Patent News 3

This is the third series of abstracts of patents relating to the use of cyclodextrins, macrocyclics and other hosts. Patents relating to the use of zeolites will not be covered, since they are already available in the publication *Zeolites*. The previous abstracts can be found in Volume 10, pp 165–175, 1991. The patents appearing below are reprinted by courtesy of *Cyclodextrin News*.

Courregelongue, J., Maffrand, J. P. (1988): *Fr. Demande* FR 2,601,959 (*C.A.* **110**: 133986).

Cholesterol is removed from animal fat by complexation with β-CD. 10 g dehydrated butter was heated at 40°C under N_2 in the presence of 0.5 g of β-CD for 3 hours, then agitated with water for 3 hours. The lipid layer was separated and washed 3 times with deionized water, 26% cholesterol was eliminated from the treated butter. Elimination of 32% was obtained with 1.0 g β-CD.

Fukazawa, R., Sato, M. (1988): *Jpn. Kokai* JP 88,240,765 (*C.A.* **110**: 113433)

The food preserving effect of an aqueous solution of the hinokitiol-CD complex was studied. The preserved food (fruit, vegetable, confectionery, etc.) are damaged by the treatment. For example fresh lemons were soaked in a 0.2% aqueous hinokitiol-β-CD complex solution, the water then shaken off and stored in cardboard boxes at 25–30°C for 106 days. Mold was observed in 8/150 versus 60/150, for controls. The lemon flavour lasted for more than 106 days, whereas no trace of flavour was recognized for the controls.

Tomida, Y., Koike, S. (1988): *Eur. Pat. Appl.* EP 280,458 (*C.A.* **110**: 116888)

Using α-CD a storage-stable ink has been prepared for ink-jet recording, for copying or bond paper.

Rendleman, J. A. (1988): *U.S. Pat. Appl.* US 159,990 (*C.A.* **110**: 156398)

CD containing mixtures can be fractionated by affinity chromatography on matrices which bear hydrophobic ligands. The size and structure of the hydrophobic ligands can be selected accordingly to the size of the different CDs. Br-CN-activated Bio-Gel was mixed with 4-phenylbutylamine to prepare a chromatographic packing material which could be used to separate glucose and different CDs.

Nishida, K., Takahashi, C., Kawaguchi, T., Horie, M., Chiwa, M. (1988): *Jpn. Kokai* JP 88,03,00 (*C.A.* **110**: 152766)

A siloxane-type silica gel can be used for the separation and purification of CDs from reducing sugar containing solutions.

Pitha, J. (1988): *U.S. Pat. Appl.* US 94,597 (*C.A.* **110**: 101782)

Crystalline complexes of steroid hormones with γ-CD are prepared and administered by contact with the mucosa, which avoids the difficulties associated with oral or parental steroid dosages. Testosterone 1 g and γ-CD 57 g were added to 500 mL water and the mixture was stirred at 25°C for 7 days; the 1:2 testosterone-γ-CD complex precipitated and was removed by filtration. In a human subject, sublingual administration of testosterone-γ-CD complex containing 10 ng testosterone gave serum testosterone levels of 1800–1200 ng/mL 2–3 h after administration, whereas these levels were 900–700 ng/mL after gastric tube administration.

Kamikama, K., Yoshida, A., Uehara, M. (1988): *Jpn. Kokai* JP 88,218,663 (*C.A.* **110**: 101775)

Pharmaceutical preparations, useful as coronary vasodilators, antihypertensives, etc. when modified by conjugating the dihydropyridine derivatives, to enable them to pass the brain blood barrier, generally become very poorly soluble in water. Therefore they have to be solubilized for example with hydroxy-

propyl-β-CD. Nimodipine (1 g) was mixed with 11.5 g hydroxypropyl-β-CD and 3 mL methanol for 1 h and dried to give 1:3 nimodipine-hydroxypropyl-β-CD inclusion compound, which was much more easily dissolved in water than nimodipine itself. Suppositories were prepared from 240 g nimodipine-hydroxypropyl-β-CD (degree of substitution 8.0) inclusion compound and 1760 g Witepsol H-15.

Furukawa, M., Hara, K. (1988): *Jpn. Kokai* JP 88,132,846 (*C.A.* **110**: 199204)

The CO_2 complex can be used as tablet disintegrating substance. On contacting with water the CO_2 is released resulting in disintegration of the compressed tablet.

Pitha, J. (1988): *U.S. Patent* US 4,727,064 (*C.A.* **110**: 179558)

The preparation of hydroxypropyl-β-CD and its application to improve the solubility and bioavailability of estradiol is described. The solubility of estradiol in water is less than 1.6 mg/mL, while in 40% hydroxypropyl-β-CD solution more than 28.0 mg/mL. The hydroxypropyl-β-CD with medium degrees of substitution (5–7) is a more effective solubilizer than the higher substituted derivatives. No microbial growth in such solutions was observed for several months at room temperature.

Kamikama, K., Yomo, K. (1988): *Jpn. Kokai* JP 88,135,402 (*C.A.* **110**: 179512)

The solubilization of drugs (digitoxin, nifedipine, flurbiprofen, isosorbid nitrate, phenytoin, progesterone, and testosterone was studied by maltosyl-β-CD. For example while the solubility of digitoxin in water is only 15 μg/mL, in a maltosyl-β-CD solution it was more than 300 μg/mL.

Suzuki, O., Yokochi, T., Ninomiya, Y., Higuchi, T. (1987): *Jpn. Kokai* JP 87,79,732 (*C.A.* **107**: 133049)

Milk or milk powder can be enriched in γ-linolenic acid by mixing with the milk or milk powder γ-linolenic acid containing triglycerides in CD complexed form. For example 10 g β-CD in 10 mL water was homogenized with 5 mL 70% γ-linolenic acid containing triglycerides. The powdered milk was mixed with inclusion complex to give an enriched product containing 0.1% γ-linolenic acid.

