CYCLODEXTRIN NEWS
VOLUME 30. No. 2. FEBRUARY 2016 ISSN 0951-256X

Potential of NIR Techniques for Quality Control of Cyclodextrins and Cyclodextrin Complexes

Near InfraRed (NIR) spectroscopy is a popular technique due to its advantages including the non-intrusive and non-destructive nature and wide applicability. Specifically, the NIR region covers the overtone and combination transitions of the C–H, O–H, N–H, and C=O groups, and since cyclodextrins (CDs) frequently possess these groups, the technique can be used for analysis of CDs and CD complexes, as well. Recently, NIR spectroscopy has become a routine technique in the quality control of pharmaceutical industry, but its application in the analysis of cyclodextrins has been limited so far [1].

Infrared spectroscopy (IR) was used for demonstration of complex formation; however, the traditional IR delivers only qualitative data. While the drug/CD mixture shows no appreciable spectral changes compared to the drug, when complex formation takes place frequency shifts of characteristic chromophore groups were observed if they were not covered by strong absorption bands of CD molecules [2]. This phenomenon can be applied to get quantitative data on drug-CD complexes using NIR technique.

In the case of CD derivatives, Fourier-transformed infrared (FTIR) technique was applied to get more characteristic data. Among the C–H stretching signals, the IR spectrum of (2-hydroxypropyl)-β-cyclodextrin (HPBCD) shows the specific methyl signal of the hydroxypropyl groups. As the amount of hydroxypropyl groups increases, this methyl signal becomes more pronounced. Measuring the ratio of the methyl C–H stretching signal of the hydroxypropyl groups and the overall C–H stretching signals of HPBCD, good correlation with the average degree of substitution (DS) determined with ^{1}H-NMR was demonstrated. FTIR provides a convenient, reproducible and safe method for DS determination, but calibration with an absolute method is needed [3].

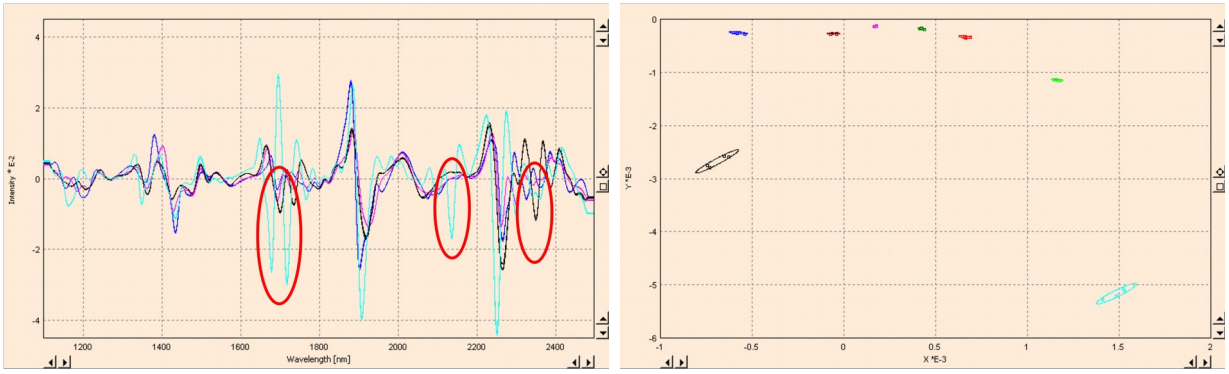
The NIR technique was first introduced for characterization of CDs and CD complexes in 1994 on the 7th International Cyclodextrin Symposium in Tokyo [4]. In this work we showed that the developed NIR methods were suitable for determination of the free and complexed fraction of Molsidomine guest molecule in CD complexes. The calibration curves were developed using partial least square (PLS) method. The control results were obtained with absolute methods: HPLC for total Molsidomine content and DSC for free, non-complexed Molsidomine content. NIR absorption in the 900-1800 nm region was used to estimate the association constants of the

inclusion complexes between aromatic compounds (e.g., phenol, 4-chlorophenol, sodium 2-naphthalenesulfonate, and sodium 2-pyrenesulfonate) and α-, β- and γ-CD [5].

It was also demonstrated in the above work that NIR method was able to detect the chemical modification of CD, the technique could be used for identification and as screen method in quick, routine determination of DS.

NIR and FT-IR spectroscopy were used to collect the physical and chemical fingerprints of 27 CD derivatives building a spectrum library in order to identify, differentiate and qualify the CDs quickly. Cluster analysis was provided as sensitive tool to detect the chemical modifications like acetylation, methylation or hydroxypropylation [6].

The type of CD derivative and the DS can be followed in three wavelength regions between 1650–1750 nm, 2090–2170 nm and 2300–2370 nm [7], (Fig. 1A). The effect of acetylation is very characteristic around 1700 and 2140 nm (increased intensity, appearance of new peak). The effects of random methylation are specific around 2350 nm (vibration of methyl groups). The Polar Quality Systems (PQS) evaluation method was applied [8]. The quality points of CDs and substituted CDs are spread in quality plane (Fig. 1B). α-, β- and γCDs and their hydroxypropyl derivatives are located around a "straight" line while acetylation and random methylation caused higher variation in quality measured by NIR.



A B

Figure 1: 2nd derivative of the spectra of different CD derivatives (typical wavelength ranges characteristic to the substituent and to the DS are marked (A) and Quality points of αCD, βCD, γCD, HP-α-CD, HP-β-CD, HP-γ-CD, randomly methylated βCD and acetylyted βCD using PQS evaluation (B)

Complete characterization of CD derivatives in general requires the use of different analytical methods. For example, at least four different analytical methods are applied to determine the main characteristic properties of HPBCD. HPLC is used for measuring the content of non-substituted, natural β-cyclodextrin (BCD), whereas gas chromatography (GC) is suitable for analysis of residual propylene glycol content. DS is determined with NMR method, while Karl-Fischer titration or loss on drying should be used for quantification of water (moisture) content of the samples.

Applying NIR technique there are two wavelength regions in 2nd derivative spectra (1700–1770 nm and 2290–2320 nm) where the hydroxypropylation of BCD can be followed sensitively (Fig. 2).

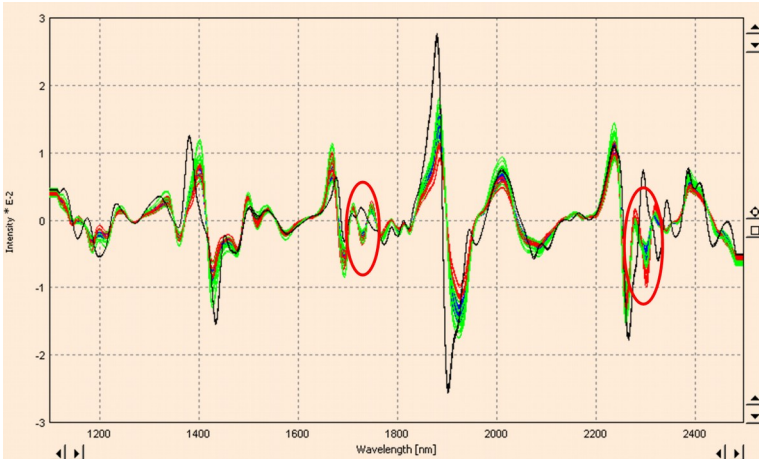


Figure 2. 2nd derivative spectra of BCD and HPBCD samples (DS < 3, 3 < DS < 5, DS > 5) Marked wavelength regions 1700–1770 nm and 2290–2320 nm

The first overtone of C–H stretching of CH_2 group (1725 nm) and the C–H combination band of the same group (2310 nm) are responsible for these changes. The degree of substitution can be predicted based on the change of peak between 2300–2305 nm (Fig. 3).

