CYCLODEXTRIN NEWS

VOLUME 31. No. 08-09. SEPTEMBER-AUGUST 2017 ISSN 0951-256X

Itraconazole/HPBCD solution 20 years on the market

The patent on water soluble cyclodextrin (CD) complex of itraconazole was filed by Janssen Pharmaceutica N.V. (today subsidiary of Johnson & Johnson) with the priority date of 18.03.1992 (Heeres et al. 1992). It took only 5 years to start marketing the CD-solubilized form of this already approved drug in 1997 (DailyMed, 2017).

Itraconazole is a triazole antifungal agent with a broad spectrum of activity (Fig. 1), discovered in 1984. It is a racemic mixture of 4 diastereomers (two enantiomeric pairs) each possessing 3 chiral centers. It is extremely hydrophobic, practically insoluble in water. In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

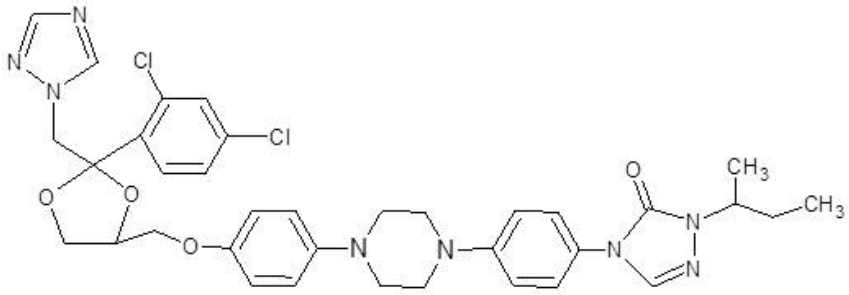

Fig. 1 Chemical formula of itraconazole

The very first paper on cyclodextrin complexation of itraconazole was published in 1988 by the researchers of State University of Gronningen, the Netherlands (Van Doorne et al., 1988). Beta-CD was used in this study and the increased solubility resulting in enhanced antifungal effect against *A. niger, S. cerevisiae, T. cutaneum* and *C. albicans* was shown.

Since then 342 further publications have been published according to Scopus (this is the number of hits for keywords itraconazol AND cyclodextrin). Not less than 86 of these papers used Sporanox (this is the brand name of HPBCD/itraconazole complex aqueous solution formulation marketed by Janssen). The authors with the highest number of publications on the topic are Brewster, M.E. (13), Loftsson, T. (11) and Stevens, D.A. (11).

It was shown that HPBCD as a carrier highly enhanced the plasma concentration of itraconazole after single dose administration to mice (Hostetler et al., 1992).

In a murine model of disseminated cryptococcosis, itraconazole at doses of up to 120 mg/kg/day solubilized in PEG were found not to be effective. However, itraconazole at doses of 30 mg/kg/day solubilized in HPBCD markedly prolonged survival and a relationship between dose and survival was seen (Hostetler et al., 1993). It was found to be effective in a rabbit model of invasive aspergillosis (Patterson et al., 1993) and many other fungal infections. The efficacy was proved for a variety of indications including gastroenteropathy (Stevens, 1999). The HPBCD-solubilized drug was discovered to be useful in the treatment of HIV-related candidosis unresponsive to other azole therapy (Cartledge et al., 1994). As the oral solution showed more consistent absorption characteristics than the capsule formulation, the solution was developed for approval and the marketing started in 1997.

Now, Sporanox® is available as oral solution, injection for intravenous infusion and as a capsule. The oral solution contains 10 mg/mL itraconazole and 400 mg/mL hydroxypropyl betadex (Fig. 2). The injection for intravenous infusion is supplied as a kit containing one 25 mL colorless glass ampule of itraconazole 10 mg/mL sterile, pyrogen-free solution with hydroxypropyl betadex, one 50 mL bag of 0.9% NaCl solution and one filtered infusion set (drugs.com, 2017). The capsule does not contain cyclodextrin.

SPORANOX oral solution is indicated for:

- the treatment of oral and/or oesophageal candidiasis in HIV-positive or other immunocompromised patients.

- prophylaxis of fungal infections in neutropenic patients (Janssen 2017).