Ilyang Pharm. Co. Ltd. (1988): *Jpn. Kokai* JP 88,198,959 (*C.A.* **110**: 113442)

Beverages of carrot extracts containing a CD syrup as a stabilizer prevent sediment formation. Thus, 100 mL of a beverage was prepared containing a carrot liquid extract 450, 100 mg of a CD syrup with 14 other components including citric acid, Na glutamate, Na benzoate, riboflavin, etc. The beverage stored at 40°C for 1 month did not produce any precipitate.

Koike, T. (1988): *Jpn. Kokai* JP 88,198,936 (*C.A.* **110**: 113473)

Ginger is pickled with CD and acidic seasonings and preserved for more than one month. When ginger is pickled with seasoning solutions without CD and stored at room temperature for 1 month, it produces an unpleasant odour. Thus, 12 parts by weight ginger was soaked in 10 parts of a seasoning solution consisting of vinegar (acidity 8%) 11.1, citric acid 1.2, sugar 10.5, sorbitol 6.7, salt 4.9, β-CD 0.7, Red. No. 102 0.3, Na glutamate, and water to 100% by weight.

Toda, T. (1988): *Jpn. Kokai* JP 88,317,059 (*C.A.* **110**: 172023)

β- and/or γ-CD improves the storage stability of cooked soybeans.

Hane, H., Kenmasa G. (1989): *Jpn. Kokai* JP 89,02,552 (*C.A.* **110**: 191267)

The extract of Gymnema sylvestre is useful for pharmaceutical and low-calorie foods, has a bitter taste, which can be strongly reduced by CD, particularly by γ-CD.

Hasebe, K., Ando, Y., Chikamatsu, Y., Hayashi, K. (1988): *Jpn. Kokai* JP 88,08,309 (*C.A.* **110**: 121031)

A bath preparation containing aromatic essential oil-CD complexes and hinokitiol-CD complex was studied. Such a bath preparation contains Na_2SO_4 45-48, $NaHCO_3$ 39-42, borax 2, a coloring agent trace, and the inclusion compound 1–8% by weight.

Kishi, T., Iwakawa M. (1988): *Jpn. Kokai* JP 88,303,917 (*C.A.* **110**: 198972)

An oral odor reducing patch preparation is disclosed, which is made of a shape-retaining soft material having adhesive properties to the oral mucosa. This material contains CDs or CD derivatives as odor absorbents. The compositions control oral odor for a prolonged time and cause no adverse effects on mucous membrane.

Isoda, S., Kamiyama T., Kawakubo, H. (1988): *Jpn. Kokai* JP 88,238,166 (*C.A.* **110**: 59155)

Numerous materials – among them CDs – contain functional groups capable of electron transfer by quantum mechanical tunneling to make the transfer direction anisotropic.

Suzuki, A., Mochizuki, N., Sasaki, M. (1987): *Jpn. Kokai* JP 87,152,787 (*C.A.* **108**: 66034)

The media, which are useful for gradation imaging, comprise a heat-fusible ink layer containing an inclusion compound. Thus, a heat-fusible ink containing Sudan Red 460 as a guest, and α-CD as a host, modified lanolin oil, carnauba wax, paraffin wax, liquid paraffin, and a dispersant was prepared, mixed with vinyl chloride–vinyl acetate copolymer resin, and coated on a polyester film to give a thermal-transfer recording media. A magenta colored imager was recorded on the media with a thermal head.

Baker, T. S., Perry, M. J., Fleming, I. M. (1987): *PCT Int. Appl.* WO 87,02,774 (*C.A.* **108**: 71679)

A device for performing an enzyme-labeled binding assay comprises an absorbent material provided with reagent zones and an indicator reagent zone which includes a reagent capable of immobilizing an enzyme-labeled reagent and a developing solution. β-CD is used in a two site sandwich immunoassay for TSH determination.

Resul, B. (1987): *Swed.* SE 452,251 (*C.A.* **110**: 152653)

In test strips for occlusive epicutaneous tests for contact allergies the test substance is incorporated as the CD complex. The CD acts as a stabilizer. A perfume mixture (geraniol, cinnamaldehyde, hydroxycitronellal, cinnamyl, alcohol, eugenol, isoeugenol, etc.) was complexed with β-CD in water, then Klucel GF (hydroxypropylcellulose) was added to form a gel. This gel was then spread on an appropriate plastic film, after drying was cut into pieces and placed on self-adhering acylic type strip. These strips were packed in aluminium foil and stored at 40°C for 1.5 month and analyzed. 70–80% of the original perfume components have been retained, while without β-CD after two weeks for all components less than 5% remained.

Sakai, S., Yamamoto N., Chiwa M., Hashimoto H., Hara K. (1988): *Jpn. Kokai* JP 88,44,886 (*C.A.* **110**: 191424)

The preparation of an immobilized CGTase enzyme is described. A polymer comprising glycidylmethacrylate and ethylene glycol dimethacrylate was treated with tripropylamine. The product contained 1.42 meq anion exchange groups/dry g and 1.85 mmol alcoholic —OH groups/dry g. After treatment with 1 N NaOH, 1 g of this polymer was able to absorb 0.68 mg of CGTase enzyme, which has a long-lasting continuous activity due to its hydrophilic property and reversible binding with the high molecular weight substance.

Rohrbach, R. P., Scherl, D. S. (1988): *U.S. Patent* US 4,748,237 (*C.A.* **110**: 133709)

The yield of CDs is enhanced when C_{1-6} alcohols are added to the conversion mixture. For example adding 5% tert-butanol to a 5 wt.% partially hydrolyzed starch solution on immobilized CGT enzyme, the production of β-CD was elevated from 18.6 to 35.8 wt.%.

Kobayashi, S., Shibuya, N. (1988): *Jpn. Kokai* JP 88,216,492 (*C.A.* **110**: 152832)

Neotrehalose and centose can be produced from potato starch by the CGT enzyme under appropriate conditions. The mixture of these two sugars has been prepared in a 45% yield from enzymatically liquefied potato starch using 300 Tilden Hudson unit/g of the substrate.