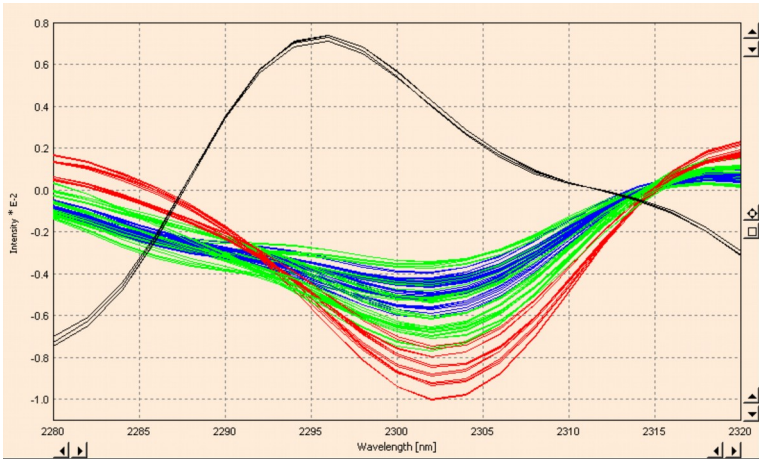


Figure 3. NIR spectra of HPBCD samples with different DS in the range of 2280–2320 nm

The quality of hydroxypropylated samples with different DS can be distinguished with PQS method (Fig. 4). Segregation of high DS (> 5) material was obvious while the prediction of DS smaller than 5 need bigger sample set.

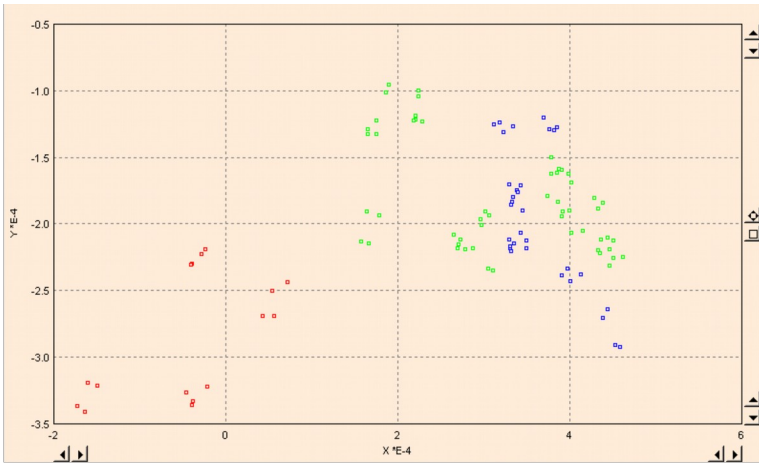


Figure 4. PQS quality points of HPBCD samples (DS < 3, 3 < DS < 5, DS > 5)

The prediction equation of DS indicates a standard error of calibration (SEC) 0.3 which precision is acceptable and the scatter plot confirms the poor sensitivity of reference method (vertical location of points at given reference value) compared to NIR method (Fig. 5A).

Similar calibration curves were obtained for the BCD, propylene glycol and water content. The precision was 0.1–0.2% for BCD in a 0–3.3% range; while for the water content the standard error of cross validation (SECV) was 0.20% in a quite broad (4.8–9.0%) range. The residual propylene glycol (PG) content of HPBCD products were determined with high preciseness, SECV was only 5.12% in a 0–180 mg/100 g range and with low scattering using NIR model (Fig. 5B).

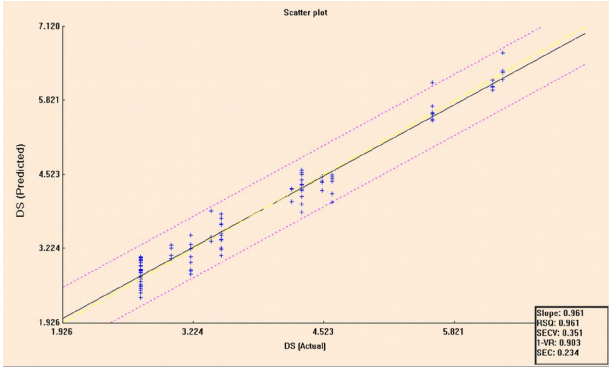


Figure 5A: Calibration curve for determination of DS

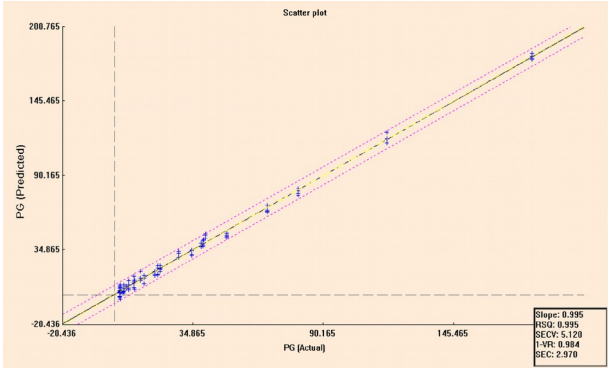


Figure 5B: Calibration curve for determination of PG content

Conclusion

The versatility and economic benefits of NIR spectroscopy opens new perspectives in the simple, quick and reliable quality control of cyclodextrins and cyclodextrin complexes and generally in pharmaceutical research, technology and quality control [9].