Fig. 2 Label of Sporanox oral solution

The main advantage of HPBCD formulation is the enhanced solubility (Fig. 3), which depends on the pH: at pH 2 the molar ratio of host:guest is dominantly 2:1 mole/mole, while also 3:1 mole/mole complexes are formed at pH 7 (Peeters et al. 2002). The lower order of complexation observed at lower pH was related to substructure protonation, which reduced HPBCD interaction.

Molecular mechanics studies also indicated 3:1 complex formation for the neutral species, and revealed the possible interaction sites (in order of binding): triazole > 1,4-diaminophenyl > 2-butyl ≋ piperazine (Fig. 4).

As the solubility isotherm is of Ap type, the effect of intraluminal dilution was studied on the behavior and performance of orally administered Sporanox solution to healthy volunteers with or without a glass of water (Berben et al. 2017). No gastric precipitation was observed independently of dilution, but after transfer into duodenum precipitation occurred and was more pronounced in the condition with water. It resulted in 7.6-fold decrease in duodenal $AUC_{0\text{-}3h}$ compared to the condition without water, but, surprisingly, there was no difference in the plasma concentrations. The permeation (absorption) seemed to counterbalance the solubility. The results show that in the case of an Ap-type interaction with cyclodextrins, the trade-off between solubility and permeability may be affected by intraluminal dilution.

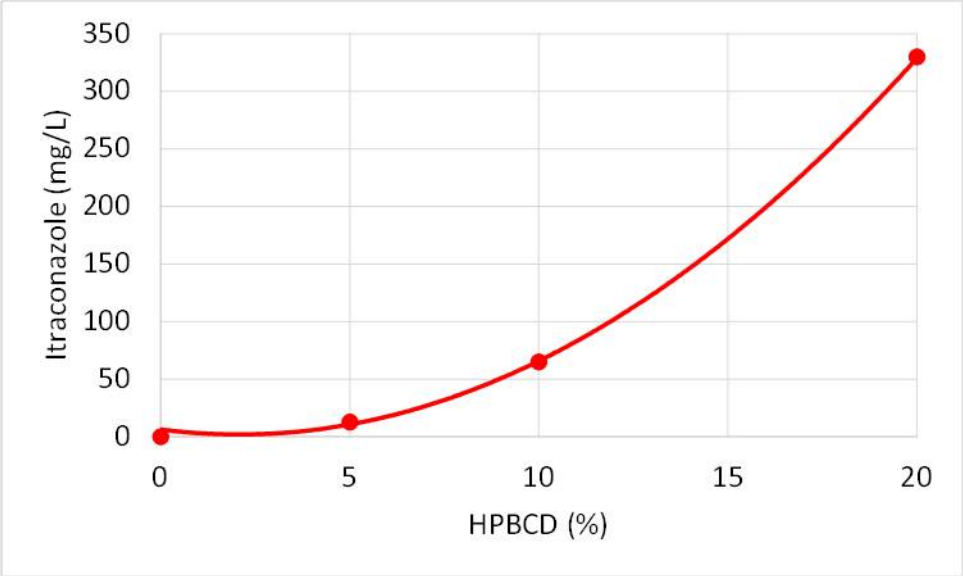

Fig. 3 Solubility of itraconazole in HPBCD solutions in water at room temperature (redrawn after Brewster et al. 2007)

For the cyclodextrin chemists it is also interesting to know that acetyl and alkylated BCDs (dimethyl > ethyl > cyanoethyl >carboxyethyl) as well as aminopropyl BCD performed better in enhancing the solubility of itraconazole than HPBCD, the pharmaceutically accepted CD derivative (Brewster et al. 2007).

