VOLUME 32. No. 2. FEBRUARY 2018 ISSN 0951-256X

# Cyclodextrin-enabled Cannabinoid Formulations

Cannabinoids are diverse chemical compounds acting on cannabinoid receptors CB1 and CB2. There are three main sources of cannabinoids: endocannabinoids produced naturally in the body of animals, phytocannanbinoids found in plants and synthetic cannabinoids.

Endocannabinoids, such as anandamide (arachidonoylethanolamine, AEA) and 2-arachidonylglycerol (2-AG) are produced in the human organism from the omega-6 fatty acid arachidonic acid (Fig. 1). They are neurotransmitters regulating several physiological functions, such as appetite, pain, mood, immune function, memory, inflammation, and body temperature, through binding to CB1 and CB2 receptor proteins.

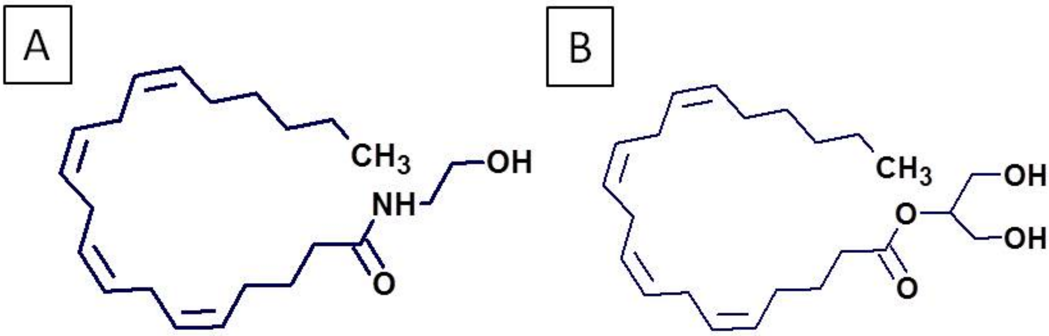


Fig. 1 Chemical structure of anandamide (A) and 2-AG (B)

The plant-derived cannabinoids act on the same receptors. In *Cannabis sativa* plant (Fig. 2), the richest source of phytocannabinoids there are around 70 such compounds. The most well-known is delta-9-tetrahydrocannabinol (THC, Fig. 3), primarily responsible for the euphoric and psychoactive effects of cannabis.

Fig. 2 Cannabis sativa

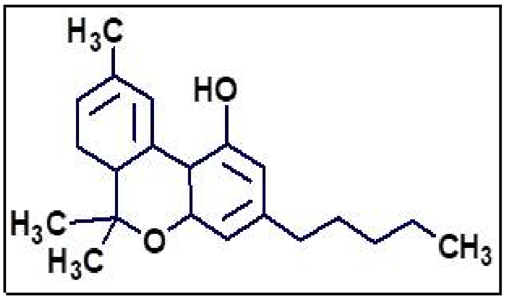


Fig. 3 Chemical formula of THC

Cannabis has been used for medicinal purposes for thousands of years. Its active compounds produce pharmacological effects throughout the body, especially in the central nervous system and the immune system. THC was found to relieve pain and inflammation, has muscle relaxant effect, it is neuroprotective and antioxidant. It has benefits in the treatment of cancer-related side effects (anti-vomiting effect), helps reduce the nausea and weight-loss associated with HIV/AIDS chemotherapy, has indications in the treatment of multiple sclerosis, chronic neuropathic pain and glaucoma (Grotenhermen, 2004). Cannabidiol (CBD), the second most common cannabinoid in medicinal marijuana provides potent therapeutic benefits without psychoactive effects (euphoria or lethargy).

The two main modes of cannabinoid administration, oral ingestion of tetrahydrocannabinol (THC) and smoking of dry cannabis plant material, both have specific advantages and disadvantages (Grotenhermen, 2004). Disadvantages of oral ingestion (oil drops, capsules, tea) include slow and insufficient absorption, delayed onset of action and low systemic bioavailability, whereas disadvantages of smoking include mucosal damage and short duration of effect. In recent years several new modes of cannabinoid delivery have been studied.

To avoid or at least reduce the formation of carcinogenic combustion products found in cannabis smoke alternative route of systemic pulmonary administration with a vaporizer was developed. The more and more popular electronic cigarettes or vapor producing devices, which heat the e-liquid or e-juice and creates vapor (aerosol) to be inhaled by the user, apply cannabis oil or extract diluted with glycerol or propylene glycol. Sublingual (buccal) administration of liquid cannabis extracts (sprays) might be another option enabling easier dose titration than oral capsules.

Topical administration (creams and oils) is useful for local pain relief. Transdermal patches have longer lasting effect than inhalation or oral administration. Rectal administration of THC-hemisuccinate suppositories resulted in systemic bioavailability twice as high as with oral administration because of the reduced first-pass effect (Brenneisen et al., 1996).

The aerosols, sprays, eye drops, etc. require aqueous solutions of these highly lipophylic active compounds. In addition to the development of water-soluble agonists to the cannabinoid receptor, such as Dexanabinol, cyclodextrins (CDs) were also used to enhance the solubility of cannabinoids. The HPBCD-solubilized THC was found useful also for intrathecal and intracerebroventricular administration (Agabio et al., 2017). Table 1 gives examples on CD application in various formulations aimed for improved sublingual, pulmonary, oral and nasal mucosal, as well as topical absorption.