References

1. H. Viernstein, P. Weiss-Greiler, P. Wolschann, Quantitative determination of water in γ-CD by NIR spectroscopy, Pharm. Ind. 67(1) (2005) 122-125
2. Y. Nakai, A.E. Aboutaleb, K. Yamamoto, S.I. Saleh, M.O. Ahmed, Study of the interaction of clobazam with cyclodextrins in solution and in solid state, Chem. Pharm. Bull. 38 (1990) 728-732
3. J. Michaud, S. Icart, Determination of the substitution of hydroxypropylbetadex using fourier transform infrared spectrometry, Pharmeur. 13 (2001) 714-716
4. J. Szemán, A. Salgó, Gy. Dely-Szabó, Z. Fábián, J. Szejtli, Near Infrared spectroscopy: A novel and simple tool for characterization of cyclodextrin complexes and derivatives, Proceedings of 7th International Cyclodextrins Symposium, page 179-181, Tokyo, 1994
5. M.J. Politi, C.D. Tran, G.H. Gao, Near-Infrared Spectroscopic Investigation of Inclusion Complexes between Cyclodextrins and Aromatic Compounds, J. Phys. Chem. 99(38) (1995) 14137-14141
6. S. Gergely, Á. Nemesszeghy, Z.E. Rutkay, J. Szemán, L. Szente, A. Salgó, Investigation of cyclodextrins and their derivatives by near- and Fourier-transformed infrared spectroscopy, 15th International Cyclodextrins Symposium, 2010. Vienna, Austria (Poster presentation) Abstract book No. P-127
7. J. Szemán, R.N. Kedei, Sz. Gergely, I. Kolbe, L. Szente, A. Salgó, Near Infrared Spectroscopy: a fast and simple tool for characterization of Hydroxypropyl β-cyclodextrin, 13th International Cyclodextrins Symposium, 2006. Torino, Italy, https://www.researchgate.net/publication/296313508
8. K.J. Kaffka, Zs. Seregély, PQS (polar qualification system) the new data reduction and product qualification method. Acta Alim. 31(1) (2002) 3-20
9. A. Salgó, Sz. Gergely, NIR spectroscopy in:Instrumetal methods of pharmaceutical research. Ed: P. Sohár MKE 2015 pp. 307-330

Sz. Gergely[1], J. Szemán[2], A. Salgó[1]

[1] Department of Applied Biotechnology and Food Science, Budapest University of Technology and Economics, Budapest, HUNGARY

[2] CycloLab Cyclodextrin R&D Laboratory, Ltd., Budapest, HUNGARY

BIBLIOGRAPHY & KEYWORDS

1. CDs: Derivatives, Production, Enzymes, Toxicity

Bhamidimarri, S.; Prajapati, J.; van den Berg, B.; Winterhalter, M.; Kleinekathöfer, U.

Role of electroosmosis in the permeation of neutral molecules: CymA and cyclodextrin as an example

α-Cyclodextrin, Translocation and binding events

Biophysical Journal, 2016, 110, 600-611; DOI:10.1016/j.bpj.2015.12.027

Česla, P.; Vaňková, N.; Křenková, J.; Fischer, J.

Comparison of isocratic retention models for hydrophilic interaction liquid chromatographic separation of native and fluorescently labeled oligosaccharides

Maltose, Maltoheptaose, Derivatives with 2-aminobenzoic acid, 2-aminobenzamide, 2-aminopyridine and 8-aminonaphthalene-1,3,6-trisulfonic acid

Journal of Chromatography A, 2016, 1438, 179-188; DOI:10.1016/j.chroma.2016.02.032

Chmielarz, P.; Park, S.; Sobkowiak, A.; Matyjaszewski, K.

Synthesis of β-cyclodextrin-based star polymers via a simplified electrochemically mediated ATRP

n-Butyl acrylate, 2-Bromoisobutyryl bromide, Gel-permeation chromatography

Polymer, 2016, 88, 36-42; DOI:10.1016/j.polymer.2016.02.021

Gómez-Galván, F.; Pérez-Álvarez, L.; Matas, J.; Álvarez-Bautista, A.; Poejo, J.; Duarte, C. M.; Ruiz-Rubio, L.; Vila-Vilela, J. L.; León, L. M.

Preparation and characterization of soluble branched ionic β-cyclodextrins and their inclusion complexes with triclosan

Epichlorohydrin, Chloroacetic acid, Choline chloride, Cytotoxicity, Caco-2 cells, Water solubility

Carbohydrate Polymers, 2016, 142, 149-157; DOI:10.1016/j.carbpol.2016.01.046

Kettel, M. J.; Schaefer, K.; Pich, A.; Moeller, M.

Functional PMMA nanogels by cross-linking with cyclodextrin methacrylate

Surfactant-free precipitation polymerization, Hydrodynamic radii, Number of vinyl groups per CD molecule, Phenolphtalein

Polymer, 2016, 86, 176-188; DOI:10.1016/j.polymer.2016.01.063

Li, Z.; Duan, X.; Wu, J.

Improving the thermostability and enhancing the Ca^{2+} binding of the maltohexaose-forming α-amylase from *Bacillus stearothermophilus*

Site-directed mutagenesis

Journal of Biotechnology, 2016, 222, 65-72; DOI:10.1016/j.jbiotec.2016.02.013

Man, R. C.; Ismail, A. F.; Fuzi, S. F. Z. M.; Ghazali, N. F.; Illias, R. M.

Effects of culture conditions of immobilized recombinant *Escherichia coli* on cyclodextrin glucanotransferase (CGTase) excretion and cell stability

Immobilized cell, Free cell, Cell lysis, Plasmid stability, Porous hollow fiber membrane

Process Biochemistry, 2016, *In Press*; DOI:10.1016/j.procbio.2016.01.002

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

Gebhardt, J.; Hansen, N.

Calculation of binding affinities for linear alcohols to α-cyclodextrin by twin-system enveloping distribution sampling simulations

1-Hexanol, 1-Dodecanol, Molecular dynamics, Free energy, Force field

Fluid Phase Equilibria, 2016, *In Press*; DOI:10.1016/j.fluid.2016.02.001

Ho, T. M.; Howes, T.; Bhandari, B. R.

Encapsulation of CO_2 into amorphous alpha-cyclodextrin powder at different moisture contents - Part 1: Encapsulation capacity and stability of inclusion complexes

Crystallization, Complexed powder, Solid encapsulation

Food Chemistry, 2016, 203, 348-355; DOI:10.1016/j.foodchem.2016.02.076

Li, L.; Chen, X.; Xia, Q.; Wei, X.; Liu, J.; Fan, Z.; Guo, M.

Formation and characterization of pseudo-polyrotaxanes based on poly(*p*-dioxanone) and cyclodextrins

Heat-cool cycles, Hydrophilicity, Degradation

Carbohydrate Polymers, 2016, 142, 82-90; DOI:10.1016/j.carbpol.2016.01.034

Linden, L.; Goss, K.-U.; Endo, S.

Exploring 3D structural influences of aliphatic and aromatic chemicals on α-cyclodextrin binding

Linear and variously branched aliphatic chemicals, Small aromatic chemicals, Steric effect, Inclusion complex, Cyclodextrin water partitioning

Journal of Colloid and Interface Science, 2016, 468, 42-50; DOI:10.1016/j.jcis.2016.01.032

Ondo, D.

Calorimetric study on the interaction of didecyldimethylammonium and decyltrimethylammonium cations with native cyclodextrins in water

Sequentional binding model, Enthalpy-entropy compensaton analysis, Inclusion complex stability, Binding thermodynamics

The Journal of Chemical Thermodynamics, 2016, 97, 235-243; DOI:10.1016/j.jct.2016.01.027

Roy, M. N.; Roy, K.; Das, K.; Barman, B. K.

Self-assembly inclusion of green solvent with oligosaccharides

Ionic liquid, α-CD, β-CD, Hydrophobicity, Formation constants

Journal of Molecular Liquids, 2016, 216, 132-136; DOI:10.1016/j.molliq.2015.12.097

Yang, X.; Tu, J.; Lei, M.; Zuo, Z.; Wu, B.; Zhou, H.

