

DSC XIX - Cyclodextrin Studies

(cyclodextrin-drug studies, selected references since 1994)

Al Marzouqi A. H., Shehatta I., Jobe B., and Dowaidar A. (2006) Phase solubility and inclusion complex of itraconazole with beta-cyclodextrin using supercritical carbon dioxide. *J Pharm Sci* **95**, 292-304.

Abstract: Phase-solubility techniques were used to assess the formation of inclusion complex between itraconazole and beta-cyclodextrin. The stability constant and free energies of transfer of itraconazole from aqueous solution to the cavity of beta-cyclodextrin were calculated. Itraconazole solubility in supercritical carbon dioxide (SC CO₂) was measured at different temperatures and pressures. Drug formulations of itraconazole were prepared by complexation of the drug into beta-cyclodextrin using SC CO₂. Effects of temperature and pressure on inclusion yield of the prepared complexes were studied. The solvent-free inclusion complexes obtained from this method were characterized by UV spectroscopy, differential scanning calorimetry, powder X-ray diffraction, and scanning electron microscopy and compared to those obtained from physical mixing and coprecipitation methods. Results showed that beta-cyclodextrin significantly improved solubility of itraconazole in aqueous solutions. The free energies of transfer of itraconazole from aqueous solution to the cavity of beta-cyclodextrin increased negatively with increasing beta-cyclodextrin concentration. Higher inclusion yields were obtained in the SC CO₂ method compared to physical mixing and coprecipitation methods. Both temperature and pressure had significant effects on itraconazole solubility in SC CO₂ and the inclusion yield of the complex prepared by SC CO₂ method.

Al Omari M. M., Zughul M. B., Davies J. E., and Badwan A. A. (2006) Sildenafil/cyclodextrin complexation: stability constants, thermodynamics, and guest-host interactions probed by ¹H NMR and molecular modeling studies. *J Pharm Biomed Anal* **41**, 857-865.

Abstract: Guest-host interactions of sildenafil (Sild) with cyclodextrins (CyDs) have been investigated using several techniques including phase solubility diagrams (PSD), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), proton nuclear magnetic resonance (¹H NMR) and molecular mechanical modeling (MM+). Estimates of the complex formation constant (K₁₁) show that the tendency of Sild to complex with CyDs follows the order: beta-CyD > HP-beta-CyD > gamma-CyD, alpha-CyD, where K₁₁ values at pH 8.7 and 30 degrees C were 150, 68 and 46, 43 M⁻¹, respectively. Ionization of Sild reduces its tendency to complex with beta-CyD, where protonated (at pH 3.6) and anionic Sild (at pH 12.1) species have K₁₁ values of 17 and 42 M⁻¹, respectively, compared with 150 M⁻¹ for neutral Sild (at pH 8.7). The hydrophobic character of Sild was found to provide 39% of the driving force for complex stability, while other factors including specific interactions contribute -7.9 kJ/mol. Complex formation of Sild with beta-CyD (DeltaG degrees=-22.9 kJ/mol) is largely driven by enthalpy (DeltaH degrees=-19.8 kJ/mol) and slight entropy (DeltaS degrees=10.3 J/molK) changes. ¹H NMR and MM+ studies indicate formation of two isomeric 1:1 complexes: one involving complete inclusion of the phenyl-moiety into the beta-CyD cavity while the other pertaining to partial inclusion of the pyrimidinone moiety. The dominant driving force for complexation is evidently van der Waals with very little electrostatic contribution. DSC, XRPD and ¹H NMR studies proved the formation of inclusion complex in solution and the solid state.

Ammar H. O., Ghorab M., El nahhas S. A., Omar S. M., and Ghorab M. M. (1995) Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. 4. Chlorpromazine hydrochloride. *Pharmazie* **50**, 805-808.

Abstract: The potentiality of interaction of chlorpromazine hydrochloride (CPZ) with beta-cyclodextrin (beta-CD) was investigated by spectrophotometry, vapour pressure osmometry and DSC thermograms. The results revealed a very strong evidence for molecular interaction between CPZ and beta-CD. The continuous variation method was used to elucidate the stoichiometry of such interaction by spectrophotometric as well as vapour pressure measurements. Both types of data revealed the formation of a 1:1 complex. The stability constant of the complex was determined at different temperatures by the vapour pressure osmometric method. The enthalpy and entropy of interaction were evaluated and the results indicate that the interaction is exothermic. The CPZ/beta-CD complex was prepared, lyophilized and photochemical stability of the drug, its physical mixture with beta-CD as well as the prepared complex was investigated at different pH-values in presence of different buffer systems. The results revealed that the stability of the drug is greatly improved in presence of beta-CD and the great dependency of stability on the pH of the solution is decreased in presence of beta-CD. The partition coefficient of CPZ and its complex

with beta-CD was determined. The data reveal a higher p.c. of the complex compared to the parent drug. The effect of beta-CD on the bioavailability of CPZ was investigated by measuring the miotic response intensity in volunteers receiving a single oral dose of the drug, drug/beta-CD physical mixture or complex. The results revealed a distinct improvement of the biological performance of CPZ by beta-CD as evidenced by an increased intensity of drug action and its duration as well as augmenting its bioavailability without affecting the time for maximum effect.

