MOFs, Self-assembly, Ibuprofen, Busulfan, Naproxen, Volatile essential oils, Non-volatile cosmeceuticals, Lemon essential oil

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 117

Di Donato, C.; D'Abrosca, G.; Isernia, C.; Lavorgna, M.; Malgieri, G.; Russo, C.; Russo, L.; Iacovino, R.

Inclusion complexes between 5-fluorouracil with different cyclodextrins: Characterization and cytotoxic activity evaluation

α-CD, β-CD, HPβ-CD, Chemoterapeutic agent, Kneading method, MTT-assay on MCF-7 breast cancer cell line, Hep G2 hepatocyte carcinoma cell line and A549 alveolar basal epithelial carcinoma cell line

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 122

Ishida, Y.; Kaul, S. C.; Wadhwa, R.; Terao, K.

Enhancement of anti-cancer activity of caffeic acid phenethyl ester by complexation with gamma-cyclodextrin

New Zealand propolis, Human cancer cells, Cytotoxicity, Suppressed in vivo tumor progression and metastasis of an aggressive fibrosarcoma in mice

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 139

Jullian, C.; Cifuentes, T.; Cayupi, J.; Puyol, S.; Faundez, E.; Abarca, B.; Celis-Barros, C.; Zapata-Torres, G.

2,6 Dimethyl-β-cyclodextrin assisted solubilization of [1,2,3]triazolo[1,5-a]pyridine derivatives in aqueous medium. A DNA-interaction study

Antibiotic, Antineoplastic, Anti-HIV15, Antifungal, Antileishmanial agents

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 141

Kitagshi, H.; Nakagami, A.; Kano, K.

Oligoarginine-conjugated cyclodextrin as a cell-penetrating host molecule

HeLa cells, Cellular uptake, Photo-induced cytotoxicity, TRIMEB, Click chemistry

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 144

Leão, I. C.; Spilere, C. I.; Petrechko, O.; Hildreth, J. E. K.

Antiviral synergy between 2-hydroxypropyl-β-cyclodextrin and FDA-approved anti-HIV drugs

Cholesterol depleting effects, Synergism with many of the nucleoside/nucleotide analogs tested, Tenofovir

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 145

Loftsson, T.

γ-Cyclodextrin nanoparticles for topical drug delivery to the eye

Bioavailability, Phase II studies, Non-invasive treatment, HPGCD, SBEGCD, Metabolized by porcine pancreatic amylase, Dorzolamide

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 53

Murthy, N.; Maurya, A.; Shivakumar, H. N.

Finite dose administration of testosterone gel: Enhanced dermal delivery of drug due to captisol complexation

Rats, Amount of testosterone in the skin, Hydrogel formulation, Rendering skin more permeable to steroidal drug

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 157

Murthy, S. N.; Juluri, A.; Shankar, V.

Complexation with Captisol® as an approach to enhance the bioavailability of therapeutic agents

Iontophoresis mediated transdermal transport of lipophilic drugs, Silymarin, Permeation enhancer, Propofol, Ibuprofen

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 156

Murthy, S. N.; Juluri, A.; Manda, P.; Shivakumar, H. N.

Transdermal delivery of Captisol enabled propofol: Plasma and brain pharmacokinetics

Ability of iontophoresis to deliver propofol in the form of Captisol® complex via transdermal route

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 159

Murthy, S. N.; Shankar, V. K.

Oral bioavailability enhancement of silymarin constituents by Captisol® complexation

Permeability, Oral bioavailability, Phase solubility

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 158

Ohyama, A.; Otosu, Y.; Higashi, T.; Motoyama, K.; Arima, H.

Cancer treatment utilizing tumor-targeting nucleic acid drugs delivery by folate-PEG-appended dendrimer (G4) conjugate with α-cyclodextrin

Fol-PaC (G4) with higher generation, Polo-like kinase 1 (siPLK1) and miR-125a, Systemic tumor-targeting nucleic acid drugs carrier in vitro and in vivo

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 163

Sohajda, T.; Tuza, K.; Fábián, Á.; Fülesdi, B.; Tassonyi, E.; Szente, L.