Selection of carbon sources for enhancing 3D conductivity in the secondary structure of $LiFePO_4$/C cathode

Charge transfer resistance, PEG and β-CD as mixing carbon sources, Li-ion diffusion coefficients, Low-temperature performance

Electrochimica Acta, 2016, 193, 206-215; DOI:10.1016/j.electacta.2016.02.068

Ye, R.; Nie, X.; Zhou, Y.; Wong, C. F.; Gong, X.; Jiang, W.; Tang, W.; Wang, Y. A.; Heine, T.; Zhou, B.

Exploring host-guest complexation mechanisms by a molecular dynamics/quantum mechanics/continuum solvent model approach

β-CD, 2,6-Di-methyl-β-CD, Solvent effects

Chemical Physics Letters, 2016, 648, 170-177; DOI:10.1016/j.cplett.2016.02.006

Zaboub, A.; Madi, F.; Merdes, R.; Mohamedi, M.; Nouar, L.

A combined DFT and experimental study of proline/β-cyclodextrin inclusion complex

UV–visible and FTIR techniques, Energetic analysis, Charge transfer, B3LYP/3-21G+

Journal of Molecular Liquids, 2016, 216, 716-723; DOI:10.1016/j.molliq.2016.01.082

3. CDs in Drug Formulation

Aloisio, C.; de Oliveira, A. G.; Longhi, M.

Cyclodextrin and meglumine-based microemulsions as a poorly water-soluble drug delivery system

Soya oil–based O/W microemulsions, Sulfamerazine, Indomethacin, β-Cyclodextrin, Methyl-ßCD

Journal of Pharmaceutical Sciences, 2016, *In Press*; DOI:10.1016/j.xphs.2015.11.045

Amhaoul, H.; Ali, I.; Mola, M.; Eetveldt, A. V.; Szewczyk, K.; Missault, S.; Bielen, K.; Kumar-Singh, S.; Rech, J.; Lord, B.; Ceusters, M.; Bhattacharya, A.; Dedeurwaerdere, S.

P2X7 receptor antagonism reduces the severity of spontaneous seizures in a chronic model of temporal lobe epilepsy

Vehicle, Hydroxyprolyl-β-cyclodextrin

Neuropharmacology, 2016, 105, 175-185; DOI:10.1016/j.neuropharm.2016.01.018

Azuma, H.; Li, J.; Youda, R.; Suzuki, T.; Miyamoto, K.; Taniguchi, T.; Nagasaki, T.

Improved isolation procedure for shikonin from the root of the Chinese medicinal

plant *Lithospermum erythrorhizon* and its solubilization with cyclodextrins

Solid phase "high-speed vibration milling", Sulfobutylether-β-CD

Journal of Applied Research on Medicinal and Aromatic Plants, 2016, *In Press*; DOI:10.1016/j.jarmap.2016.01.002

Barabási, B.; Csondor, A.; Martín-Pozas, T.; Sánchez, A. P.; Antalffy, G.; Siklós, L.; Gómez-Pinedo, U.; Párducz, Á.; Hoyk, Z.

Effect of axotomy and 17β-estradiol on P2X7 receptor expression pattern in the hypoglossal nucleus of ovariectomized mice

2-Hydroxypropyl-β-cyclodextrin, Estrogen receptor, Microglia

Neuroscience, 2016, 319, 107-115; DOI:10.1016/j.neuroscience.2016.01.049

Barros, M. C.; Ramos, M. L.; Burrows, H. D.; Esteso, M. A.; Leaist, D. G.; Prazeres, P. A.; Ribeiro, A. C.

Effect of 2-hydroxypropyl-β-cyclodextrin on the diffusion behaviour of L-dopa in aqueous solutions

Coupled diffusion, Cross-diffusion coefficients, Levodopa, Parkinson disease, NMR spectroscopy

The Journal of Chemical Thermodynamics, 2016, 97, 122-126; DOI:10.1016/j.jct.2016.01.010

Cheng, X.; Jin, Y.; Sun, T.; Qi, R.; Li, H.; Fan, W.

An injectable, dual pH and oxidation-responsive supramolecular hydrogel for controlled dual drug delivery

α-CD, Nanoparticles, Indomethacin, Rhodamine B, Oxidation-triggered degradation, Polyurethane

Colloids and Surfaces B: Biointerfaces, 2016, 141, 44-52; DOI:10.1016/j.colsurfb.2016.01.034

Conte, C.; Fotticchia, I.; Tirino, P.; Moret, F.; Pagano, B.; Gref, R.; Ungaro, F.; Reddi, E.; Giancola, C.; Quaglia, F.

Cyclodextrin-assisted assembly of PEGylated polyester nanoparticles decorated with folate

Core-shell folate-targeted nanoparticles, Poly(ε-caprolactone), (2-Hydroxypropyl)-β-cyclodextrin, Biodegradable polymers

Colloids and Surfaces B: Biointerfaces, 2016, 141, 148-157; DOI:10.1016/j.colsurfb.2016.01.035

Gannimani, R.; Ramesh, M.; Mtambo, S.; Pillay, K.; Soliman, M. E.; Govender, P.

γ-Cyclodextrin capped silver nanoparticles for molecular recognition and enhancement of antibacterial activity of chloramphenicol

Pseudomonas aeruginosa, Enterococcus faecalis, Klebsiella pneumoniae, Staphylococcus aureus, Inclusion complex, Characterization

Journal of Inorganic Biochemistry, 2016, 157, 15-24; DOI:10.1016/j.jinorgbio.2016.01.008

Holm, R.; Olesen, N. E.; Hartvig, R. A.; Jørgensen, E. B.; Larsen, D. B.; Westh, P.

Effect of cyclodextrin concentration on the oral bioavailability of danazol and cinnarizine in rats

Excessive CD concentrations, Hydroxypropyl-β-cyclodextrin, In vivo, Complexation

European Journal of Pharmaceutics and Biopharmaceutics, 2016, 101, 9-14; DOI:10.1016/j.ejpb.2016.01.007

Jeon, H.; Kim, J.; Lee, Y. M.; Kim, J.; Choi, H. W.; Lee, J.; Park, H.; Kang, Y.; Kim, I.-S.; Lee, B.-H.; Hoffman, A. S.; Kim, W. J.

Poly-paclitaxel/cyclodextrin-SPION nano-assembly for magnetically guided drug delivery system

Superparamagnetic iron oxide nanoparticle, β-Cyclodextrin, Polymerized paclitaxel, Enhanced anticancer effects in vivo as well as in vitro, Multivalent host-guest chemistry

Journal of Controlled Release, 2016, *In Press*; DOI:10.1016/j.jconrel.2016.01.006

Krukiewicz, K.; Zak, J. K.

Biomaterial-based regional chemotherapy: Local anticancer drug delivery to enhance chemotherapy and minimize its side-effects

Reservoirs of anticancer drugs, Anticancer implants, Biomaterials

Materials Science and Engineering: C, 2016, *In Press*; DOI:10.1016/j.msec.2016.01.063

Li, X.; Bian, J.; Wang, N.; Qian, X.; Gu, J.; Mu, T.; Fan, J.; Yang, X.; Li, S.; Yang, T.; Sun, H.; You, Q.; Zhang, X.