Table 1 CD application for cannabinoid formulations

| Cannabinoid | CD | Effect | Reference |
|---|---|---|---|
| Endocannabinoids | | | |
| Anandamide and derivatives | HPBCD | ↑ aqueous solubility and stability<br>↑ corneal penetration | Jarho et al., 1996a<br>Jarho et al., 1996b<br>Juntunen et al., 2005 |
| Phytocannabinoids | | | |
| Cannabis extract | CD (not specified) | ↑ sublingual and pulmonal bioavailability | Stittes, 2017 |
| THC | BCD | ↑ stability and sublingal bioavailability | Shoyama et al., 1983<br>Mannila et al. 2006 |
| | HPBCD | ↑ solubility (1000 fold) | Jarho et al., 1998<br>Degeeter & Johnson, 2017 |
| | RAMEB | ↑ solubility and oral and sublingual bioavailability | Mannila et al., 2005<br>Hazekamp & Verpoorte, 2006 |
| | GCD | ↑ absorption through the oral mucosa | Zerde & Paiement, 2011 |
| THC hemiglutarate | RAMEB | ↑ solubility and transcorneal permeability | Hingorani et al., 2012 |
| THC hemisuccinate | HPBCD, RAMEB | ↑ solubility | Upadhye et al., 2010 |
| THC monovaline-hemisuccinate ester | HPBCD | ↑ solubility, stability, transcorneal permeability | Adelli et al., 2017 |
| D-8 THC | HPBCD, RAMEB and SBEBCD | ↑ solubility and transcorneal permeability | Hippalgaonkar et al., 2011 |
| cannabidiol (CBD) | BCD | ↑ dissolution rate and absorption via sublingual admin. | Mannila et al., 2007 |
| | HPBCD | ↑ solubility and lowering intraocular pressure | Arsenovic et al., 2000 |
| | DIMEB | ↓ nasal absorption | Paudel et al., 2010 |
| | GCD | ↑ dissolution rate | Jarho et al., 2009 |
| cannabigerol (CBG) | RAMEB | ↑ solubility | Hazekamp & Verpoorte, 2006 |
| cannabinol derivatives | DIMEB* | ↑ solubility and analgesic effect | Korbonits et al., 1985 |
| b-caryophyllene** | BCD | ↑ oral bioavailability and attenuation of non-inflammatory chronic muscle pain | Liu et al., 2013<br>Quintas-Júnior et al., 2016 |
| | HPBCD | ↑ solubility and bioavailability | Lou et al., 2017 |
| Synthetic cannabinoids and cannabinoid mimics | | | |
| MDA7*** | HPBCD | ↑ solubility, bioavailability and antiallodynic effect | Asruc-Diaz et al., 2013 |
| Nabilone | RAMEB | ↑ aqueous solubility | Viernstein & Wolschann, 2012 |
| R-(+)-WIN 55,212-2 mesylate | RAMEB | ↑ solubility and nasal bioavailability | Agu et al., 2006<br>Hingorani et al., 2012 |

*The concentrated DIMEB solution itself showed slight analgesic effect

** natural bicyclic sesquiterpene binding selectively binding to CB2 receptor, beneficial for colitis, osteoarthritis, diabetes, Alzheimer disease, anxiety, depression, etc., "dietary cannabinoid" found in cannabis and other plants (Hartsel et al., 2016)

***methylenedioxyamphetamine derivative

The above studies show that the parent CDs give water-insoluble complexes with cannabinoids useful for sublingual administration in solid form (Mannila et al., 2007), while using the complexation with soluble CD derivatives, especially with HPBCD and RAMEB, concentrated aqueous solutions can be obtained. The cannabinoids dissolved in CD solutions are degraded in a lower extent compared to ethanolic solutions. The complex association constants calculated from the phase-solubility studies show high affinity of these CDs especially of methylated CDs to cannabinoids (Table 2).

Table 2 Complex association constants for 1:1 cannabidiol:CD complexes

| | AEA | THC | CBD |
|---|---|---|---|
| HPBCD | $3.9x10^4$ [a] | $4.2x10^3$ [b] | $1.4x10^4$ [b] |
| HPGCD | $1.5x10^4$ [a] | | |
| DIMEB/RAMEB | $7.4x10^5$ [a] | $2.0x10^4$ [b] | $4.8x10^5$ [b] |

[a] Jarho et al., 1996b [b]Jarvinen et al., 2005

The data in Table 2 were calculated for 1:1 molar ratio, but the stoichiometry based on the Job's plot (continuous variation plot) was found to be 2:1 (guest:host) for THC/RAMEB complex (Hazekamp & Verpoorte, 2006). NMR studies revealed that one of the THC molecules is included in the cavity while the second THC is in non-inclusion interaction between the methyl groups from CHT and RAMEB (Fig. 4).

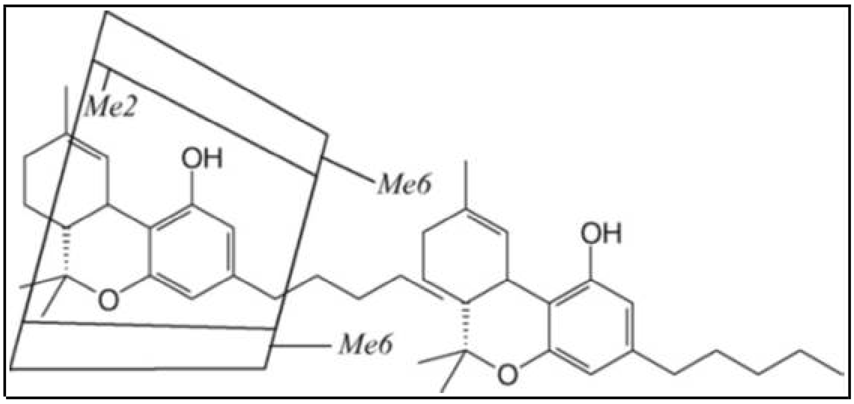


Fig. 4 Possible structure of CHT/RAMEB 2:1 complex based on detailed NMR study (Hazekamp & Verpoorte, 2006)

Concerning the practical applications of CD solubilized/stabilized cannabinoids several Chinese patents disclose various herbal compositions containing also cannabis seed-oil stabilized by BCD. For instance, herbal medicine pill for treating constipation (Li & Zhang, 2012), fructus cannabis pill for treatment of constipation and bowel discomfort (Zhou & Zhou, 2013, Tan et al., 2016), tea for patients in gastric cancer (Hu, 2014), intestine-lubricating and bowel-relaxing granules (Yuan, Y.F., 2016) have been patented. Yoghurt enriched with herbal excipients, such as cannabis seeds, and BCD as health food is claimed useful for soothing nerves, reducing blood pressure and blood fat, dispelling wind-damp, cold and heat, losing weight, resisting aging and relaxing bowels (Gao, 2017).