Mizukoshi, M., Yorozu, H. (1988): *Jpn. Kokai* JP 88,148,938 (*C.A.* **110**: 153053)

CO_2 containing complexes can be used in foods and beverages. 100 g β-CD was pressurized with CO_2 (8 kg/cm^2) to obtain a product containing 3 g CO_2. A cake baked using this complex had a specific volume of 4.21 cm^3/g versus 1.95–2.05 for cakes using other kinds of swelling agents. In addition the flavor was better.

Yajima, M., Kitahira, R. (1988): *Jpn. Kokai* JP 88,104,991 (*C.A.* **110**: 153049)

CD complexation improves the taste of phytic acid and protects it from discoloration. The phytic acid is used as a food additive, and its discoloration should be avoided.

Motono, M. (1988): *Jpn. Kokai* JP 88,208,510 (*C.A.* **110**: 141302)

A skin-lightening composition was prepared, which inhibits melamin formation, complexing kojic acid with maltosyl CD. The low stability of the kojic acid is strongly improved, the composition of a lotion with the usual lotion components is described.

Oishi, T., Nakanishi, F., Yamamoto, T. (1988): *Eur. Pat. Appl.* EP 279,016 (*C.A.* **110**: 160215)

The preparation of a hair dye powder is described, which contains a CD-dye inclusion complex. This powder has a longer shelf-life and color-fastness than the conventional hair dyes, they are easier to control in manufacture storage and transport. Such hair dyes can be presented as one-component formulations, wherein the powder dye and a solid oxidizing agent are packed together; two-component formulations contain the powder dye and a liquid oxidizing agent for example H_2O_2. β-CD inclusion complexes of *p*-toluylenediamine, *m*-aminophenol or resorcinol were prepared. The composition of the hair preparation is described.

Shibagaki, H. (1988): *Jpn. Kokai* JP 88,317,044 (*C.A.* **110**: 172040)

Upon standing and cooling tea (hot-water extracts of tea) becomes turbid. This so called 'milk down' can be prevented by adding CD to the solution.

Onishi, K., Kotake, K. (1988): *Jpn. Kokai* JP 88,43,959 (*C.A.* **110**: 153047)

Anthocyanin pigments are stabilized by linking the OH group of glycosides with sugars, for example CDs, optionally using CGT as a catalyst. The stabilized anthocyanins are light- and heat-resistant and stable even at high pH. For example pigments from red cabbage were treated with 1 g α-CD and 2 mL CGT enzyme at pH 6.0 and 35–40°C for 10 hours. This stabilized pigment can be used in soft drinks with strongly improved heat-resistance.

Kikuchi, K., Sugiyama, H. (1988): *Jpn. Kokai* JP 88,191,802 (*C.A.* **110**: 191271)

CD fatty acid esters are useful as surfactants and can be prepared in high selectivity and yield by esterification of CDs with C_{8-22} fatty acid in the presence of hydrolase. Thus, a suspension of 28.4 g stearic acid and 9.8 g α-CD in phosphate buffer was stirred with 0.4 g lipase (from Rhizopus delemer) at 37°C for 5 hours to give 7.0 g ester selectivity esterified at primary hydroxy groups.

Miyasaka, T., Kitaguchi, H. (1988): *Jpn. Kokai* JP 88,256,679 (*C.A.* **110**: 215082)

Functional organic films comprising an amphiphilic organic compound mono- or multilayer film chemically bonded to CD derivatives on a support are useful for sensors. A long alkyl chain containing aralkylalkyl-sulphoxide-amide derivative forms a monomolecular layer on tristearylsilanolated hydrophobic glass plate, and then it was immersed in an aqueous solution of an aminoethylthio-β-CD derivative. The CD derivative was fixed on the thin film, and showed excellent reversible inclusion of 1-anilino-8-naphthalenesulfonic acid as shown by fluorescence intensity measurement.

Kusuda, M., Matsuoka, Y. (1988): *Jpn. Kokai* JP 88,101,342 (*C.A.* **110**: 172855)

p-Iodophenol can be prepared at high selectivity by treatment of phenol with iodine in the presence of β-CD. About 50% of the phenol was converted to the iodophenol derivative, the *para*/*ortho* ratio was 92:8.

Tamaoki, T., Ohashi, S., Sakuragi, M., Ichimura, K., Arima, I. (1988): *Jpn. Kokai* JP 88,223,084 (*C.A.* **110**: 145046)

The photochromic spirobenzopyran derivatives, when included in CD, show excellent heat stability and quick responses and are useful in optical recording materials.

Horie, M., Chiwa, M. (1988): *Jpn. Kokai* JP 88,314,201 (*C.A.* **110**: 175437)

The preparation of a new polymer is described, in which CD is fixed in crosslinked polymers. Glycidyl monovinyl ester or glycidyl monovinyl ether units containing crosslinked polymers are treated with HCl for ring opening and then treated with CD. This way 0.33 g β-CD/g polymer was prepared.

Takeva, Y. (1988): *Jpn. Kokai* JP 88,124,037 (*C.A.* **110**: 144590)

A structurally regular nonlinear optical inclusion compound was prepared by substituting up to 40% of the OH groups of a β-CD by palmitoyl chains. Reacting this β-CD derivative with *p*-nitroaniline and applied as a layer on a quartz glass gave a guest-host inclusion membrane having a maximum UV spectrum absorption at 360 nm, and green color when irradiated with a Nd:YAG laser.

Kitaguchi, H., Miyasaka, T. (1988): *Jpn. Kokai* JP 88,268,786 (*C.A.* **110**: 183043)

The photochromic properties of spiro(indolinonaphthoxazine) derivatives are improved in the presence of β-CD. Such photochromic compositions are useful for recording and memory materials, copying materials, optical filters, etc.

Ammeraal, R. N., Hedges, A. R., Gottneid, D. J. (1989): *Brit. UK Pat. Appl.* GB 2,206,583 (*C.A.* **110**: 233523)

The purification and separation of branched CD's is described. First the cyclic dextrins are precipitated by *p*-xylene, the precipitate formed is filtered and dried. In the second step this solid *p*-xylene complex is mixed with water, the dissolved fraction is separated by filtration, and evaporated to dryness. After redissolving toluene is used as a second precipitant, and the isolated substance contains 76% branched CD. A second reprecipitation by toluene resulted in 79% branched CD content.