Novel naphtho[2,1-d]oxazole-4,5-diones as NQO1 substrates with improved aqueous solubility: Design, synthesis, and in vivo antitumor evaluation

Hydroxyprolyl-β-cyclodextrin, Rapid drug clearance from the blood, ortho-Naphthoquinone analogs of β-lapachone

Bioorganic & Medicinal Chemistry, 2016, 24, 1006-1013; DOI:10.1016/j.bmc.2016.01.024

Li, X.; Xie, S.; Pan, Y.; Qu, W.; Tao, Y.; Chen, D.; Huang, L.; Liu, Z.; Wang, Y.; Yuan, Z.

Preparation, characterization and pharmacokinetics of doxycycline hydrochloride and florfenicol polyvinylpyrroliddone microparticle entrapped with hydroxypropyl-β-cyclodextrin inclusion complexes suspension

Antibacterial activity, Encapsulation efficiency, Intramuscular administration to pig

Colloids and Surfaces B: Biointerfaces, 2016, 141, 634-642; DOI:10.1016/j.colsurfb.2016.02.027

Liebscher, G.; Vanchangiri, K.; Mueller, T.; Feige, K.; Cavalleri, J.-M.; Paschke, R.

***In vitro* anticancer activity of Betulinic acid and derivatives thereof on equine melanoma cell lines from grey horses and *in vivo* safety assessment of the compound NVX-207 in two horses**

2-Hydroxyprolyl-β-cyclodextrin, Promising antitumor agent, Cytotoxicity

Chemico-Biological Interactions, 2016, 246, 20-29; DOI:10.1016/j.cbi.2016.01.002

Liu, J.; Luo, Z.; Zhang, J.; Luo, T.; Zhou, J.; Zhao, X.; Cai, K.

Hollow mesoporous silica nanoparticles facilitated drug delivery via cascade pH stimuli in tumor microenvironment for tumor therapy

PEG shielding, 3-(3,4-Dihydroxyphenyl) propionic acid functionalized β-CD, PEG conjugated adamantane, Cellular uptake, Cell apoptosis, In vivo

Biomaterials, 2016, 83, 51-65; DOI:10.1016/j.biomaterials.2016.01.008

Marcos, X.; Pérez-Casas, S.; Llovo, J.; Concheiro, A.; Alvarez-Lorenzo, C.

Poloxamer-hydroxyethyl cellulose-α-cyclodextrin supramolecular gels for sustained release of griseofulvin

Cooperative effects, Inclusion complex formation between poly(ethylene oxide) blocks and HEC with αCD, Sol-gel transition, Antifungal activity

International Journal of Pharmaceutics, 2016, 500, 11-19; DOI:10.1016/j.ijpharm.2016.01.015

Mihailiasa, M.; Caldera, F.; Li, J.; Peila, R.; Ferri, A.; Trotta, F.

Preparation of functionalized cotton fabrics by means of melatonin loaded β-cyclodextrin nanosponges

Biofunctional textiles, Nanosponge adsorption, Reservoir diffusion controlled system, Cellulose fabrics, Elemental analysis, DSC, SEM, XRD, FT-IR spectroscopy

Carbohydrate Polymers, 2016, 142, 24-30; DOI:10.1016/j.carbpol.2016.01.024

Nguyen, D. H.; Lee, J. S.; Choi, J. H.; Park, K. M.; Lee, Y.; Park, K. D.

Hierarchical self-assembly of magnetic nanoclusters for theranostics: Tunable size, enhanced magnetic resonance imagability, and controlled and targeted drug delivery

Superparamagnetic iron oxide nanoparticles, Biocompatibility, Covalently conjugated β-CD, PEG, Paclitaxel, Enhanced magnetic resonance, Improved cellular uptake

Acta Biomaterialia, 2016, *In Press*; DOI:10.1016/j.actbio.2016.02.020

Olesen, N. E.; Vana, V.; Holm, R.

Does the digestibility of cyclodextrins influence the *in vivo* absorption of benzo[a]pyrene in rats?

Overdosing of cyclodextrins, Limit the oral absorption, β-CDs, γ-CD

Journal of Pharmaceutical Sciences, 2016, *In Press*; DOI:10.1016/j.xphs.2015.10.027

Parra, A.; Clares, B.; Rosselló, A.; Garduño-Ramírez, M. L.; Abrego, G.; García, M. L.; Calpena, A. C.

***Ex vivo* permeation of carprofen from nanoparticles: A comprehensive study through human, porcine and bovine skin as anti-inflammatory agent**

Poly(d,l-lactide-co-glycolide) acid nanoparticles, Dermal delivery, Hydroxypropyl-β-cyclodextrin, Cryoprotectant, TPA-induced mouse ear edema model

International Journal of Pharmaceutics, 2016, 501, 10-17; DOI:10.1016/j.ijpharm.2016.01.056

Quintans-Júnior, L. J.; Araújo, A. A.; Brito, R. G.; Santos, P. L.; Quintans, J. S.; Menezes, P. P.; Serafini, M. R.; Silva, G. F.; Carvalho, F. M.; Brogden, N. K.; Sluka, K. A.

β-Caryophyllene, a dietary cannabinoid, complexed with β-cyclodextrin produced anti-hyperalgesic effect involving the inhibition of Fos expression in superficial dorsal horn

Non-inflammatory chronic muscle pain mice model, Oral treatment

Life Sciences, 2016, 149, 34-41; DOI:10.1016/j.lfs.2016.02.049

Radu, C.-D.; Parteni, O.; Ochiuz, L.

Applications of cyclodextrins in medical textiles — review

Drug deposits on the surface of a textile, Patients suffering from skin disorders, Protection against insects, Drug release

Journal of Controlled Release, 2016, 224, 146-157; DOI:10.1016/j.jconrel.2015.12.046

Sudha, N.; Yousuf, S.; Israel, E. V.; Paulraj, M. S.; Dhanaraj, P.

On the accessibility of surface–bound drugs on magnetic nanoparticles. Encapsulation of drugs loaded on modified dextran–coated superparamagnetic iron oxide by β-cyclodextrin

Aminoethylaminodextran-coated iron oxide nanoparticles, β-Cyclodextrin-complex formation of the drugs on the surface of the nanoparticles

Colloids and Surfaces B: Biointerfaces, 2016, 141, 423-428; DOI:10.1016/j.colsurfb.2016.02.020

Tan, J.; Meng, N.; Fan, Y.; Su, Y.; Zhang, M.; Xiao, Y.; Zhou, N.

Hydroxypropyl-β-cyclodextrin–graphene oxide conjugates: Carriers for anti-cancer drugs

Hemolysis test, Cytotoxicity, Paclitaxel, Blood compatibility

Materials Science and Engineering: C, 2016, 61, 681-687; DOI:10.1016/j.msec.2015.12.098

Tang, P.; Ma, X.; Wu, D.; Li, S.; Xu, K.; Tang, B.; Li, H.