On the analogy of powdered alcohol (Palcohol) prepared by complexing alcoholic drinks with CD, powdered weed, the cyclodextrin-encapsulated cannabinoid is expected to get on the market (High Times, 2015).

Capsules marketed under the trade name of Energy contain Hydro Hemp™ (a completely water-soluble micelle preparation of true Full Spectrum Hemp Oil Powder), D-Ribose, Capsaicin, DMG, and Alpha Cyclodextrin to help naturally promote overall performance and feelings of vigor (CBD.co, 2018)

Fig. 5 Powdered weed (High Times, 2015)

**References**

Adelli, G.R., Bhagav, P., Taskar, P., Hingorani, T., Pettaway, S., Gul, W., ElSohly, M.A., Repka, M.A., Majumdar, S. (2017) Development of a Δ9-tetrahydrocannabinol amino acid-dicarboxylate prodrug with improved ocular bioavailability. Invest. Ophthalmol. Vis. Sci. 58, 2167–2179

Agabio, R., Sanna, F., Lobina, C., Monduzzi, M., Nairi, V., Cugia, F., Mameli, S., Pisanu, G.M., Melis, M.R. (2017) Is 2-Hydroxypropyl-β-cyclodextrin a suitable carrier for central administration of Δ9-Tetrahydrocannabinol? Preclinical evidence. Drug Dev. Res. 78, 411–419

Arsenovic, J.; Tucker, I.G.; Davies, N.M. (2000) Formulating aqueous solutions of cannabinoids using cyclodextrins for effective lowering of intraocular pressure. Proc. Int. Symp. Controlled Release Bioact. Mater., 27th, 606–607

Astruc-Diaz, F., McDaniel, S.W., Xu, J.J., Parola, S., Brown, DL., Naguib, M., Diaz, P. (2013) In vivo efficacy of enabling formulations based on hydroxypropyl-beta-cyclodextrins, micellar preparation, and liposomes for the lipophilic cannabinoid CB2 agonist, MDA7. J. Pharm. Sci. 102(2), 352–364

Brenneisen, R., Egli, A., Elsohly, M.A., Henn, V., Spiess, Y. (1996) The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. Int. J. Clin. Pharmacol. Ther. 34(10), 446–452.

CBD.co (2018) https://cbd.co/product/energy-cbd-complex/

Degeeter, D.M. & Johnson, L. (2017) Water soluble cannabinoid inclusion complexes. WO2017183011

Grotenhermen, F. (2004) Cannabinoids for therapeutic use: designing systems to increase efficacy and reliability. Am. J. Drug Del. 2(4), 229–240

Gao, J.F. (2017) Set yogurt and preparation method thereof. CN106942376

Gu, H. (2003) Regioselective process for the synthesis of Δ-tetrahydrocannabinol. WO2004092101

Hartsel, J.A., Eades, J., Hickory, B., Makriyannis, A. (2016) *Cannabis sativa* and Hemp. In: Gupta, R.C. (ed.) Neutraceuticals. Efficacy, Safety and Toxicity. Academic Press. pp. 735–754

High Times (2015) Forget powdered alcohol, is powdered weed the next? High Times, Marijuana News, March 16. https://hightimes.com/news/forget powdered alcohol is powdered weed next

Hingorani, T., Gul, W., Elsohly, M., Repka, M.A., Majumdar, S. (2012) Effect of ion pairing on in vitro transcorneal permeability of a DELTA9-tetrahydrocannabinol prodrug: Potential in glaucoma therapy. J. Pharm. Sci. 101(2), 61–626

Hippalgaonkar, K., Gul, W., ElSohly, M.A., Repka, M.A., Majumdar, S. (2011) Enhanced solubility, stability, and transcorneal permeability of δ-8-tetrahydrocannabinol in the presence of cyclodextrins. AAPS PharmSciTech 12, 723–731

Hu, A. (2014) Tea capable of alleviating gastric cancer. CN104171205

Korbonits, D., Szejtli, J., Stadler-Szőke, A., Antus, S., Gottsegen, A., Nogradi, M., Furst, Zs., Knoll, J. (1985) Cannabinoids with an ether side chain. synthesis. solubilization and analgesic properties. Eur. J. Med. – Chim. Ther, 20, 492–494

Jarho, P., Urtti, A., Jarvinen, K., Pate, D.W., Järvinen, T. (1996a) Hydroxypropyl-β-cyclodextrin increases aqueous solubility and stability of anandamide. Life Sci. 58(10), 181-185

Jarho, P., Urtti, A., Pate, D.W., Suhonen, P., Järvinen, T. (1996b) Increase in aqueous solubility, stability and in vitro corneal permeability of anandamide by hydroxypropyl-β-cyclodextrin. Int. J. Pharm. 137(2), 209–216