Designing Sugammadex follow-ups as artificial receptors for the reversal of neuromuscular blockade

Carboxymethyl-γ-cyclodextrin, Sulfobutylether-γ-cyclodextrin, Randomly substituted CD derivatives

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 170

Song, B.; Puskás, I.; Szente, L.; Hildreth, J. E. K.

Supramolecular assembly of cyclodextrin, polylysine, and hyaluronic acid as a novel

delivery system for HIV drugs

Poly-L-lysine, Hyaluronic acid, SBECD, Zidovudine, Lamivudine, Sustained drug release

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 171

Trotta, F.; Cavalli, R.; Femminò, S.; Angotti, C.; Caldera, F.; Penna, C.

Reduction of cellular mortality after hypoxia/reoxygenation protocol by using a oxygen delivered by α-cyclodextrin or α-cyclodextrin based polymers

Oxygen loaded nanosponges, Cellular line of cardiomyoblast, Reduction of cellular mortality

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 176

Zhang, H.-Y.; Chen, L.-X.; Liu, Y.

Bridged bis(β-cyclodextrin)s-based polysaccharide nanoparticle for controlled paclitaxel delivery

Dual-stimulus drug delivery system, Adamantane-grafted hyaluronic acid, Disulfide-containing bridged bis(β-cyclodextrin)s, Redox-active disulfide bonds

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 184

Zhang, P.; Wang, A.; Dune, L. E.; Klassen, J.; Ling, C.-C.

Synthesis and inclusion properties of polyionic cyclodextrin derivatives

Needs for structually well-defined excipients, SulfoPEG thioether CDs (sugammadex analog), Polysulfonates, Polycarbonates, PEG to improve biocompatibility, Self-inclusion with ACD derivative, Maximum tolerated dose study, 100 g scale no chromatography

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 148

4. CDs in Cell Biology

Chen, Y.; Shi, R.-J.; Liu, Y.

Cyclodextrin-based polycationic supramolecular amphiphilic assembly as gene delivery vector

Polycationic supramolecular amphiphilic assembly, Methylimidazoliumyl arms, Hepta-imidazoliumyl-BCD

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 121

Maeda, Y.; Motoyama, K.; Higashi, T.; Horikoshi, Y.; Takeo, T.; Nakagata, N.; Kurauchi, Y.; Katsuki, H.; Kondo, Y.; Ishitsuka, Y.; Irie, T.; Era, T.; Arima, H.

Effects of methylated cyclodextrins on GM1-ganglioside level in both fibroblasts derived from a GM1-gangliosidosis patient and brains of GM1-gangliosidosis model mice

Excessive accumulation of GM1-ganglioside, Deficiency of β-galactosidase, DM-α-CD, M-β-CD, Lowered GM1-ganglioside levels in endolysosomes of EA1 cells, Intraventricular administration of DM-α-CD, GM1-gangliosidosis model mice.

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 152

Mohammed, A. F. A.; Ohyama, A.; Higashi, T.; Motoyama, K.; Arima, H.

Evaluation of polyamidoamine dendrimer (G3) conjugates with glucuronylglucosyl-β-cyclodextrin as siRNA carriers

KB cells, Human HeLa cell line, Cellular uptake, Folate-appended GUG-beta-CDE

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 155

Negi, S.; Ogasawara, T.; Iede, H.; Nakayama, C.; Kawamura, N.; Kitagishi, H.; Kano, K.; Sugiura, Y.

Reversible control of DNA binding of GAL4 transcription factor by a cyclodextrin-porphyrin supramolecular complex

Per-O-methylated β-cyclodextrin, GAL4 zinc finger protection, Transpeptidation reaction

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 162

5. CDs in Food, Cosmetics and Agrochemicals

Aytac, Z.; Keskin, N. O. S.; Kusku, S. I.; Tekinay, T.; Durgun, E.; Uyar, T.

Efficient encapsulation of active agents in electrospun polymeric nanofibers by cyclodextrin inclusion complexation

Electrospun polymeric nanofibers incorporating CD-ICs with thymol, α-tocopherol, and quercetin, Controlled release, Antibacterial/antioxidant properties, Food packaging

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 112

Azzi, J.; Auezova, L.; Danjou, P.-E.; Greige-Gerges, H.; Fourmentin, S.