Posaconazole/hydroxypropyl-β-cyclodextrin host–guest system: Improving dissolution while maintaining antifungal activity

Phase solubility study, In vitro antifungal susceptibility testing, Inclusion complex, Characterization

Carbohydrate Polymers, 2016, 142, 16-23; DOI:10.1016/j.carbpol.2016.01.042

Terauchi, M.; Inada, T.; Tonegawa, A.; Tamura, A.; Yamaguchi, S.; Harada, K.; Yui, N.

Supramolecular inclusion complexation of simvastatin with methylated β-cyclodextrins for promoting osteogenic differentiation

Hydroxypropyl-β-cyclodextrin, Randomly methylated β-cyclodextrin, MC3T3-E1 cells, Sialoprotein, Osteocalcin, Bone regeneration

International Journal of Biological Macromolecules, 2016, *In Press*; DOI:10.1016/j.ijbiomac.2016.01.114

Vieira, A. C.; Serra, A. C.; Veiga, F. J.; Gonsalves, A. M. R.; Basit, A. W.; Murdan, S.

Diclofenac-β-cyclodextrin for colonic drug targeting: *In vivo* performance in rats

Prodrug conjugate, Sulfasalazine, Colonic metabolism, Large intestine, Microbiota, Gut

International Journal of Pharmaceutics, 2016, 500, 366-370; DOI:10.1016/j.ijpharm.2016.01.024

Wang, C.; Wang, X.; Xu, X.; Liu, B.; Xu, X.; Sun, L.; Li, H.; Zhang, J.

Simultaneous high-throughput determination of interaction kinetics for drugs and cyclodextrins by high performance affinity chromatography with mass spectrometry detection

Ketoprofen, Trimethoprim, Indapamide, Acetaminophen, Cyclodextrin supramolecular systems

Analytica Chimica Acta, 2016, 909, 75-83; DOI:10.1016/j.aca.2015.12.026

Wani, W. A.; Prashar, S.; Shreaz, S.; Gómez-Ruiz, S.

Nanostructured materials functionalized with metal complexes: In search of alternatives for administering anticancer metallodrugs

Review, Curcubit[n]urils, Cyclodextrins, Liposomes, Carbon nanotubes, Platinum metallodrugs, Functionalization strategies, Co-delivery of metallodrugs, Toxicity of nanoformulations

Coordination Chemistry Reviews, 2016, 312, 67-98; DOI:10.1016/j.ccr.2016.01.001

Xu, P.; Tang, S.; Jiang, L.; Yang, L.; Zhang, D.; Feng, S.; Zhao, T.; Dong, Y.; He, W.; Wang, R.; Zhang, J.; Liang, Z.

Nanomaterial-dependent immunoregulation of dendritic cells and its effects on biological activities of contraceptive nanovaccines

Contraceptive peptide, Acetalated β-cyclodextrin, Poly(lactic-co-glycolic acid), Inflammatory cytokines, Immunization of male mice with nanovaccines, Peptide antigen, pH-responsive, Intracellular delivery

Journal of Controlled Release, 2016, 225, 252-268; DOI:10.1016/j.jconrel.2016.01.043

Zhu, Z.-Y.; Luo, Y.; Liu, Y.; Wang, X.-T.; Liu, F.; Guo, M.-Z.; Wang, Z.; Liu, A.-J.; Zhang, Y.-M.

Inclusion of chrysin in β-cyclodextrin and its biological activities

Plant flavone, Antioxidant potential, Antimicrobal activity, Anti-tumor activity, Water solubility

Journal of Drug Delivery Science and Technology, 2016, 31, 176-186; DOI:10.1016/j.jddst.2016.01.002

4. CDs in Cell Biology

Badwaik, V. D.; Aicart, E.; Mondjinou, Y. A.; Johnson, M. A.; Bowman, V. D.; Thompson, D. H.

Structure-property relationship for *in vitro* siRNA delivery performance of cationic 2-hydroxypropyl-β-cyclodextrin: PEG-PPG-PEG polyrotaxane vectors

Extracellular and intracellular barriers, Pluronic®-based, cholesterol end-capped cationic polyrotaxanes, Silencing efficiency, Cryoelectron microscopy, Small angle X-ray scattering

Biomaterials, 2016, 84, 86-98; DOI:10.1016/j.biomaterials.2015.11.032

Davidson, C.; Fishman, Y.; Puskas, I.; Szeman, J.; Sohajda, T.; Sikora, J.; Vanier, M. T.; Szente, L.; Walkley, S. U.; Dobrenis, K.

Different cyclodextrins for the treatment of Niemann-Pick disease type C

Molecular Genetics and Metabolism, 2016, 117, S38-; DOI:10.1016/j.ymgme.2015.12.232

Inagaki, S.; Kimizuka, R.; Kokubu, E.; Saito, A.; Ishihara, K.

***Treponema denticola* invasion into human gingival epithelial cells**

Metabolic inhibitors, Methyl-β-cyclodextrin, Lipid rafts

Microbial Pathogenesis, 2016, *In Press*; DOI:10.1016/j.micpath.2016.01.010

Litz, J.; Thakkar, N.; Portet, T.; Keller, S.

Depletion with cyclodextrin reveals two populations of cholesterol in model lipid membranes

Methyl-β-cyclodextrin, Phosphatidylcholine

Biophysical Journal, 2016, 110, 635-645; DOI:10.1016/j.bpj.2015.11.021

Lorza-Gil, E.; Salerno, A. G.; Wanschel, A. C.; Vettorazzi, J. F.; Ferreira, M. S.; Rentz, T.; Catharino, R. R.; Oliveira, H. C.

Chronic use of pravastatin reduces insulin exocytosis and increases β-cell death in hypercholesterolemic mice

Removing cholesterol from isolated islets using methyl-beta-cyclodextrin, Insulin secretion, Statins, LDL receptor, SNARE proteins, Diabetes

Toxicology, 2016, 344-346, 42-52; DOI:10.1016/j.tox.2015.12.007

Porter, F. D.; Farhat, N. Y.; Ottinger, E. A.; McKew, J. C.; Weissfeld, L.; Machielse, B.; Berry-Kavis, E. M.; Vite, C. H.; Walkley, S. U.; Ory, D. S.

Phase 1/2 evaluation of intrathecal 2-hydroxypropyl-β-cyclodextrin for the treatment of Niemann-Pick disease type C1

Molecular Genetics and Metabolism, 2016, 117, S97-; DOI:10.1016/j.ymgme.2015.12.411

Textor, M.; Keller, S.

Chapter Six - Calorimetric quantification of cyclodextrin-mediated detergent extraction for membrane-protein reconstitution

Transition from micelles to bilayer membranes, Cyclodextrin/detergent inclusion complex, Lipid/detergent phase diagram, Critical micellar concentration, Isothermal titration calorimetry

Calorimetry, Feig, A. L. Ed., Academic Press, 2016, 567, 129-156; DOI:10.1016/bs.mie.2015.07.033

Torres, M.; Corchete, P.