Kurihara, K., Murano, M. (1988): *Eur. Pat. Appl.* EP 294,239 (*C.A.* **110**: 199234)

The cyclosporin solubilized by α-CD in aqueous solution showed a more than 20-fold better bioavailability in the cornea of rabbits, than the cyclosporin dissolved in peanut oil.

Fukazawa, R., Sato, M. (1987): *Jpn. Kokai* JP 87,236,440 (*C.A.* **108**: 130284)

Mushrooms were preserved in a plastic container containing hinokitiol-β-CD inclusion compound-treated paper in the bottom.

Chikahisa, N., Cho, S. (1989): *Jpn. Kokai* JP 89,40,567 (*C.A.* **110**: 233242)

Powders of porous silica filled with a fragrance and coated with β-CD give a uniform release of pleasant odor. Such controlled-release compositions with CDs can be prepared for cosmetics, coatings, greenhouse films, etc.

Ishii, T. (1989): *Jpn. Kokai* JP 89,30,563 (*C.A.* **110**: 211327)

Concentrated Japanese apricot or watermelon juices were mixed with β-CD, powdered cellulose and $CaCO_3$ and dried. The final product contained 50% of β-CD and 50% of the dry material of the concentrated fruits.

Kamikama, K., Tawara, Y., Isane, T., Yamada, T. (1988): *Jpn. Kokai* JP 88,162,627 (*C.A.* **110**: 237146)

Sustained-release pharmaceutical preparations can be prepared by complexing the well soluble drug with poorly soluble CD derivatives, like diltiazem with 2,6-diethyl-β-CD.

Luider, T., Hummelen, J. C., Koek, J. N., Wynberg, H. (1988): *Eur. Pat. Appl.* EP 261,719 (*C.A.* **110**: 208912)

Thermochemiluminescent CD complexes of adamantylideneadamantane 1,2-dioxetanes were prepared as labels for immunoassays.

Markarian, B. M., Cohen, G. L. (1989): *Eur. Pat. Appl.* EP 274,444 (*C.A.* **111**: 23899)

α-CD, γ-CD and methylated β-CD complexes of ibuprofen were prepared by mixing the drug with the CD in aqueous solution at elevated temperatures. A 1:1 inclusion complex was formed from ibuprofen and DIMEB the solubility of the ibuprofen was originally 0.3 mg/5 mL water which has been elevated by complexing with DIMEB to 53.1 mg/5 mL water.

Mesens, J., Van Peer, A. P., Heykants, J. J. P. (1989): *Eur. Pat. Appl.* EP 292,050 (*C.A.* **111**: 28561)

Pharmaceuticals contain surfactants, CDs or derivatives thereof as carriers, optional adjuvants, and flunarizine, or a stereoisomer of flunarizine. Hard gelatin capsules contained a mixture of flunarizine-2HCl 4.13, NaOH 0.692, H_2O 1.058, and Cremophor RH-40 94.12 mg. The relative bioavailability of flunarizine-2HCl from this formulation was 115%: from a formulation co-administered with bicarbonate and ranitidine (for reduced gastric acidity) it was 145%, compared to a relative bioavailability of flunarizine-2HCl of 100% from a formulation containing flunarizine-2HCl 5.9, lactose 61.4, starch 20.0, talc 9, Mg stearate 2, and Aerosil 0.4 mg.

Szejtli, J., Fenyvesi, E., Sarkozi, P., Felmeray, I., Zsoldos, A. (1988): *Ger. Offen.* DE 3,819,498 (*C.A.* **111**: 102736)

Iodine inclusion compounds with CD containing polymers are capable of controlling the release of iodine and contain release-controlling amounts of alkali iodides or alkali bromides. The iodine content of the inclusion compound prepared in H_2O, KI or KBr was 0.19, 0.43 and 0.1 meq/g; the inclusion compound prepared in the presence of KI contained 0.19 meq iodine and 0.24 meq I^-. When placed in 0.1% NaCl, the inclusion compound prepared in the presence of H_2O released 46.5% iodine in 1 min and 55.4% iodine in 5 min; the compound prepared in the presence of KBr released 73.0% iodine in 1 min; the compound prepared in the presence of KI released 8.1% iodine in 1 min and 14.6% iodine in 5 min. A powder contained a β-CD-iodine inclusion compound 50, CD 49.5, and Aerosil 0.5 g. The resulting inclusion compounds can be used in wound treatment powders.

Ogino, S., Kamiya, H. (1988): *Jpn. Kokai* JP 88,194,726 (*C.A.* **111**: 83845)

Emulsions for cosmetic purposes can be produced using methylated-β-CDs. The methylated β-CD is a stabilizer for the cosmetic emulsions, the average degree of the substitution is 8–11. The oil phase contained the isostearyl phosphate 1.2% sorbitan monostrearate (HLB 4.7) 2.0% and liquid paraffin 30.0%, while the aqueous phase contained L-arginine 0.6% and methylated-β-CD 0.5% by weight.

Sawaguchi, M., Kawada, M., Aoki, Y., Kawasaki, T. (1988): *Jpn. Kokai* JP 88,130,502 (*C.A.* **111**: 92334)

A mat for insect control consists of a volatile insecticide-CD inclusion compound. 1 g Pyrethrin and 0.01 g EDTA in 10 mL EtOH were gradually added to 50 mL 10% β-CD solution to form a precipitate. The precipitate (300 mg) was dried, dissolved in 20% poly(vinyl alcohol), and painted on a thick paper (10 cm^2) to form a mat.