Encapsulation of nerolidol, an antimicrobial sesquiterpene, in cyclodextrins, liposomes and nerolidol-in-cyclodextrin-in-liposomes

Food-flavouring, α-CD, β-CD, γ-CD, HP-β-CD, RAMEB, CRYSMEB, SBE-β-CD, Encapsulation efficiency

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 127

Furune, T.; Ikuta, N.; Okamoto, H.; Ishida, Y.; Nakata, D.; Yoshikawa, Y.; Terao, K.; Sakamoto, N.

A study on the inhibitory mechanism of triglyceride absorptionby α-cyclodextrin administration

Decreasing effects of αCD on the solubility, Effect of αCD on the solubility of fatty acids in the small intestinal fluid

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 130

Kfoury, M.; Auezova, L.; Greige-Gerges, H.; Larsen, K. L.; Fourmentin, S.

Investigation of the release kinetics of trans-anethole from β-cyclodextrin inclusion complexes by mutliple headspace extraction

Freeze-drying, Coprecipitation, Zero order swelling-controlled release

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 128

Kfoury, M.; Pipkin, J.; Antle, V.; Fourmentin, S.

Captisol®: An efficient encapsulant and solubilizing agent for essential oils and their components

Sulfobutylether-γ-CD, Sulfobutylether-β-CD, Static headspace-gas chromatography, Total organic carbon, Phase solubility diagrams, Tee tree oil, Mandarin oil

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 126

Trotta, F.; Cavalli, R.; Dianzani, C.; Barrera, G.; Argenziano, M.; Pizzimenti, S.; Caldera, F.

A new strategy based on GSH-responsive nanosponges for enhancing doxorubicin intracellular efficacy: An *in vitro* and *in vivo* evaluation

Glutathione-responsive cyclodextrin nanosponges, Disulfide bridges, Cancer cells, One-step synthesis, Hydroxyethyl disulfide, Nanoparticles, No burst effect, Retarded release, Pyromellitic anhydride

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 175

Uekaji, Y.; Onishi, M.; Nakata, D.; Yoshii, H.; Terao, K.

Reduction of coenzyme Q10 via micelle formation by using complexation with γ-cyclodextrin

Oxidized form (ubiquinone), Reduced form (ubiquinol), Polyglycerol fatty acid esters, Micelle formation, Vitamin C, Decaglycerol lauric acid ester, Replacement reaction of the surfactant to ubiquinone/γ-CD inclusion complex

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 177

6. CDs for other Industrial Applications

Agócs, T. Z.; Puskás, I.; Varga, E.; Molnár, M.; Fenyvesi, É.

Photocatalytic effect of cyclodextrin-stabilized nano titanium dioxide on degradation of waste water pollutants

Accelerated decomposition and mineralization of the pollutant, Carboxymethylated beta-CD polymer, Methylene blue

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 125

Blanford, W. J.

Methods for determining the distribution of hydrophobic organic chemicals in cyclodextrin–water–air–solid sorbent systems as a function of salinity, temperature, and CD concentration

Mathematical models, Van't Hoff and Setchenow equations, Calculating HOC phase distribution in air-water-CD-solid sorbent systems

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 116

Boving, T.

Soil and groundwater remediation with cyclodextrin

In situ chemical oxydation, Peroxone activated persulfate, CMBCD, HPBCD, Ozone/CD complexation

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 17

Celebioglu, A.; Uyar, T.

Molecular filtration performance of electrospun poly-cyclodextrin nanofibers

Waste treatment applications, CD included polymeric nanofibrous web, Air filtration, Integrating suitable crosslinking agents to the electrospinning system, Removing dye molecules (methylene blue) and polycyclic aromatic hydrocarbons (PAH)

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 43

Celebioglu, A.; Uyar, T.

Optimization study on electrospinning of insoluble poly-cyclodextrin nanofibers

Crosslinked CD polymer, Different kind of crosslinking agents, insoluble CD nanofibers, Durability

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 118

Ertas, Y.; Celebioglu, A.; Uyar, T.