Gene expression and flavonolignan production in fruits and cell cultures of *Silybum marianum*.

Hepatoprotectant flavonolignan silymarin, Taxifolin, Coniferyl alcohol, Elicitation with methyl jasmonate or cyclodextrins, Flavonolignan accumulation

Journal of Plant Physiology, 2016, 192, 111-117; DOI:10.1016/j.jplph.2016.02.004

Uçan, U.; Küçük, N.; Ahmad, E.; Naseer, Z.; Ceylan, A.; Serin, İ.; Aksoy, M.

Effect of different sugars supplemented to the extender in combination with cholesterol-loaded cyclodextrin (CLC) on post-thaw quality of ram spermatozoa

Number of total active sperm, Trehalose, Sucrose, Fructose

Small Ruminant Research, 2016, 136, 243-246; DOI:10.1016/j.smallrumres.2016.01.021

5. CDs in Food, Cosmetics and Agrochemicals

Bosquez-Molina, E.; Zavaleta-Mejía, L.

Chapter 2 - New bioactive biomaterials based on chitosan

Grafting of functional groups, Functionalized chitosan, Chemical or enzymatic modifications

Chitosan in the Preservation of Agricultural Commodities, Jiménez-Aparicio, S. B.-B. R. Ed., Academic Press, 2016, 33-64; DOI:10.1016/B978-0-12-802735-6.00002-1

Liu, F.; Antoniou, J.; Li, Y.; Majeed, H.; Liang, R.; Ma, Y.; Ma, J.; Zhong, F.

Chitosan/sulfobutylether-β-cyclodextrin nanoparticles as a potential approach for tea polyphenol encapsulation

Epigallocatechin gallate, Job's method

Food Hydrocolloids, 2016, 57, 291-300; DOI:10.1016/j.foodhyd.2016.01.024

López-Miranda, S.; Serrano-Martínez, A.; Hernández-Sánchez, P.; Guardiola, L.; Pérez, H.; Fortea, I.; Gabaldón, J. A.; Núñez-Delicado, E.

Use of cyclodextrins to recover catechin and epicatechin from red grape pomace

Extract phenolic compounds

Food Chemistry, 2016, 203, 379-385; DOI:10.1016/j.foodchem.2016.02.100

6. CDs for other Industrial Applications

Chate, A. V.; Rathod, U. B.; Kshirsagar, J. S.; Gaikwad, P. A.; Mane, K. D.; Mahajan, P. S.; Nikam, M. D.; Gill, C. H.

Ultrasound assisted multicomponent reactions: A green method for the synthesis of *N*-substituted 1,8-dioxo-decahydroacridines using β-cyclodextrin as a supramolecular reusable catalyst in water

One-pot, multicomponent cyclization of dimedone, Tandem Michael addition reaction

Chinese Journal of Catalysis, 2016, 37, 146-152; DOI:10.1016/S1872-2067(15)61005-1

Jaouadi, M.; Hbaieb, S.; Guedidi, H.; Reinert, L.; Amdouni, N.; Duclaux, L.

Preparation and characterization of carbons from β-cyclodextrin dehydration and from olive pomace activation and their application for boron adsorption

Adsorbents, Amorphous carbon from cyclodextrin, Activated carbon, Oxidation, Porosity

Journal of Saudi Chemical Society, 2016, *In Press*; DOI:10.1016/j.jscs.2016.01.001

Li, R.; Wu, Z.; Wang, Y.; Ding, L.; Wang, Y.

β-Cyclodextrin preventing protein aggregation in foam fractionation of bovine serum albumin

Phenylalanine residues

Journal of Biotechnology, 2016, 220, 33-34; DOI:10.1016/j.jbiotec.2016.01.007

Liu, R.-L.; Zhang, Z.-Q.; Jing, W.-H.; Wang, L.; Luo, Z.-M.; Chang, R.-M.; Zeng, A.-G.; Du, W.; Chang, C.; Fu, Q.

β-Cyclodextrin anchoring onto *pericarpium granati*-derived magnetic mesoporous carbon for selective capture of lopid in human serum and pharmaceutical wastewaters samples

Magnetic solid-phase extraction

Materials Science and Engineering: C, 2016, *In Press*; DOI:10.1016/j.msec.2016.02.004

Mousset, E.; Huguenot, D.; van Hullebusch, E. D.; Oturan, N.; Guibaud, G.; Esposito, G.; Oturan, M. A.

Impact of electrochemical treatment of soil washing solution on PAH degradation efficiency and soil respirometry

PAH extraction followed by advanced oxidation treatment of the washing solution, Electro-fenton process, Hydroxypropyl-β-cyclodextrin, Recirculation, Soil microbial activity, Tween® 80

Environmental Pollution, 2016, 211, 354-362; DOI:10.1016/j.envpol.2016.01.021

Noreña-Caro, D.; Álvarez-Láinez, M.

Functionalization of polyacrylonitrile nanofibers with β-cyclodextrin for the capture of formaldehyde

Crosslinking of β-Cyclodextrin on electrospun PAN fibers

Materials & Design, 2016, 95, 632-640; DOI:10.1016/j.matdes.2016.01.106

Rana, V.; Kissner, R.; Gaspard, S.; Levalois-Grützmacher, J.

Cyclodextrin as a complexation agent in the removal of chlordecone from water

Control the proliferation of various insects such as babana root borer, Activated carbon (AC), β-CD, γ-CD, Hybrid material (AC-γ-CD), Inclusion complex

Chemical Engineering Journal, 2016, 293, 82-89; DOI:10.1016/j.cej.2016.02.032

Škulcová, L.; Neuwirthová, N.; Hofman, J.; Bielská, L.

Assessment of the biological and chemical availability of the freshly spiked and aged DDE in soil

Bioaccumulation, Earthworms, Hydroxypropyl-β-cyclodextrin extraction, XAD, SPME

Environmental Pollution, 2016, 212, 105-112; DOI:10.1016/j.envpol.2016.01.042

Wang, M.; Fang, G.; Liu, P.; Zhou, D.; Ma, C.; Zhang, D.; Zhan, J.

Fe_3O_4@β-CD nanocomposite as heterogeneous Fenton-like catalyst for enhanced degradation of 4-chlorophenol (4-CP)

Pseudo-first-order kinetics, Radical scavengers, Superparamagnetic, Electron paramagnetic resonance (EPR)

Applied Catalysis B: Environmental, 2016, 188, 113-122; DOI:10.1016/j.apcatb.2016.01.071

Yao, Z.-J.; Hong, S.; Zhang, W.; Liu, M.; Deng, W.

Copper-catalyzed regioselective hydroboration of terminal alkynes in aqueous medium

Cyclodextrin–bispyridine ligand, Recyclable

Tetrahedron Letters, 2016, 57, 910-913; DOI:10.1016/j.tetlet.2016.01.049

7. CDs in Sensing and Analysis

Das, T.; Poria, D. K.; Purkayastha, P.