Jarho, P., Pate, D.W., Brenneisen, R., Järvinen, T. (1998) Hydroxypropyl-β-cyclodextrin and its combination with hydroxypropyl methyl cellulose increases aqueous solubility of Δ9-tetrahydrocannabinol. Life Sci. 63(26), 381–384

Jarho, P., Mannila, J., Järvinen, T. (2002) Natural cyclodextrin complexes. US7592328

Järvinen, T., Mannila, J., Jarho, P. (2002) Novel methylated cyclodextrin complexes. US7423026

Juntunen, J., Järvinen, T., Niemi, R. (2005) In-vitro corneal permeation of cannabinoids and their water-soluble phosphate ester prodrugs. Journal of Pharmacy and Pharmacology, 57(9), 1153-1157

Li, Z.H., Zhang, X.J. (2012) Chinese herbal medicine pill for treating constipation. CN102688379

Liu, H., Yang, G., Tang, Y., Cao, D., Qia, T., Qi, Y., Fan, G. (2013) Physicochemical characterization and pharmacokinetics evaluation of β-caryophyllene/β-cyclodextrin inclusion complex. Int. J. Pharm. 450, 304–310

Lou, J., Teng, Z., Zhang, L., Yang, J., Ma, L., Wang, F., Tian, X., An, R., Yang, M., Zhang, Q., Xu, L., Dong, Z. (2017) β-Caryophyllene/hydroxypropyl-β-cyclodextrin inclusion complex improves cognitive deficits in rats with vascular dementia through the cannabinoid receptor type 2-mediated pathway front. Pharmacol., doi: 10.3389/fphar.2017.00002

Mannila, J., Järvinen, T., Jaervinen, K., Tarvainen, M., Jarho, P. (2005) Effects of RM-beta-CD on sublingual bioavailability of Δ9-tetrahydrocannabinol in rabbits. Eur. J. Pharm. Sci. 26(1), 71–77

Mannila, J., Järvinen, T., Järvinen, K., Tervonen, J., Jarho, P. (2006) Sublingual administration of Δ9-tetrahydrocannabinol/ β-cyclodextrin complex increases the bioavailability of Δ9-tetrahydrocannabinol in rabbits. Life Sci. 78(17), 1911–1914

Mannila, J., Järvinen, T., Järvinen, K., Jarho, P. (2007) Precipitation complexation method produces cannabidiol/beta- cyclodextrin inclusion complex suitable for sublingual administration of cannabidiol. J. Pharm. Sci. 96(2), 312–319

Paudel, K.S., Hammell, D.C., Agu, R.U., Valiveti, S., Stinchcomb, A.L. (2010) Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers. Drug Dev. Ind. Pharm. 36(9), 1088–1097

Quintans-Júnior, L.J., Araújo, A.A.S., Brito, R.G., Santos, P.L., Quintans, J.S.S., Menezes, P.P., Serafini, M.R., Silva, G.F., Carvalho, F.M.S., Brogden, N.K., Slukaf, K.A. (2016) β-caryophyllene, a dietary cannabinoid, complexed with β-cyclodextrin produced anti-hyperalgesic effect involving the inhibition of Fos expression in superficial dorsal horn. Life Sci. 149, 34–41

Shoyama, Y., Morimoto, S., Nishioka, I. (1983) Cannabis. XV. Preparation and stability of Δ9-tetrahydrocannabinol-b-cyclodextrin inclusion complex. J. Nat. Prod. 46(5), 633–637

Stittes, A. (2017) Cannabinoid compositions for sublingual spray nebulizer. WO2017193110

Tan, X.Z., Jin, H.Y., Zhou, Y.P. (2016) Traditional Chinese medicine for treating constipation and preparation method of traditional Chinese medicine. CN105582124

Upadhye, S.B., Kulkarni, S.J., Majumdar, S., Avery, M.A., Gul, W., ElSohly, M.A., Repka, M.A. (2010) Preparation and characterization of inclusion complexes of a hemisuccinate ester prodrug of δ9-tetrahydrocannabinol with modified beta-cyclodextrins. AAPS PharmSciTech 11, 509–517

Viernstein, H., Wolschann, P. (2012) The Complexation of nabilone with methylated beta-cyclodextrins? A theoretical and an experimental study. 16th Int. Symp. Cyclodextrin, Tianjin, P. R.China (2012) PP-078

Yuan, Y.F. (2016) Intestine-lubricating and bowel-relaxing granules as well as preparation method thereof. CN105795303

Zerbe, H.G., Paiement, N. (2011) Oral mucoadhesive dosage form. US 8735374

Zhou, T., Zhou, D. (2013) Fructus cannabis pill. CN103191234

# Cyclodextrin News Retrospective

## *We wrote 10, 20 and 30 years ago*

10 years ago, Cyclodextrin News editorial summarized the major results collected from 120 papers and publications dedicated to the interaction betwen CDs and genetic materials (nucleic acids, DNA, RNA siRNA, nucleotides etc) and surveyed the knowledge accummulated around the utilization of CDs in delivery of genetic material. The collection covered a 37-year time period, from the first papers on the interaction of nucleotides and CDs until the announcement of the first human trial of CD-assisted transfection.
Szente, L. „Utilization of cyclodextrins in delivery of genetic material", CD News VOLUME 22. No. 2. FEBRUARY 2008

Due to the increasing interest and the endless potential of this important research area, this topic was one of the hottest fields at last year's European Cyclodextrin Conference held in Lisbon. The advances were just recently re-visited in one of the CD News editorials published at the end of last year.