Iida, A., Shimada, S. (1988): *Jpn. Kokai* JP 88,254,174 (*C.A.* **111**: 41458)

A CD-perfume complex has been used to deodorize the cationic epoxy resins, which is used for electrophoretic undercoating of automobile bodies. This composition contains 7-20% CD-perfume inclusion compound, which is mixed with the electrophoretic coating compositions which consists of amine-containing epoxy resins and crosslinking agents. A typical composition is as follows: an amine modified epoxy resin mixed with isocyanate mixture 15.7 parts, pigments 4.3 parts, solvents 3.9 parts, additive 0.3 and water 76.1 parts, it is mixed with 10 parts of Cellresin AR 205 (CD-coffee fragrance

inclusion compound) and it is applied electrophoretically to a test panel, and baked for 30 minutes at 165–185°C. The composition emitted no unpleasant odour during baking and gave a film with a good appearance.

Szucs, M., Frigyik Szemjonova, O., Csaplaros, S. J., Palotas, T. A. (1988): *Ger. Offen.* DE 3,820,592 (*C.A.* **111**: 87309)

The use of CDs is described in the sensitization reduction of silver-halide photographic emulsions. Silver halide photographic emulsions are reduction-sensitized without increasing the fog by using an inclusion complex of a hydrazine derivative with a substituted CD or a water-soluble CD polymer. The molar ratio of the CD derivatives to the hydrazine derivatives in the inclusion complex is 4:1 to 80:1, preferably 10:1 to 50:1. The complex is added to the emulsion before the precipitation of the silver halide crystals, or during the period of crystal growth or thereafter. The addition of a tris(carboxymethoxy)CD/ $PhNHNH_2$ complex (molar ratio 40) to a gelatin-Ag(Br, Cl) emulsion showed improved sensitivity during crystal growth with no increase in fog.

Kuze, S., Koboshi, S. (1988): *Jpn. Kokai* JP 88,276,050 (*C.A.* **111**: 87293)

Branched CDs or CD polymers can be used in silver halide photographic developer solutions.

Khanna, P., Dworschack, R. (1989): *Eur. Pat.* EP 301,847 (*C.A.* **111**: 9286)

Surfactants can be removed from solutions and surfaces (for example small amounts of surfactants after cleaning and rinsing) by contacting with CDs to provide a CD-bound surfactant which is separated from the solution or surface. For example Li-dodecyl sulfate can be fully removed from aqueous solution by β-CD.

Aoki, H., Yu, E. K. C., Misawa, M. (1988): *PCT Int. Appl.* WO 88,08,031 (*C.A.* **111**: 22201)

CGT enzyme was isolated from Bacillus licheniformis by ammonium-sulfate precipitation and column chromatography. Homogeneity was proven by isoelectric focusing. The optimum temperature of the enzyme was 65–70°C and it was stable between pH 6.0 and 9.5. It was a dimer of 72,000 dalton subunits. The β: α = 5:1 ratio resulted using non-prehydrolyzed starch.

Novo Industri A/S (1989): *EP* 0308181

The systemic absorption after non-enteral, transmucosal delivery of certain drugs in particular pharmacologically active polypeptides, is enhanced from formulations containing a monosaccharide or an oligosaccharide, preferably a CD. The polypeptide is insulin, an insulin derivative or a mixture of insulin and at least one insulin derivative or a mixture of insulin derivatives or glucagon.

A method of making preparations for non-enteral, transmucosal drug delivery, which method comprises dispersing a pharmaceutically active agent in a vehicle comprising at least one saccharide as defined above and optionally one or more auxiliary constituents selected from the group consisting of a powdery, waxy or liquid diluent, a pH-buffering agent, a preservative and an osmotic pressure controlling agent.

Warner-Lamber Company (1989): *EP* 0306455

The invention provides CD complexes of bis-biguanido hexane compounds such as chlorohexidine and its salts which act to increase the water solubility of chlorohexidine or its salts, mask their bitter after taste and increase their bio-availability. The invention also provides aqueous-based anti-bacterial oral preparations containing such complexes which may also contain alcohol, colorants, flavorants, sweeteners, fluorides and polishing agents.

Pharmatec (1989): *US Patent* 4,727,064

Pharmatec (Gainesville, Florida) obtained a licence from the US Department of Commerce for the US Patent 4,727,064 for the application of chemically modified CDs to enhance the solubility and stability of drugs which are poorly soluble in water or unstable. The J. of Commerce (31 March 1989) reported

that the patent had been granted on 23rd February 1988, and has been based on the research work done in the Laboratory of the National Institute of Health, Baltimore.

Nang, L. S., Leninot, M., Pourrat, A. (1989): *Fr. Demande* FR 2,612,398 (*C.A.* **111**: 63958)

Enilospirone does not form an inclusion complex with β-CD, nevertheless the β-CD increases the gastrointestinal bioavailability of enilospirone. Mice were administered orally 64 mg/kg enilospirone alone, or together with β-CD and 30 minutes after administration the mice were placed in an enclosed space and their movements were counted with IR cells for 100 ms. The number of movements was 15–30% higher in the case of that group which obtained the enilospirone together with β-CD.

Szente, L., Szejtli, J., Magisztrak, H., Horvath, E. (1988): *PCT Int. Appl.* WO 88,08,304 (*C.A.* **111**: 102724)

Inhalant pharmaceuticals or air scenting compounds comprise a volatile active agent-CD inclusion complex, a competitor host molecule, and conventional excipients. The competitor host molecule forms a more stable CD complex than the volatile active agent to be set free. In an inhalation model, N_2 was bubbled through a flask at a constant rate into an ice-cooled gas washing bottle containing 50% aqueous EtOH and the amount of volatile substance absorbed was determined by UV photometry. A compound containing chamomile oil-CD 15, menthol oil-CD 25, eucalyptus oil-CD 80, and pine oil-CD complex 45 g (volatile content 10%) was added to water at 90°C and host competitor molecules were added; the extinction of ethereal oils absorbed in the trap was 100% for the ethereal oils complex mixture alone; for the ethereal oil-complex mixture and BzOH (host competition) it was 237%, for 2-$HOC_6H_4CO_2H$ (host competitor) it was 178%, and for the complex mixture and tryptophan it was 111%. The volatilization of benzoic acid from the complex was negligible. An inhalant powder contained eucalyptus oil-β-CD complex (10–11% volatile material) 89, peppermint oil-β-CD complex (10–11% volatile material) 78.5, chamomile-β-CD complex (10–12% volatile material) 16.7, and benzoic acid 5 kg; the powder was homogenized and used, either in tablet or powder form.