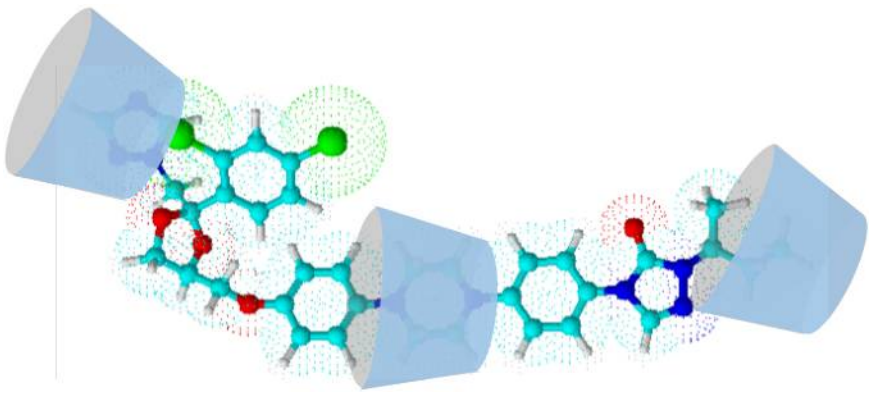

Fig. 4 Scheme of the 3:1 HPBCD/itraconazole complex

Recently, promising anticancer activity in various cancers has been discovered as a new indication: Sporanox oral solution showed antiangiogenic and anticancer activities in non-small cell lung cancer (Aftab et al. 2011). It significantly enhanced the antitumor efficacy of cisplatin in the model systems. A combination therapy with Sporanox prolonged the survival of patients with metastatic pancreatic cancer and metastatic biliary tract cancer (Tsubamoto et al. 2015a and 2015b). Sporanox intravenous infusion was especially successful in phase II study in men with metastatic nonsquamous non-small cell lung cancer when applied together with permetrexed (Rudin et al. 2013). Itraconazole (administered as capsules) slightly delayed the tumor progression in phase II study in men with advanced prostate cancer (Antonarakis et al. 2013) and reduced the size of pancreatic tumor in a 64-year-old male patient according to a case study by Lockhart et al. (2016). It was successfully applied also in infantile hemangiomas (Ran et al. 2014).

Proposed mechanisms of anticancer activity of itraconazole include blocking the cholesterol release from the late endosome/lysosomes causing hyper-accumulation of cholesterols in the organelle (so-called Niemann-Pick C phenotype) (Shim and Liu,2014). This leads to the inhibition of mTOR (mammalian target of rapamycin) activity and vascular endothelial growth factor (VEGFR2) glycosylation in endothelial cells. Itraconazole is also known to inhibit Smoothened (SMO) activation in Hedgehog signaling (Carratore et al. 2012). It has not been discussed in this paper if the vehicle (HPBCD) counteract to the blockade in cholesterol trafficking. Liu et al. found that while the antifungal effect of the itraconazole stereoisomers do not differ in a high extent, the antiangiogenic effect measured as lanosterol 14α-demethylase (14DM) inhibitory activity is higher for the cis isomers than for the trans isomers especially when administered in optically pure form (Liu et al. 2013).

The repositioning of itraconazole as anticancer drug opens new indications for Sporanox and after 20-year marketing further market growth is expected.

References

Aftab, B.T., Dobromilskaya, I., Liu, J.O., Rudin, C.M. (2011) Itraconazole inhibits angiogenesis and tumor growth in non-small cell lung cancer. Cancer Res., 71 (21), 6764–6772

Antonarakis, E.S., Heath, E.I., Smith, D.C., Rathkopf, D., Blackford, A.L., Danila, D.C., King, S., Frost, A., Ajiboye, A.S., Zhao, M., Mendonca, J., Kachhap, S.K., Rudek, M.A., Carducci, M.A. (2013) Repurposing itraconazole as a treatment for advanced prostate cancer: a noncomparative randomized phase II trial in men with metastatic castration-resistant prostate cancer. Oncol., 18 (2), 163–173

Berben, P., Mols, R., Brouwers, J., Tack, J., Augustijns, P. (2017) Gastrointestinal behavior of itraconazole in humans – Part 2: The effect of intraluminal dilution on the performance of a cyclodextrin-based solution. Int. J. Pharm., 526, 235–243

Brewster, M.E., Neeskens, P., Peeters, J. (2007) Solubilization of itraconazole as a function of cyclodextrin structural space. J. Incl. Phenom. Macrocycl. Chem., 57(1-4), 561–566

Brewster, M.E., Vandecruys, R., Peeters, J., Neeskens, P., Verreck, G., Loftsson, T. (2008) Comparative interaction of 2-hydroxypropyl-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin with itraconazole: Phase-solubility behavior and stabilization of supersaturated drug solutions. Eur. J. Pharm. Sci., 34(2–3), 94–103