„CD-based drug and gene delivery systems on the 5th European Cyclodextrin Conference", CD News VOLUME 31. No. 10. October 2017

20 years ago, the use of cyclodextrins in eyedrop formulations was discussed along Ph.D. dissertation of Pekka Jarho: Cyclodextrins in eyedrop formulations: at the University of Kuopio, 1997.
It is just a mere coincidence that the previous isssue of CD News reported on a success of Oculis' investigational ocular product developed by Prof. Loftsson's group based on a revolutionary idea that the formation of cyclodextrin-drug microparticulate aggregates is not a phenomenon to be best avoided. Right on the contrary! These agglomerates can be really suitable and effective drug carriers even in the treatment of such a sensitive organ like the eye.
„Cyclodextrin microparticles for ocular drug delivery targeted to the posterior segment of the eye", CD News VOLUME 32. No. 1. January 2018

30 years ago, the highlighted topic was cyclodextrins in chromatography. The versatility of cyclodextrins was demonstrated by the use in gas chromatograpy, thin layer chromatography, gel-inclusion chromatography, HPLC, affinity chromatography and electrokinetic chromatography. Since then, the technique reached scientific interest as high as sky (literally) since Curiosity Mars Rover (still active to date) carries a so-called Mars Organic Molecule Analyzer Instrument. This device includes CP Chirasil Dex CB (Agilent) enantioselective column containing cyclodextrin bonded to dimethylpolysiloxane aimed to distinguish organic enantiomers. One path to finding life on other planets or moons involves looking for amino acids which are critical to life on Earth. Nevertheless looking for these molecules on Mars or other planetary surfaces has been a major challenge. The Curiosity rover attempted to accomplish this, but the rover's experiments to identify organic chemicals in Martian samples were complicated by reactions with other materials in the samples. Recently a research group at Jet Propulsion Laboratory, California Institute of Technology created novel methods based on capillary electrophoresis to process soil or ice samples and detect 17 different amino acids simultaneously using beta- and gamma-cyclodextrins (Jessica S. Creamer , Maria F. Mora, and Peter A. Willis (2017): Enhanced resolution of chiral amino acids with capillary electrophoresis for biosignature detection in extraterrestrial samples. Anal. Chem., 89 (2), 1329–1337). We hope that the trust in cyclodextrins will eventually worth true breakthrough explorations on Earth and beyond!

# Bibliography & Keywords of Selected Publications of the Month

Qiu C.; Wang, J.; Fan, H.; Bai, Y.; Tian, Y.; Xu, X.; Jin, Z.

**High-efficiency production of γ-cyclodextrin using β-cyclodextrin as the donor raw material by cyclodextrin opening reactions using recombinant cyclodextrin glycosyltransferase**

*Cyclodextrin opening reactions in the presence of maltose*

Carbohydrate Polymers, 2018, 182, 75 - 80;

DOI:https://doi.org/10.1016/j.carbpol.2017.11.014

Kuczora, S.

**14 - Authorised EU health claim for alpha-cyclodextrin**

*Review, Health claim for alpha-cyclodextrin, Reduction of post-prandial glycaemic responses*

Foods, Nutrients and Food Ingredients with Authorised EU Health Claims, 219 – 228, Editor: Sadler, M. J. 2018, Woodhead Publishing Series in Food Science, Technology and Nutrition

DOI: https://doi.org/10.1016/B978-0-08-100922-2.00014-0

Jansook, P.; Ogawa, N.; Loftsson, T.

**Cyclodextrins: structure, physicochemical properties and pharmaceutical applications**

*Review, CD aggregate formation, Effect of too much or too little CD on drug bioavailability*

International Journal of Pharmaceutics, 2018, 535, 272 - 284;

DOI:https://doi.org/10.1016/j.ijpharm.2017.11.018

Li, X.; Uehara, S.; Sawangrat, K.; Morishita, M.; Kusamori, K.; Katsumi, H.; Sakane, T.; Yamamoto, A.

**Improvement of intestinal absorption of curcumin by cyclodextrins and the mechanisms underlying absorption enhancement**

*Rat intestine, Claudin-4, Membrane fluidity, Paracellular and transcellular pathways*

International Journal of Pharmaceutics, 2018, 535, 340 - 349;

DOI:https://doi.org/10.1016/j.ijpharm.2017.11.032

Sali, N.; Csepregi, R.; Kőszegi, T.; Kunsági-Máté, S.; Szente, L.; Poór, M.

**Complex formation of flavonoids fisetin and geraldol with β-cyclodextrins**

*Chemically modified cyclodextrins, Fluorescence enhancers of flavonoids, HepG2 tumor cell line*

Journal of Luminescence, 2018, 194, 82 - 90;
DOI:https://doi.org/10.1016/j.jlumin.2017.10.017

Semeraro, P.; Chimienti, G.; Altamura, E.; Fini, P.; Rizzi, V.; Cosma, P.

**Chlorophyll a in cyclodextrin supramolecular complexes as a natural photosensitizer for photodynamic therapy (PDT) applications**

*Amphipathic porphyrin, 2-HP-BCD, 2-HP-GCD, DIMEB, TRIMEB, Human colorectal adenocarcinoma HT-29 cell line, Phototoxicity*

Materials Science and Engineering: C, 2018, 85, 47 - 56;

DOI:https://doi.org/10.1016/j.msec.2017.12.012

Yu, S. H.; Lee, M. J.; Youn, S. Y.; Oh, T. K.; Na, K.; Lee, S. E.

**β-cyclodextrin-phenylacetic acid mesh as a drug trap**

*Biodegradable mesh, Bioinspired by the spider web, Electrospinning using GCD conjugated with phenylacetic acid, 4-week drug release*

Carbohydrate Polymers, 2018, 184, 390 - 400;

DOI:https://doi.org/10.1016/j.carbpol.2017.12.078

Tao, J.; Xu, J.; Chen, F.; Xu, B.; Gao, J.; Hu, Y.