Kishi, T. (1988): *Jpn. Kokai* JP 88,280,010 (*C.A.* **111:** 45076)

A deodorant adhesive tape for underarm application consists of a nonwoven polyurethane fiber stretchable to more than 100%, a CD or its derivative and an adhesive layer. The concentration of the CD or its derivatives in the adhesive layer is more than 3% by weight. A mixture of α-, β- and γ-CD at a 6:3:1 ratio by weight was added 3 parts to 100 parts 30% by weight of 2-ethylhexyl acrylate-iso-Bu methacrylate-methacrylic acid copolymer in AcOEt to give an adhesive solution. This was applied to a nonwoven sheet prepared from polyester polyurethane fibers (average length 25 mm, average diameter 150 μm) to give a deodorant tape.

Kishi, T., Iwakawa, M. (1988): *Jpn. Kokai* JP 88,280,014 (*C.A.* **111**: 83911)

Oral odoring patch compounds contain CD (and/or its derivatives) and shape-retaining substrates which are water soluble and softened when absorbed water, and have good adhesion to oral mucosa. The compositions control oral odor for a prolonged time and cause no adverse effects on the mucous membrane. A water-ethanol solution containing 28 parts Pullulan, aqueous solution containing 4 parts Junlon (carboxyvinyl polymer) and aqueous solution containing 60 parts maltitol were mixed, homogenized with 8 parts glycerin and 15 parts of a mixture of α-, β- and γ-CD (6:3:1), and overcoated on a hydroxypropyl cellulose-coated film to give a patch. The patch controlled oral odor and completely dissolved in the mouth in about 3.5 hours.

Fukunaga, K., Kondo, M. (1989): *Jpn. Kokai* JP 89,86,856 (*C.A.* **111**: 56167)

The preparation of powdered syrups containing CD inclusion compounds for shaved ice is described. The syrups are formulated from sweeteners and powdered and/or granulated inclusion compounds of CD with pigments, flavors, and acidulants or natural fruit juices. Thus, a mixture of β-CD 4, flavors 0.6, pigment 0.2, acidulants 0.2, fructose 57.0, and sucrose 38 parts was dissolved to develop color and flavour when sprinkled on shaved ice.

Nakamura, M. (1989): *Jpn. Kokai* JP 89,09,914 (*C.A.* **111**: 83893)

The water soluble bactericidal 2-mercaptopyridine N-oxide metal salt-CD (or derivative) inclusion complex is useful for controlling dandruff. Methylated β-CD 1 part was mixed with 0.006 part 2-mercaptopyridine N-oxide Zn salt which was freeze-dried to give a water soluble inclusion complex. A hair lotion was prepared from 10 g of the above aqueous solution and 0.05 g perfume.

Yamakita, H., Tazawa, M., Hayakawa, K., Toada, H. (1989): *Jpn. Kokai* JP 89,51,317 (*C.A.* **111**: 99873)

NH_3 can be manufactured from alkaline aqueous solution containing nitrate or oxyacid salts of sulphur, for example NaS_2O_3 or organic electron donors like β-CD, triethanolamine, by dispersing a semiconductor powder, for example TiO_2 in the solution and irradiating the solution with light.

Ishio, N. (1989): *Jpn. Kokai* JP 89,94,342 (*C.A.* **111**: 105831)

A resin prepared from a novolak resin and a dissolution inhibitor is irradiated and developed by using aqueous alkali which contains an inclusion complex. The patterning method is useful for preparing semiconductor devices and the like, because the developer does not leave an insoluble residue. Thus, a TSMR-8800 resist on a Si substrate was imagewise irradiated and developed by using an aqueous solution containing Me_4NOH and β-CD to give a pattern without any residue.

Masuda, S., Masuda, H., Matsuda, M., Kitano, H., Matsuda, H. (1989): *Jpn. Kokai* JP 89,44,792 (*C.A.* **111**: 99143)

UV-curable ink printed cards with good odor can be produced using a β-CD complex of perfume component. The cards are printed with inks containing fragrant powders with different volatility prepared by CD inclusion and silica alumina, active silicate, phosphate or silicophosphate adsorption. Offset-printing a telephone card with a UV-curable ink containing a powder prepared from β-CD and ethanol solution of β-phenylethyl alcohol, cinnamic alcohol, $PhCH_2OAc$, terpineol, ionone, α-amylcinnamaldehyde, eugenol, isoeugenol, phenylacetaldehyde di-methyl acetal, and indole, and a powder prepared from Zr silicophosphate and ethanol solution of rose oil, geraniol, citronellol, germanium oil, linalyl acetate and ylang-ylang oil and curing gave a card with good odor for about 6 months at room temperature.

Masuda, S., Masuda, H., Matsuda, M., Kitano, H. (1989): *Jpn. Kokai* JP 89,45,471 (*C.A.* **111**: 41047)

Fragrant photocured resin films can be produced using β-CD complexes of fragrances. Layers are photopolymerized which contain a mixture of CD 100, perfume 20–100, solid fat 20–100, and photocurable liquid resin 100–500 parts. Stirring a dispersion of 200 g β-CD in 1 L hot water and a solution of 40 g peach fragrance in 200 g methanol with ice cooling gave an inclusion compound which was separated, dewatered, and ground. A calendar page printed with fruit design was coated with a mixture of the powdered inclusion compound 90, a 60:50 beeswax-orange fragrance mixture 60, and a UV-curable ink 200 g to a thickness of about 10 μm and photocured to give a glossy layer which emitted a fragrance for about 3 months.