Carratore, R., Carpi, A., Beffy, P., Lubrano, V.,Giorgetti, L., Maserti, B.E., Carluccio, M.A., Simili, M., Lervasi, G., Balzan, S. (2012) Itraconazole inhibits HMEC-1 angiogenesis. Biomed & Pharmacother. 66, 312–317

Cartledge, J.D., Midgley, J,. Youle, M., Gazzard, B.G. (1994) Itraconazole cyclodextrin solution—effective treatment for HIV-related candidosis unresponsive to other azole therapy. J. Antimicr. Chemother. 33, 1071–1073

DailyMed (2017) SPORANOX- itraconazole solution. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=AE50721D-EE15-4EE7-9FE7-AFD98C56461B. Accessed: 20.09.2017

Drugs.com (2017) Sporanox. https://www.drugs.com/pro/sporanox-injection.html

Heeres, J., Mesens, J.L., Peeters, J. (1992) Itraconazole and saperconazole stereoisomers, method of their producing, their complexes, method of producing of these complexes, pharmaceutical preparations and method of their producing. WO1993EP00552 19930310, US19920853648 19920318

Hostetler, J.S., Hanson, L.H., Stevens, D.A. (1992) Effect of cyclodextrin on the pharmacology of antifungal oral azoles. Antimicrob. Agents Chemother., 36(2), 477–480

Hostetler, J.S., Hanson, L.H., Stevens, D.A. (1993) Effect of hydroxypropyl-b-cyclodextrin on efficacy of oral itraconazole in disseminated murine cryptococcosis. J. Antimicrob. Chemother., 32(3), 459–463

Janssen (2017) Sporanox Oral Solution. Product Information. http://www.janssen.com/australia/sites/www_janssen_com_australia/files/prod_files/live/sporanox_solution_pi.pdf. Accessed: 20.09.2017

Liu, J.O., Chong, C.R., Xu J., Lu, J., Bhat, S. (2013) Chirally pure isomers of itraconazole for use as angiogenesis inhibitors. US2013102614

Lockhart, N.R., Waddell, J.A., Schrock, N.E. (2016) Itraconazole therapy in a pancreatic adenocarcinoma patient: A case report. J. Oncol. Pharm. Pract., 22(3), 528–532

Patterson, T.F., Fothergill, A.W., Rinaldi, M.G. (1993) Efficacy of itraconazole solution in a rabbit model of invasive aspergillosis. Antimicrob. Agents Chemother., 37(11), 2307–2310

Peeters, J., Neeskens, P., Tollenaere, J.P., Van Remoortere, P., Brewster, M.E. (2002) Characterization of the interaction of 2-hydroxypropyl-b- cyclodextrin with itraconazole at pH 2, 4, and 7. J. Pharm. Sci., 91(6), 1414–1422

Ran, Y., Chen, S., Dai, Y., Kang, D., Lama, J., Ran, X., Zhuang, K. (2015), Successful treatment of oral itraconazole for infantile hemangiomas: A case series. J. Dermatol., 42, 202–206

Rudin, C.M., Brahmer, J.R., Juergens, R.A., Hann, C.L., Ettinger, D.S., Sebree, R., Smith, R., Aftab, B.T., Huang, P., Liu, J.O. (2013) Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer. J. Thoracic Oncol., 8 (5), 619–623

Shim, J.S. and Liu, J.O. (2014) Recent advances in drug repositioning for the discovery of new anticancer drugs. Int. J. Biol. Sci., 10(7), 654–663

Stevens, D.A. (1999) Itraconazole in cyclodextrin solution. Parmacother., 19, 603–611

Tsubamoto, H., Sonoda, T., Ikuta, S., Tani, S., Inoue, K., Yamanaka, N. (2015a) Combination chemotherapy with itraconazole for treating metastatic pancreatic cancer in the second-line or additional setting. Anticancer Res., 35(7), 4191–4196

Tsubamoto, H., Sonoda, T., Ikuta, S., Tani, S., Inoue, K., Yamanaka, N. (2015b) Impact of itraconazole after first-line chemotherapy on survival of patients with metastatic biliary tract cancer. Anticancer Res., 35(9), 4923–4927