**Folate acid-Cyclodextrin/Docetaxel induces apoptosis in KB cells via the intrinsic mitochondrial pathway and displays antitumor activity in vivo**

*Repression of mitochondrial membrane potential, Glutathione, Overexpression of reactive oxygen species, Suppressing tumor growth*

European Journal of Pharmaceutical Sciences, 2018, 111, 540 - 548;

DOI:https://doi.org/10.1016/j.ejps.2017.10.039

Hu, J-W. Yen, M-W.; Wang, A-J.; Chu, I-M.

**Effect of oil structure on cyclodextrin-based Pickering emulsions for bupivacaine topical application**

*Triglyceride, Linear chain oil, Ring-structured oil, Release over an extended period, Permeation*

Colloids and Surfaces B: Biointerfaces, 2018, 161, 51 - 58;

DOI:https://doi.org/10.1016/j.colsurfb.2017.10.001

Perret, P.; Bacot, S.; Gaze, A.; Dit Maurin, A. G.; Debiossat, M.; Soubies, A.; Blanc-Marquis, V.; Choisnard, L.; Boutonnat, J.; Ghezzi, C.; Putaux, J. L.; Lancelon-Pin, C.; Riou, L. M.; Wouessidjewe, D.

**Biodistribution and preliminary toxicity studies of nanoparticles made of biotransesterified β-cyclodextrins and PEGylated phospholipids**

*Grafting alkyl chains, BCD-C10-nanoparticles, Increased stealthiness, Decreased in vivo elimination*

Materials Science and Engineering: C, 2018, 85, 7 - 17;

DOI:https://doi.org/10.1016/j.msec.2017.12.017

Li, Z.; Zhang, B.; Jia, S.; Ma, M.; Hao, J.

**Novel supramolecular organogel based on β-cyclodextrin as a green drug carrier for enhancing anticancer effects**

*BCD as gelator, Glycerol as solvent, 5-Fluorouracil, Methotrexate, In vitro cytotoxicity assay on human hepatocellular carcinoma cells lines*

Journal of Molecular Liquids, 2018, 250, 19 - 25;

DOI:https://doi.org/10.1016/j.molliq.2017.11.154

Huang, H.; Liu, M.; Jiang, R.; Chen, J.; Mao, L.; Wen, Y.; Tian, J.; Zhou, N.; Zhang, X.; Wei, Y.

**Facile modification of nanodiamonds with hyperbranched polymers based on supramolecular chemistry and their potential for drug delivery**

*Adamantine, Doxorubicin hydrochloride, Water dispersibility, Controlled drug release*

Journal of Colloid and Interface Science, 2018, 513, 198 - 204;

DOI:https://doi.org/10.1016/j.jcis.2017.11.009

Moruno-Manchon, F. J.; Uzor, N-E.; Kesler, R. S.; Wefel, S. J.; Townley, M. D.; Nagaraja, A. S.; Pradeep, S.; Mangala, S. L.; Sood, K. A.; Tsvetkov, S. A.

**Peroxisomes contribute to oxidative stress in neurons during doxorubicin-based chemotherapy**

*Oxidative stress, Reactive oxygen species (ROS), HPBCD, transcription factor TFEB, Autophagy, Lysosome, Pexophagy*

Molecular and Cellular Neuroscience, 2018, 86, 65 - 71;

DOI:https://doi.org/10.1016/j.mcn.2017.11.014

Zhang, Y.; Yang, D.; Chen, H.; Lim, Q. W.; Phua, Z. S. F.; An, G.; Yang, P.; Zhao, Y.

**Reduction-sensitive fluorescence enhanced polymeric prodrug nanoparticles for combinational photothermal-chemotherapy**

*BCD functionalized hyaluronic acid, Adamantane linked camptothecin/dye conjugate, Embedded disulfide bond, Tumor regression*

Biomaterials, 2018, - ;

DOI:https://doi.org/10.1016/j.biomaterials.2018.02.023

Liu, J.; Liang, H.; Li, M.; Luo, Z.; Zhang, J.; Guo, X.; Cai, K.

**Tumor acidity activating multifunctional nanoplatform for NIR-mediated multiple enhanced photodynamic and photothermal tumor therapy**

*Mesoporous silica coated gold nanorod, Indocyanine green, Peptide RLA, pH-mediated transition, Targeted accumulation of the nanoplatform in mitochondria, Reactive oxygen species, Local hyperthermia*

Biomaterials, 2018, 157, 107 - 124;

DOI:https://doi.org/10.1016/j.biomaterials.2017.12.003

Quinn, M. D. J.; Wang, T.; Al Kobaisi, M.; Craig, V. S. J.; Notley, M. S.

**PEO-PPO-PEO surfactant exfoliated graphene cyclodextrin drug carriers for photoresponsive release**

*Near-infrared (NIR) irradiation, Thermoreversible changes in viscosity, Injectable, multiple release point drug delivery depot*

Materials Chemistry and Physics, 2018, 205, 154 - 163;

DOI:https://doi.org/10.1016/j.matchemphys.2017.11.012

Sanbhal, N.; Mao, Y.; Sun, G.; Xu, R. F.; Zhang, Q.; Wang, L.

**Surface modification of polypropylene mesh devices with cyclodextrin via cold plasma for hernia repair: Characterization and antibacterial properties**

*Cold oxygen plasma treatment, Hexamethylene diisocyanate, Triclosan*

Applied Surface Science, 2018, - ;

DOI:https://doi.org/10.1016/j.apsusc.2017.12.192

Mansor, H. M.; Najberg, M.; Contini, A.; Alvarez-Lorenzo, C.; Garcion, E.; Jerome, C.; Boury, F.