Noguchi, Y., Tanaka, T., Muroga, S. (1988): *Jpn. Kokai* JP 88,129,999 (*C.A.* **111**: 73860)

Maltosyl-CD can be used as a substrate solubilizer in the determination of γ-glutamyltranspeptidase activity for clinical diagnosis. In γ-glutanyltranspeptidase determination with L-γ-glutanyl-*p*-nitroanilide, maltosyl-CD is used as a substrate solubilizer. Citric acid (2.1 g) in about 900 mL distilled water was adjusted to pH 5.0 and to this was added 50 g maltosyl-α-CD, 3.46 g L-glutamyl-4-nitroanilide and distilled water to 1 L. The substrate solution was stable at 25°C for 5 days or at 5°C for 20 days.

Aoki, H., Yu, E. K. C. (1989): *PCT Int. Appl.* WO 89,01,043 (*C.A.* **111**: 152179)

A method is described for the production of α-CD using Bacillus AL35 CTG enzyme. Corn starch in 4% solution was converted at 60°C in 24 hours, 83–94% of the produced CDs was α-CD.

Aoki, H., Yu, E. K. C. (1989): *PCT Int. Appl.* WO 89,01,044 (*C.A.* **111**: 152178)

β-CD was produced using Bacillus IT14 CTG enzyme in 4% solution at 60°C in 20–40 hours. 70–90% of the formed CDs was β-CD.

Kobayashi, S., Arahira, M. (1989): *Eur. Pat. Appl.* EP 307,534 (*C.A.* **111**: 136327)

The production of a heterogeneous multibranched CD mixture was produced by treating a mixture of glucosyl CD and maltooligosaccharide with pullulanase enzyme.

Nishida, K., Takahashi, C., Kawaguchi, T., Sakai, S., Yoshida, S., Chiwa, M. (1988): *Jpn. Kokai* JP 88,227,602 (*C.A.* **110**: 59826)

Glycosyl-CD can be separated from CDs and acyclic oligosaccharides by absorption of these oligosaccharides on silica then first to remove the oligosaccharides by washing the silica with water thereafter eluting with ethanol of increasing concentration.

Bender, M. L., D'Souza, V. T. (1988): *U.S. Patent* US 4,777,250 (*C.A.* **111**: 129801)

Imidazole derivatives of CDs are chymotrypsin analogs. Various substituted imidazole groups were introduced into the secondary side of α-, β- and γ-CDs.

Fregnan, G., Vandoni, G., Torri, G. (1988): *Eur. Pat. Appl.* EP 295,476 (*C.A.* **111**: 140502)

Dipyridamole can be complexed with CDs or methylated CDs. The molar ratio dipyridamole:CD is 1:1–1:12. The β-CD solution was acidified with formic acid below pH 3, and dipyridamole was dissolved, then this solution spray-dried. The quantity of dipyridamole dissolved in phosphate buffer was 4.5–4 times higher for complexed dipyridamole than for solutions containing noncomplexed dipyridamole or dipyridamole-lactose mixtures. Orally administered the complexed dipyridamole in rabbits gave rise to a higher platelet aggregation inhibiting activity than noncomplexed dipyridamole or dipyridamole-lactose mixtures: similarly, orally administered complexed dipyridamole in beagle dogs gave more favourable peak effects relating to systemic arterial pressure, heart frequency, coronary and carotid flow. Tablets contained complexed dipyridamole 900, Mg stearate 8, and Na amidoglycolate 22 mg each.

Sugiyama, M., Ezure, Y., Kojima, M., Miyazaki, K. (1987): *Jpn. Kokai* JP 87,267,292 (*C.A.* **109**: 209662)

Oligoglucosylmoranoline derivatives can be prepared by reacting it with CDs or starch in the presence of immobilized CTG enzyme.

Yonezawa, K., Isabe, T., Miyoshi, S., Ito, Y. (1988): *Jpn. Kokai* JP 88,245,674 (*C.A.* **111**: 129815)

Serrapeptase enzyme is treated with CD to form a stable serrapeptase-CD complex. Serrapeptase (2000 units/mg) 1, α-CD 5 g and distilled water were mixed to form a complex. Capsules were prepared containing serrapeptase-CD (1:5) complex, lactose 45, corn starch 24 and Mg stearate 1 mg.

Yaginuma, H., Tanaka, S., Shiraishi, S., Tajiri, F., Yamada, T., Hongo, I., Shibata, S. (1988): *Jpn. Kokai* JP 88,267,721 (*C.A.* **11**: 63981)

A suppository soft capsule contains a homogeneous composition of a ground mixture of emorfazone and CDs and an oil base composed of pharmaceutically acceptable oils and fats, which are oily at ordinary temperature. The suppository gave no strong irritation to the rectum in human, versus strong irritation for a control prepared by solidifying the dispersion of emorfazone in Witepsol H15.

Igari, T., Matsuyama, T., Okamoto, T., Goto, T. (1987): *Jpn. Kokai* JP 87,292,719 (*C.A.* **110**: 82488)

Cromoglycic acid containing clear topical aqueous solution can be prepared with β-CD. The sodium salt of cromoglycic acid was dissolved in the presence of β-CD, benzalkonium chloride, 2-phenylethyl alcohol and this solution kept its original color, pH, osmotic pressure and content during 3 months storage at 40°C.

Szejtli, J., Szente, L., Kaloy, K., Marton, J., Gerloczy, A. (1988): *U.S. Patent* US 4,774,232 (*C.A.* **111**: 127037)

Heptakis-(2,6-di-O-methyl)-β-CD (DIMEB) can be used as a bile substitute. Rats were orally administered 2 mL sunflower oil and 50 mg DIMEB. No significant difference was seen between the triglyceride levels in control and treated animals.

Shibauchi, I., Mihashi, M., Miyake, T. (1988): *Jpn. Kokai* JP 88,164,953 (*C.A.* **11**: 140236)

A deodorant for disposable diapers is prepared by complexing volatile deodorants with CDs. The composition consists of maltose and β-CD complex of limonene. The complex was prepared by the slurry method, and the paste formed was mixed with anhydrous maltose, dried, pulverized and then added to disposable diapers.