Van Doorne, H., Bosch, E.H., Lerk, C.F. (1988) Formation and antimicrobial activity of complexes of beta-cyclodextrin and some antimycotic imidazole derivatives. Pharm. Weekbl. Sci. Ed., 10, 80–85

Willems, L., Van der Geest, R., De Beule, K. (2001) Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J. Clin. Pharm. Ther., 26(3), 159–169. DOI: 10.1046/j.1365-2710.2001.00338.x

Éva Fenyvesi

CycloLab Cyclodextrin R&D Laboratory, Ltd.,

Budapest, HUNGARY

Bibliography & Keywords of Selected Publications of the Month

Yergey, A. L.; Blank, P. S.; Backlund, P. S.; Porter, F. D.; Cologna, S. M.; Darling, A. J.

Characterization of hydroxypropyl-beta-cyclodextrins used in the treatment of Niemann-Pick Disease type C1

Degree of substitution, Composition and fingerprint of the complex mixture, Impurity profiles

PloS one, 2017, 12, e0175478

Yamamura, H.

Chemical Modification of Cyclodextrin and Amylose by Click Reaction and Its Application to the Synthesis of Poly-alkylamine-Modified Antibacterial Sugars

Huisgen 1,3-dipolar cycloaddition, Microwave-assisted click reaction, Review

Chemical & pharmaceutical bulletin, 2017, 65, 312-317

Salzano, G.; Wankar, J.; Ottani, S.; Villemagne, B.; Willand, N.; Baulard, A. R.; Brodin, P.; Manet, I.; Gref, R.

Cyclodextrin-based nanocarriers containing a synergic drug combination: a potential formulation for pulmonary administration of antitubercular drugs

Ethionamide, Booster molecules, Polymeric β-cyclodextrin nanoparticles

International journal of pharmaceutics, 2017, Ahead of Print

Li, X.; Guo, T.; Guo, Z.; Wu, L.; Lachmanski, L.; Manoli, F.; Manet, I.; Menendez-Miranda, M.; Zhang, J.; Gref, R.

Cyclodextrin-based metal-organic frameworks particles as efficient carriers for lansoprazole: Study of morphology and chemical composition of individual particles

Assembly with γ-CD in the presence of K(+) ions, Optimized co-crystallization method, Homogeneity

International journal of pharmaceutics, 2017, Ahead of Print

Li, H.; Liu, Y.; Huang, T.; Qi, M.; Ni, Y.; Wang, J.; Zheng, Y.; Zhou, Y.; Yan, D.

Construction of Light-Harvesting Polymeric Vesicles in Aqueous Solution with Spatially Separated Donors and Acceptors

4-Chloro-7-nitro-2,1,3-benzoxadiazole, CD/Rhodamine B host-guest interactions, Artificial photosynthesis systems

Macromolecular Rapid Communications, 2017, Ahead of Print; DOI:10.1002/marc.201600818

Prado, A. R.; Yokaichiya, F.; Franco, D. K. K. M.; Goncalves da Silva, C. M.; and Oliveira-Nascimento, L.; Franz-Montan, M.; Volpato, M. C.; Cabeca, L. F.; de Paula, E

Complexation of oxethazaine with 2-hydroxypropyl-β-cyclodextrin: increased drug solubility, decreased cytotoxicity and analgesia at inflamed tissues

HPBCD, Promoted in vivo analgesia

Journal of Pharmacy and Pharmacology, 2017, 69, 652-662; DOI:10.1111/jphp.12703

Labate, C.; De Santo M. P; Lombardo, M.; Lombardo, G.

Biomechanical Strengthening of the Human Cornea Induced by Nanoplatform-Based Transepithelial Riboflavin/UV-A Corneal Cross-Linking

Riboflavin, Biodegradable polymeric nanoparticles of 2-hydroxypropyl-β-cyclodextrin, Trometamol, Ethylenediaminetetraacetic acid, UV-A irradiation, Improving the biomechanical strength of the most anterior stroma of the human cornea

Investigative ophthalmology & visual science, 2017, 58, 179-184

Ogawa, M.; Higashi, K.; Namiki, S.; Liu, N.; Ueda, K.; Limwikrant, W.; Yamamoto, K.; Moribe, K.