**Development of a non-toxic and non-denaturing formulation process for encapsulation of SDF-1a into PLGA/PEG-PLGA nanoparticles to achieve sustained release**

*Chemokines, Lysozyme as a model protein, HPBCD as a stabilizer, PLGA carboxylic acid terminal capping, sustained release, Stromal cell-derived factor-1a*

European Journal of Pharmaceutics and Biopharmaceutics, 2018, 125, 38 - 50;
DOI:https://doi.org/10.1016/j.ejpb.2017.12.020

Berben, P.; Brouwers, J.; Augustijns, P.

**The artificial membrane insert system as predictive tool for formulation performance evaluation**

*Cell- and tissue-free models to implement permeation into formulation testing, Effects of dilution on cyclodextrin-based itraconazole absorption*

International Journal of Pharmaceutics, 2018, 537, 22 - 29;

DOI:https://doi.org/10.1016/j.ijpharm.2017.12.025

Truong, M. N.; Wang, Y. R.; Movsesyan, N.

**Two-year follow-up of 2-hydroxypropyl-β-cyclodextrin for the treatment of Niemann-Pick disease type C1**

Molecular Genetics and Metabolism, 2018, 123, S141 - S142;

DOI:https://doi.org/10.1016/j.ymgme.2017.12.390

Berry-Kravis, E.; Chin, J.; Hoffmann, A.; Winston, A.; Stoner, R.; LaGorio, L.; Friedmann, K.; Hernandez, M.; Ory, S. D.; Porter, D. F.; O'Keefe, A. J.

**Long-term treatment of Niemann-Pick type C1 disease with intrathecal 2-hydroxypropyl-β-cyclodextrin**

*Investigational new drug, Cognitive/language, Gait/balance, Fine motor, Swallowing and eye movement, Stabilization of the disease, VTS-270*

Pediatric Neurology, 2018, - ;

DOI:https://doi.org/10.1016/j.pediatrneurol.2017.12.014

Okada, Y.; Ueda, E.; Kondo, Y.; Ishitsuka, Y.; Irie, T.; Higashi, T.; Motoyama, K.; Arima, H.; Matuso, M.; Higaki, K.; Ohno, K.; Nishikawa, J.; Ichikawa, A.

**Role of 6-O-α-maltosyl-β-cyclodextrin in lysosomal cholesterol deprivation in Npc1-deficient Chinese hamster ovary cells**

*Lysosomes, 6-O-α-D-glucosyl-β-cyclodextrin, Release of unesterified cholesterol*

Carbohydrate Research, 2018, 455, 54 - 61;

DOI:https://doi.org/10.1016/j.carres.2017.11.003

Tamura, A.; Yui, N.

**Polyrotaxane-based systemic delivery of β-cyclodextrins for potentiating therapeutic efficacy in a mouse model of Niemann-Pick type C disease**

*Acid-cleavable stopper molecules, Prolonged life span, Suppressed neurodegeneration in mice*

Journal of Controlled Release, 2018, 269, 148 - 158;

DOI:https://doi.org/10.1016/j.jconrel.2017.11.016

Mazzaglia, A.; Scala, A.; Sortino, G.; Zagami, R.; Zhu, Y.; Sciortino, T. M.; Pennisi, R.; Pizzo, M. M.; Neri, G.; Grassi, G.; Piperno, A.

**Intracellular trafficking and therapeutic outcome of multiwalled carbon nanotubes modified with cyclodextrins and polyethylenimine**

*Cidofovir, DNA plasmid encoding enhanced green fluorescence protein, Clathrin-dependent pathway*

Colloids and Surfaces B: Biointerfaces, 2018, 163, 55 - 63;

DOI:https://doi.org/10.1016/j.colsurfb.2017.12.028

Xu, F.; Zhong, H.; Chang, Y.; Li, D.; Jin, H.; Zhang, M.; Wang, H.; Jiang, C.; Shen, Y.; Huang, Y.

**Targeting death receptors for drug-resistant cancer therapy: Codelivery of pTRAIL and monensin using dual-targeting and stimuli-responsive self-assembling nanocomposites**

*Chemoresistance, Low-molecular-weight PEI, Crosslinked by the sulfhydryl CD, Disulfide bonds, Poly-gamma-glutamic acid, Polyplex, Tumor-associated gamma-glutamyl transpeptidase, Tumor-homing peptide*

Biomaterials, 2018, 158, 56 - 73;

DOI:https://doi.org/10.1016/j.biomaterials.2017.12.018

Hayashi, Y.; Higashi, T.; Motoyama, K.; Jono, H.; Ando, Y.; Arima, H.

***In vitro* and *in vivo* siRNA delivery to hepatocyte utilizing ternary complexation of lactosylated dendrimer/cyclodextrin conjugates, siRNA and low-molecular-weight sacran**

*Serum resistance, Endosomal escaping ability in HepG2 cells, Hepatocyte-specific siRNA delivery system*

International Journal of Biological Macromolecules, 2018, 107, Part A, 1113 - 1121;
DOI:https://doi.org/10.1016/j.ijbiomac.2017.09.085

Malhotra, M.; Gooding, M.; Evans, C. J.; O'Driscoll, D.; Darcy, R.; O'Driscoll, M. C.

**Cyclodextrin-siRNA conjugates as versatile gene silencing agents**

*Amphiphilic polycationic cyclodextrin, Human glioblastoma cells (U87), Prostate cancer cells (PC3, DU145), Adamantyl-PEG ligands, Chitosan*

European Journal of Pharmaceutical Sciences, 2018, 114, 30 - 37;

DOI:https://doi.org/10.1016/j.ejps.2017.11.024

Fernandes, A.; Rocha, A. A. M.; Santos, L. M.N.B.F.; Bras, J.; Oliveira, J.; Mateus, N.; de Freitas, V.