NIR-emitting chiral gold nanoclusters coated with γ-cyclodextrin are pH sensitive: Application as biomarker

Early detection of tumor formation, Dihydrolipoic acid incorporated γ-cyclodextrin, Fluorescent marker

Nanomedicine: Nanotechnology, Biology and Medicine, 2016, *In Press*; DOI:10.1016/j.nano.2015.12.386

Dong, L.-Y.; Wang, L.-Y.; Wang, X.-F.; Liu, Y.; Liu, H.-L.; Xie, M.-X.

Development of fluorescent FRET probe for determination of glucose based on β-cyclodextrin modified ZnS-quantum dots and natural pigment 3-hydroxyflavone

Glucose oxidase, Horseradish peroxidase, Serum, Urine

Dyes and Pigments, 2016, 128, 170-178; DOI:10.1016/j.dyepig.2016.01.032

Gholivand, M.-B.; Akbari, A.

A novel voltammetric sensor for citalopram based on multiwall carbon nanotube/(poly(p-aminobenzene sulfonic acid)/β-cyclodextrin)

Cyclic and differential pulse anodic stripping voltammetric techniques, Modified electrode

Materials Science and Engineering: C, 2016, *In Press*; DOI:10.1016/j.msec.2016.01.066

Guo, J.; Xiao, Y.; Lin, Y.; Zhang, Q.; Chang, Y.; Crommen, J.; Jiang, Z.

Influence of the linking spacer length and type on the enantioseparation ability of β-cyclodextrin functionalized monoliths

Mono-6-amino-6-deoxy-β-CD, Mono-6-ethylenediamine-6-deoxy-β-CD, Mono-6-hexamethylenediamine-6-deoxy-β-CD, Glycidyl methacrylate, Ethylene dimethacrylate

Talanta, 2016, 152, 259-268; DOI:10.1016/j.talanta.2016.02.016

Jiang, Z.; Li, G.; Zhang, M.

Electrochemical sensor based on electro-polymerization of β-cyclodextrin and reduced-graphene oxide on glassy carbon electrode for determination of gatifloxacin

Tablets and human urine samples, One-pot electro-polymerization, Differential pulse voltammetry

Sensors and Actuators B: Chemical, 2016, 228, 59-65; DOI:10.1016/j.snb.2016.01.013

Pu, W.; Lisha, W.; Li, Z.

Two rhodamine derived chemosensors excited by up-conversion lattice for cysteine detection: Synthesis, characterization and sensing behavior

Photobleaching, α-Cyclodextrin

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2016, 159, 223-230; DOI:10.1016/j.saa.2016.01.052

Shen, J.; Xin, X.; Liu, T.; Tong, L.; Xu, G.; Yuan, S.

Manipulation the properties of supramolecular hydrogels of α-cyclodextrin/Tyloxapol/carbon-based nanomaterials

Polyoxyethylene tert-octylphenyl ether, Graphene oxid, Graphene, Microstructures, Rheological properties, Optical sensor, Dispersion, Fluorescence quenching

Journal of Colloid and Interface Science, 2016, 468, 78-85; DOI:10.1016/j.jcis.2016.01.037

Shi, X.; Liu, F.; Mao, J.

The CGC enantiomer separation of 2-arylcarboxylic acid esters by using β-cyclodextrin derivatives as chiral stationary phases

2-Arylpropionic acids, 2,6-Di-O-pentyl-3-O-butyryl-β-cyclodextrin, Capillary gas chromatography

Analytica Chimica Acta, 2016, 912, 156-162; DOI:10.1016/j.aca.2016.01.037

Su, P.-G.; Lin, Y.-T.

Low-humidity sensing properties of diamine- and β-cyclodextrin-functionalized graphene oxide films measured using a quartz-crystal microbalance

Water vapor molecules, Hydrogen bonds, Adsorption dynamic analysis

Sensors and Actuators A: Physical, 2016, 238, 344-350; DOI:10.1016/j.sna.2015.11.034

Takeshita, T.; Kasaba, Y.; Hara, M.

Resonant two-photon ionization of aromatic hydrocarbons included in cyclodextrins

Sensing, Photoionization, Biphenyl, p-Terphenyl, p-Quaterphenyl, m-Terphenyl, o-Terphenyl, Laser flash photolysis, Straight-chain aromatic hydrocarbons, Inclusion complexes

Journal of Photochemistry and Photobiology A: Chemistry, 2016, 321, 128-136; DOI:10.1016/j.jphotochem.2016.01.023

Vetter, W.

Enantiomer separations by gas chromatography

Food authentication, Extraterrestrial life, Chiral stationary phase, Coordination complex, Modified cyclodextrin, α-Cyclodextrin, β-Cyclodextrin, γ-Cyclodextrin

Reference Module in Chemistry, Molecular Sciences and Chemical Engineering, Elsevier, 2016; DOI:10.1016/B978-0-12-409547-2.11723-8

Xu, J.; Gao, Y.; Li, B.; Jin, Y.

Cyclic up-regulation fluorescence of pyrene excimer for studying polynucleotide kinase activity based on dual amplification

γ-CD enhancement of pyrene excimer, Pyrene-labelled DNA

Biosensors and Bioelectronics, 2016, 80, 91-97; DOI:10.1016/j.bios.2016.01.046

Xu, J.-J.; Cao, J.; Peng, L.-Q.; Cao, W.; Zhu, Q.-Y.; Zhang, Q.-Y.

Characterization and determination of isomers in plants using trace matrix solid phase dispersion via ultrahigh performance liquid chromatography coupled with an ultraviolet detector and quadrupole time-of-flight tandem mass spectrometry

Extract isomers from different honeysuckle samples, β-Cyclodextrin

Journal of Chromatography A, 2016, 1436, 64-72; DOI:10.1016/j.chroma.2016.01.046

Yu, B.; Chi, M.; Han, Y.; Cong, H.; Tang, J.; Peng, Q.

Self-assembled and covalently linked capillary coating of diazoresin and cyclodextrin-derived dendrimer for analysis of proteins by capillary electrophoresis

Layer by layer, Lysozyme, Myoglobin, Bovine serum albumin, Ribonuclease A

Talanta, 2016, 152, 76-81; DOI:10.1016/j.talanta.2016.01.043

Zhang, M.; Zhao, H.; Yang, X.; Dong, A.; Zhang, H.; Wang, J.; Liu, G.; Zhai, X.

A simple and sensitive electrochemical sensor for new neonicotinoid insecticide Paichongding in grain samples based on β-cyclodextrin-graphene modified glassy carbon electrode

Low reduction potential, Low temperature

Sensors and Actuators B: Chemical, 2016, 229, 190-199; DOI:10.1016/j.snb.2016.01.119

Zhou, Z.; Han, Z.; Lu, Z.-R.

A targeted nanoglobular contrast agent from host-guest self-assembly for MR cancer molecular imaging

Multiple β-cyclodextrins attached POSS (polyhedral oligomeric silsesquioxane) nanoglobule, Adamantane–modified macrocyclic Gd(III) contrast agent, avβ3 integrin

Biomaterials, 2016, 85, 168-179; DOI:10.1016/j.biomaterials.2016.02.002

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