Kishi, T. (1988): *Jpn. Kokai* JP 88,280,012 (*C.A.* **111**: 140238)

A deodorant adhesive tape for underarm application consists of a nonwoven polyurethane cloth laminated with polyurethane film, stretchable more than 200%, and a CD or its derivatives and an adhesive layer. The concentration of CD or its derivative in the adhesive layer is more than 3% by weight. Such a tape applied to underarms of volunteers controlled odor for more than 30 hours.

Kishi, T. (1988): *Jpn. Kokai* JP 88,280,013 (*C.A.* **111**: 120656)

A deodorant adhesive tape is prepared which is applied to skin especially under the arm, to control the body odor. It is effective in a prolonged period. The tapes are similar to those in the former patent application.

Nogawa, Y., Nishimura, H., Matsumoto, S., Yamada, H. (1988): *Jpn. Kokai* JP 88,215,611 (*C.A.* **111**: 63765)

A cosmetic preparation is described, which contains Lansium domesticum extracts (lansic acid and lansiosides) formulated with CDs. This cosmetic is an excellent skin or hair conditioner. For example a shampoo was prepared containing lansic acid 1.0 and β-CD 0.5% by weight.

Kubota, N., Yanase, S. (1988): *Jpn. Kokai* JP 88,229,109 (*C.A.* **110**: 40264)

The preparation of the β-CD rejecting polymer membrane is described. The membrane is useful in reverse osmosis and ultrafiltration and is prepared by coating supports with solutions of sulfonated poly(2,6-dimethyl-1,4-phenylene oxide) or their alkali metal salts in solvents which swell the support and then vaporizing the solvents. Such a hollow-fiber ultrafiltration membrane can be used to concentrate the CDs.

Ogiwara, S., Handa, S. (1988): *Jpn. Kokai* JP 88,223,078 (*C.A.* **110**: 59681)

Perfumed inks can be prepared using maltosyl-CD and phenylethyl alcohol, geraniol, nerol, geranium oil and geranyl acetate in inks, used in ballpoint pens.

Sugimoto, S., Kageyama, K. (1988): *Jpn. Kokai* JP 88,161,041 (*C.A.* **111**: 23258)

CD encapsulated $(n\text{-Bu})_3\text{SnF}$ is used in the production of antifouling rubber compositions in marine construction materials. The CD complexed organic tin compounds showed better, longer lasting antifouling properties than the control prepared without using CDs.

Seikya, T., Hara, K., Oku, S. (1988): *Jpn. Kokai* JP 88,267,225 (*C.A.* **111**: 132951)

A fish bait having a long-lasting attracting effect and which is resistant to disintegration in water comprises a CD inclusion complex in combination with metal soap and fluid paraffin, or metal soap and polyethylene wax, etc. Squid oil and CD containing malt powder was mixed, spray dried and formulated to fish bait, which retained a considerable part of its original fish-attracting property, even after submerging for 30 days in water.

Nakao, M., Kusumi, T., Koga, K., Okada, S. (1989): *Jpn. Kokai* JP 89,19,092 (*C.A.* **111**: 97682)

Genipin glycosides useful as substrates for determination of α-amylase in human serum were prepared. Geniposide was reacted in acetate buffer in the presence of $CaCl_2$ with α-CD, and the reaction was catalysed by Bacillus macerans CTG enzyme. The product was isolated by chromatographic purification and it can be used for determination of α-amylase activity in human blood serum.

Oyama, S. (1988): *Jpn. Kokai* JP 88,223,077 (*C.A.* **110**: 77758)

Water-based ink composition with excellent pen point drying resistance can be prepared using 0.5–30% maltosyl-CD together with ethylene glycol with glycerin and appropriate dyes in water. A ball-point pen containing this ink showed smooth writability for 30 days when left without a cap, versus 10 days for a pen with control ink prepared without maltosyl-CD.

Kamya, H., Sawada, H., Ito, S., Kobayashi, T. (1989): *Jpn. Kokai* JP 89,110,503 (*C.A.* **111**: 136329)

Aqueous solutions of etherified CDs can be protected against microbial attack by adjusting the pH of the aqueous solution to 12 or above. E.g. adding 0.05% NaOH to a 20% aqueous methylated-β-CD solution no deterioration has been observed after 28 days.

Hara, K. (1988): *Jpn. Kokai* JP 88,02,929 (*C.A.* **110**: 160370)

A new aspirin formulation is reported, which consists of CDs, aspirin, and basic amino acid and/or aspirin basic amino acid salts. The aspirin was mixed in aqueous system with arginine, then was stirred with β-CD and finally dried. The blood level of aspirin in a rabbit that had received the aspirin-L-arginine-β-CD inclusion complex was 2 times that of the control that had received a similar inclusion complex but without arginine.

Tadamasa, H. (1989): *Jpn. Kokai* JP 89,63,354 (*C.A.* **11**: 38239)

Powdered wasabi or mustard is manufactured by kneading CD with wasabi-ethanol mixture or mustard-ethanol mixture, followed by mixing with hydrophilic gums, starches, sugars, etc. to obtain a powder preparation without drying under heating to avoid denaturation. The spice has a long-lasting flavor.

Mitsuya, K., Kuwabara, N., Shirane, Y. (1989): *Jpn. Kokai* JP 89,112,964 (*C.A.* **111**: 152424)

Bony parts of sea bream are covered with starch and CD, fried, extracted by boiling water, and the extracts are concentrated to prepare seasonings. The concentrates may be included with CD to prepare powdered and granular seasonings.

Takeshima, K. (1988): *Jpn. Kokai* JP 88,135,326 (*C.A.* **110**: 141280)

Powdery cleansing compositions contain CD-oil inclusion complex, medicinal plant components (Aloe dried powder), and freeze-dried caseins. These compounds have good cleansing action.

Harada, M., Maekawa, H. (1989): *Jpn. Kokai* JP 89,63,342 (*C.A.* **111**: 132914)

Glutathione containing compounds such as yeast extracts used as seasoning and health food can be stabilized using at least 1% γ-CD (based on the weight of the glutathione).