A Solid-Phase Mediated Methodology to Incorporate Drug into Intermolecular Spaces of CD Columns in the PEG/CD-Polypseudorotaxanes by Cogrinding and Subsequent Heating.

Piroxicam, Hydrocortisone (HCT), Salicylic acid, Salicylamide, Complexes with high CD crystallinity, Dissolution enhancement, Sublimation suppression

Crystal Growth & Design, 2017, Ahead of Print

Sauer, R-S.; Rittner, H. L.; Roewer, N.; Sohajda, T.; Shityakov, S.; Brack, A.; Broscheit, J-A.

A Novel Approach for the Control of Inflammatory Pain: Prostaglandin E2 Complexation by Randomly Methylated β-Cyclodextrins

Local treatment with RAMEB, Systemic administration of RAMEB, PGE2-binding capacity

Anesthesia & Analgesia, 2017, 124, 675-685; DOI:10.1213/ANE.0000000000001674

Morelli, L,; Cappelluti, M. A.; Ricotti, L.; Lenardi, C.; Gerges, I.

An Injectable System for Local and Sustained Release of Antimicrobial Agents in the Periodontal Pocket

In situ gelling system, BCD-based hydrogel, Poloxamer, Rapid thermally induced sol-gel phase transition at body temperature, Chlorhexidine digluconate

Macromolecular Bioscience, 2017, Ahead of Print, DOI:10.1002/mabi.201700103

Purpura, M.; Lowery, R. P.; Wilson, J. M.; Mannan, H.; Munch, G.; Razmovski-Naumovski, V.

Analysis of different innovative formulations of curcumin for improved relative oral bioavailability in human subjects

γ-Cyclodextrin curcumin formulation, Plasma concentrations of curcumin, demethoxycurcumin, and total curcuminoids

European Journal of Nutrition, 2017, Ahead of Print-; DOI:10.1007/s00394-016-1376-9

Mistry, R. H.; Verkade, H. J.; Tietge, U. J. F.

Absence of intestinal microbiota increases beta-cyclodextrin stimulated reverse cholesterol transport

Non-digestible oligosaccharides, Prebiotics, Increased macrophage-to-feces cholesterol transport, Cardiovascular health benefits

Molecular Nutrition & Food Research, 2017, 61, n/a-; DOI:10.1002/mnfr.201600674

Hissa, B.; Oakes, P. W.; Ramirez-San, J. G.; Gardel, M. L.; Pontes, B.

Cholesterol depletion impairs contractile machinery in neonatal rat cardiomyocytes

Methyl-beta-cyclodextrin, Rate of cell contraction, Cell relaxation, Membrane tension, Ca(2+) spikes frequency, intracellular Ca(2+) concentration, Channel regulation, Signaling cascade

Scientific reports, 2017, 7, 43764

Danielli, M.; Capiglioni, A. M.; Marrone, J.; Calamita, G.; Marinelli, R. A.

Cholesterol can modulate mitochondrial aquaporin-8 expression in human hepatic cells

Cholesterol loading with methyl-β-cyclodextrin/cholesterol complexes, Cholesterol depletion

IUBMB Life, 2017, 69, 341-346; DOI:10.1002/iub.1615

Wudiri, G. A.; Nicola, A. V.

Cellular cholesterol facilitates the post-entry replication cycle of herpes simplex virus 1

Hydrocarbon tail of cholesterol facilitating viral synthesis, Multiple roles for cholesterol, Transport of viral capsids to the nucleus, Cell-to-cell spread of infection

Journal of virology, 2017, Ahead of Print

Pinzon Barrantes, J. J.; Maggio, B.; de Rossi, R. H.; Vico, R. V.

Cavity Orientation Regulated by Mixture Composition and Clustering of Amphiphilic Cyclodextrins in Phospholipid Monolayers

Monoacylated amphiphilic β-cyclodextrin (βCD-C16), Phospholipid 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), Clusters enriched in βCD-C16

Journal of Physical Chemistry B, 2017, 121, 4482-4491; DOI:10.1021/acs.jpcb.7b01247

Ohmori, K.; Ooya, T.; Takeuchi, T.