**Blackberry anthocyanins: β-cyclodextrin fortification for thermal and gastrointestinal stabilization**

*Blackberry purees*

Food Chemistry, 2018, 245, 426 - 431;

DOI:https://doi.org/10.1016/j.foodchem.2017.10.109

Catchpole, O.; Mitchell, K.; Bloor, S.; Davis, P.; Suddes, A.

**Anti-gastrointestinal cancer activity of cyclodextrin-encapsulated propolis**

*Anti-gastrointestinal cancer, Anti-inflammatory, Anti-oxidant*

Journal of Functional Foods, 2018, 41, 1 - 8;

DOI:https://doi.org/10.1016/j.jff.2017.12.023

Cui, H.; Bai, M.; Lin, L.

**Plasma-treated poly(ethylene oxide) nanofibers containing tea tree oil/beta-cyclodextrin inclusion complex for antibacterial packaging**

*Electrospun nanofibers, Escherichia coli*

Carbohydrate Polymers, 2018, 179, 360 - 369;

DOI:https://doi.org/10.1016/j.carbpol.2017.10.011

Shlar, I.; Droby, S.; Rodov, V.

**Antimicrobial coatings on polyethylene terephthalate based on curcumin/cyclodextrin complex embedded in a multilayer polyelectrolyte architecture**

*Polyethylene terephthalate, Poly-L-lysine, Poly-L-glutamic acid, Carboxymethyl-BCD*

Colloids and Surfaces B: Biointerfaces, 2018, - ;

DOI:https://doi.org/10.1016/j.colsurfb.2018.02.008

Liu, W.; Lv. Y.; Tian, S.; Zhang, M.; Shu, T.; Hu, N.; Wu, Z.

**Foam fractionation for effective recovery of resveratrol from the leaching liquor of Polygonum cuspidatum by using partially ethylated β-cyclodextrin as collector and frother**

*Partially ethylated BCD, Generating stable foam*

Industrial Crops and Products, 2018, 112, 420 - 426;

DOI:https://doi.org/10.1016/j.indcrop.2017.12.035

Seema, K. M.; Mamba, B. B.; Njuguna, J.; Bakhtizin, R. Z.; Mishra, A. K.

**Removal of lead (II) from aqueous waste using (CD-PCL-$TiO_2$) bio-nanocomposites**

*Cyclodextrin-polycaprolactone titanium dioxide, Solution blending method*

International Journal of Biological Macromolecules, 2018, 109, 136 - 142;
DOI:https://doi.org/10.1016/j.ijbiomac.2017.12.046

Villaverde, J.; Rubio-Bellido, M.; Lara-Moreno, A. Merchan, F.; Morillo, E.

**Combined use of microbial consortia isolated from different agricultural soils and cyclodextrin as a bioremediation technique for herbicide contaminated soils**

*HPBCD, Enhancing pollutant bioavailability*

Chemosphere, 2018, 193, 118 - 125;

DOI:https://doi.org/10.1016/j.chemosphere.2017.10.172

Li, X.; Zhou, M.; Jia, J.; Ma, J.; Jia, Q.

**Design of a hyper-crosslinked β-cyclodextrin porous polymer for highly efficient removal toward bisphenol a from water**

*Crosslinking benzylated β-CD with dichloroxylene*

Separation and Purification Technology, 2018, 195, 130 - 137;

DOI:https://doi.org/10.1016/j.seppur.2017.12.007

Xuan, H.; Dai, W.; Zhu, Y.; Ren, J.; Zhang, J.; Ge, L.

**Self-healing, antibacterial and sensing nanoparticle coating and its excellent optical applications**

*BCD-modified poly(ethylenimine), Adamantane-modified poly(acrylic acid), Suppressing bacterial adhesion*

Sensors and Actuators B: Chemical, 2018, 257, 1110 - 1117;

DOI:https://doi.org/10.1016/j.snb.2017.11.078

Quirino, J. P.

**Sodium dodecyl sulfate removal during electrospray ionization using cyclodextrins as simple sample solution additive for improved mass spectrometric detection of peptides**

*Proteomics, Improved peptide analysis, Electrospray ionization mass spectrometry*

Analytica Chimica Acta, 2018, 1005, 54 - 60;

DOI:https://doi.org/10.1016/j.aca.2017.12.012

Lakkakula, R. J.; Divakaran, D.; Thakur, M.; Kumawat, M. K.; Srivastava, R.

**Cyclodextrin-stabilized gold nanoclusters for bioimaging and selective label-free intracellular sensing of $Co^{2+}$ ions**

*Glutathione protected ultra-small fluorescent gold nanoclusters*

Sensors and Actuators B: Chemical, 2018, - ;

DOI:https://doi.org/10.1016/j.snb.2018.01.219

Munoz, J.; Gonzalez-Campo, A.; Riba-Moliner, M.; Baeza, M.; Mas-Torrent, M.

**Chiral magnetic-nanobiofluids for rapid electrochemical screening of enantiomers at a magneto nanocomposite graphene-paste electrode**

*Electrocatalytic properties of chiral magnetic-nanobiofluids, Tryptophan, Cobalt ferrite loaded with gold nanoparticles carrying a thiolated BCD*

Biosensors and Bioelectronics, 2018, 105, 95 - 102;

DOI:https://doi.org/10.1016/j.bios.2018.01.024

Wu, M.; Li, P.; Zhu, Q.; Wu, M.; Li, H.; Lu, F.

**Functional paper-based SERS substrate for rapid and sensitive detection of Sudan dyes in herbal medicine**

*Illegally added fat-soluble dyes in herbal medicine, Mono-6-thio-cyclodextrin, Sudan dyes*

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2018, - ;
DOI:https://doi.org/10.1016/j.saa.2018.02.014