Water-insoluable cross-linked cyclodextrin/polybenzoxazine composite nanofibers by electrospinning for waste water treatment

HPβCD, HPγCD, MβCD, Citric acid, Crosslinking agent, Removal of polycyclic aromatic hydrocarbons (PAHs) and dye molecules, Benzoxazine monomer, Bisphenol-A, Aniline, Paraformaldehyde

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 123

Fenyvesi, É.

Cyclodextrins in environmental technologies for soil remediation

Microbial bioavailability of organic pollutants, PAHs, PCBs, Bioremediation, RAMEB

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 124

Hernández-Pascacio, J.; García, E.; Campos-Terán, J.; Costas, M.; Campbell, R.; Piñeiro, Á.

Cyclodextrin based viscoelastic films spontaneously formed at water/air interfaces

α-CD, Sodium dodecyl sulfate, Functional coatings, Separation of contaminants

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 166

Mazzaglia, A.; Tosto, R.; Sortino, G.; Scala, A.; Piperno, A.; Villari, V.; Mineo, P.; Giuffrida, M.; Natale, G. D.; Micali, N.; Pappalardo, G.

Peptides-tailored cyclodextrin nanomagnets for amyloid-β targeting

Magnetic-field-assisted bio-separation, biointeraction, imaging and drug delivery, Heptakis(2-oligo(ethyleneoxide)-6-hexadecylthio-)-β-CD (SC16OH)-capping Fe_3O_4, Amphiphilic CD olygoethyleneglycol chains

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 154

Saito, R.; Matsumoto, M.

Cyclodextrin/poly(amideimide) complexes as novel binders/dispersants for lithium

ion battery

Poly(acylic acid), Poly(amideimide), RAMEB and BCD modified primary hydroxy groups with poly(acrylic acid) oligomer, Improved dispersion of carbon nano-materials in water

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 168

Wang, L.; Liang, X.; Li, B.-J.; Zhang, S.

An efficient magnetic enantioseparation of naphthylamine via host-guest interaction

Covalently linked magnetic nano-particles and β-cyclodextrin derivatives, Chiral selector

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 179

7. CDs in Sensing and Analysis

Benkovics, G.; Fejős, I.; Darcsi, A.; Béni, S.; Malanga, M.; Bálint, M.

Single-isomer carboxymethylated cyclodextrins as chiral resolving agents for capillary electrophoresis

Hexakis(2,3-di-O-methyl-6-carboxymethyl)-α-CD, Heptakis(2,3-di-O-methyl-6-carboxy-methyl)-β-CD, Otakis(2,3-di-O-methyl-6-carboxymethyl)-γ-CD, Silylated intermediers, Enantioseparation

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 115

Biscotti, A.; Bonnet, C.; Toth, E.; Barbot, C.; Estour, F.; Gouhier, G.

New MRI contrast agents based on modified cyclodextrins: Hydration spheres effects studies

Gadolinium, Relaxivity, Percarboxylated BCD, Permethylated BCD, Conjugating the chelating agent to BCD

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 134

Fujiwara, S.; Yamada, T.; Hashimoto, T.; Hayashita, T.

Development of coumarin fluorescent probe modified cyclodextrin for phosphate anion sensing in water

Dipicolylamine modified CD, Metal ion recognition, Phosphate anion recognition, Multi-point recognition

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 129

Sugita, K.; Mizuta, Y.; Tsuchido, Y.; Hashimoto, T.; Hayashita, T.

Selective sugar recognition by fluorinated boronic acids fluorophore/cyclodextrin complexes in water

Phenylboronic acid fluorophore, Glucose, Galactose, Anthracene, Pyrene

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 137

Wang, L.-H.; Zhang, Y.-H.; Liu, Y.

Polysaccharide–quantum dots conjugate for controlled DNA condensation and cellular

imaging

Multicomponent nanoparticles, Adamantane-modified anthracene, π-intercalation of anthracene into the grooves of DNA, Active targeting

Book of Abstracts of IC18, Gainesville, Florida, May 18-21, 2016, 181

Edited and produced by: CYCLOLAB
Homepage: www.cyclolab.hu
H-1525 P.O. 435, Budapest, Hungary
Tel.: (+361)347-6060
Fax.: (+361)347-6068
e-mail: cyclolab@cyclolab.hu