Monocarboxylated α-Cyclodextrin [2]Rotaxane Capable of Angiotensin III Recognition

Synthetic receptors selective for target peptides or proteins model peptide, Angiotensin III (Arg-Val-Tyr-Ile-His-Pro-Phe)

Chemistry - A European Journal, 2017, 23, 4708-4712; DOI:10.1002/chem.201700206

Neoh, T. L.; Ariyanto, H. D.; Yoshii, H.; Menendez, G. P.

Controlled release of 1-methylcyclopropene from its functionalized electrospun fibers under constant and linearly ramped humidity

α-CD, Irregular release profiles, Active packaging, Autoregressive model, Humidity ramping release

Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, 2017

Aytac, Z.; San K.; Nalan, O.; Tekinay, T.; Uyar, T.

Antioxidant α-tocopherol/γ-cyclodextrin-inclusion complex encapsulated poly(lactic acid) electrospun nanofibrous web for food packaging

Inhibition of lipid oxidation, Enhanced oxidative stability of the meat

Journal of Applied Polymer Science, 2017, 134, n/a-; DOI:10.1002/app.44858

Lannoy, A.; Bleta, R.; Machut-Binkowski, C.; Addad, A.; Monflier, E.; Ponchel, A.

Directed Synthesis of Gold-Modified TiO2 Materials and Evaluation of Their Photocatalytic Activity in the Removal of a Pesticide from Water: Effect of Porosity and Particle Size

Visible-light-driven plasmonic photocatalysts, Native α-CD, β-CD and γ-CD, RAMEB, HPBCD, Interconnected pore structure, Wastewater

ACS Sustainable Chemistry & Engineering, 2017, 5, 3623-3630; DOI:10.1021/acssuschemeng.6b03059

Hapiot, F.; Menuel, S.; Ferreira, M.; Leger, B.; Bricout, H.; Tilloy, S.; Monflier, E.

Catalysis in Cyclodextrin-Based Unconventional Reaction Media: Recent Developments and Future Opportunities

Supramolecular hydrogels, Low melting mixtures, Stabilization of organometallic or metal nanoparticle catalysts

ACS Sustainable Chemistry & Engineering, 2017, 5, 3598-3606; DOI:10.1021/acssuschemeng.6b02886

Ling, Y.; Klemes, M. J.; Xiao, L.; Alsbaiee, A.; Dichtel, W. R.; Helbling, D. E.

Benchmarking micropollutant removal by activated carbon and porous β-cyclodextrin polymers under environmentally relevant scenarios

Natural organic matter, Selective uptake, Wastewater treatment

Environmental science & technology, 2017

Kalikova, K.; Slechtova, T.; Tesarova, E.

Cyclic Oligosaccharide-Based Chiral Stationary Phases Applicable to Drug Purity Control; A Review

Chromatographic techniques, Chiral selectors, Cyclodextrin- or cyclofructan-based chiral stationary phases

Current Medicinal Chemistry, 2017, 24, 829-848; DOI:10.2174/0929867323666160813221615

Boon, Y. H.; Raoov, M.; Zain, N. N. M.; Mohamad, S.; Mohamad, S.; Osman, H.

Combination of Cyclodextrin and Ionic Liquid in Analytical Chemistry: Current and Future Perspectives

Cooperative effect between CD and ionic liquid, Solid phase extraction (SPE), magnetic solid phase extraction (MSPE), cloud point extraction (CPE), microextraction (ME), GC, HPLC, CE, Electrochemical sensors as electrode modifiers

Critical reviews in analytical chemistry, 2017

Fejos, I.; Varga, E.; Benkovics, G.; Malanga, M.; Sohajda, T.; Szeman, J.; Beni, S.

Characterization of a single-isomer carboxymethyl-beta-cyclodextrin in chiral capillary electrophoresis

Heptakis-(2,3-di-O-methyl-6-O-carboxymethyl)-β-CD, Tadalafil, Tapentadol, Dapoxetine

Electrophoresis, 2017, Ahead of Print; DOI:10.1002/elps.201700004

Rabilloud, T

A single step protein assay that is both detergent and reducer compatible: the cydex blue assay

Determination of protein concentration, Coomassie blue-based assay,

Complexation of detergents

arXiv.org, e-Print Archive, Quantitative Biology, 2017, 1-19

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