Ammar H. O., Ghorab M., El nahhas S. A., Omar S. M., and Ghorab M. M. (1996) Improvement of some pharmaceutical properties of drugs by cyclodextrin complexation. 5. Theophylline. *Pharmazie* **51**, 42-46.
Abstract: The interaction of theophylline (TPH) with beta-cyclodextrin (beta-CD) was investigated by spectrophotometry, vapour pressure osmometry and DSC. The results revealed a molecular interaction between TPH and beta-CD. The continuous variation method was used to elucidate the stoichiometry of such an interaction by spectrophotometric as well as vapour pressure measurements. Both types of data revealed the formation of two-to-one TPH/beta-CD complex. The stability constant of the complex was determined at different temperatures by the vapour pressure osmometric method. The enthalpy and entropy of the interaction were evaluated and the results indicate the liberation of little heat during complexation and the disorder of the guest molecule upon complexation. The effect of beta-CD on the solubility of TPH indicates that beta-CD exhibits a definite solubilizing effect towards the drug with a typical Bs isotherm. The stability constant of the complex and the amount of drug solubilized in the form of complex reveal that complex-formation is the only factor governing the solubilizing effect of beta-CD towards the drug. The dissolution rates of TPH, TPH/beta-CD physical mixture as well as the prepared complex were determined according to U.S.P. method and at pH 1.2. In both cases, the dissolution profile of the complex reveals enhanced dissolution properties compared to the drug. The effect of beta-CD on the partition properties of TPH reveals decrease in presence of beta-CD. The effect of beta-CD on the bioavailability of TPH was investigated in human subjects. A clear difference in the biological performance between the drug and the complex was revealed. The pharmacokinetic parameters including C_{max}, t_{max}, C_{min}, t_{1/2}, K_e, MRT and AUC revealed that inclusion complexation of theophylline in B-cyclodextrin results in not only an improvement in the bioavailability of the drug, but also to acquired sustained release properties for the drug.

Anselmi C., Centini M., Ricci M., Buonocore A., Granata P., Tsuno T., and Facino R. M. (2006) Analytical characterization of a ferulic acid/gamma-cyclodextrin inclusion complex. *J Pharm Biomed Anal* **40**, 875-881.

Abstract: Ferulic acid (FA) is a well-known antioxidant of natural source with promising properties as photoprotective agent (approved in Japan as sunscreen) and its derivatives (alkyl ferulates) are under screening for the prevention of photoinduced skin tumours. In the present work we describe the preparation of a solid inclusion complex between ferulic acid and gamma-cyclodextrin (gamma-CD) and its characterization by different analytical techniques: differential scanning calorimetry (DSC), X-ray diffractometry (XRD), nuclear magnetic resonance spectroscopy (1H NMR) and by supporting information of molecular modelling. All these approaches indicate that ferulic acid is able to form an association complex with gamma-CD but only 1H NMR and molecular modelling studies give an unequivocal evidence that the antioxidant molecule is embedded into the gamma-CD cavity to form an inclusion complex. In detail it is entrapped inside the hydrophobic core of gamma-CD with the lipophilic aromatic ring and the ethylenic moieties, leaving the more polar functional groups close to wider rim or outside the cavity.

Araujo M. V., Macedo O. F., Nascimento C. D., Conegero L. S., Barreto L. S., Almeida L. E., Costa N. B., Jr. and Gimenez I. F. (2008) Characterization, phase solubility and molecular modeling of alpha-cyclodextrin/pyrimethamine inclusion complex. *Spectrochim. Acta A Mol Biomol. Spectrosc (epublication)*.
Abstract: An inclusion complex between the dihydrofolate reductase inhibitor pyrimethamine (PYR) and alpha-cyclodextrin (alpha-CD) was prepared and characterized. From the phase-solubility diagram, a linear increase of PYR solubility was verified as a function of alpha-CD concentration, suggesting the formation of a soluble complex. A 1:1 host-guest stoichiometry can be proposed according to the Job's plot, obtained from the difference of PYR fluorescence intensity in the presence and absence of alpha-CD. Differential scanning calorimetry (DSC) measurements provided additional evidences of complexation such as the absence of the endothermic peak assigned to the melting of the drug. The inclusion mode characterized by

two-dimensional (1)H NMR spectroscopy (ROESY) involves penetration of the p-chlorophenyl ring into the alpha-CD cavity, in agreement to the orientation optimized by molecular modeling methods

Babu R. J., Dayal P. and Singh M. (2008) Effect of cyclodextrins on the complexation and nasal permeation of melatonin. *Drug Deliv.* **15**, 381-388.

Abstract: The inclusion complexation of melatonin (MT) with modified cyclodextrins (CDs) was studied with an objective of improving the solubility and nasal absorption of MT. The formation of inclusion complex of MT with Hydroxypropyl beta CD (HPbeta CD) and randomly methylated beta CD (RMbeta CD) was characterized in solution and solid states by phase solubility and differential scanning calorimetry analyses. The phase solubility data indicate a linear increase in the solubility of MT with CDs demonstrating Higuchi's A(L)-type phase solubility profiles. The effect of CDs on the permeation of MT across EpiAirway(TM)-100 cultures was studied using a modified nonstatic diffusion setup. CDs were employed at different concentrations with 1% w/v micronized MT suspension in hydroxypropyl methyl cellulose (HPMC) vehicle. At low CD concentrations (1% w/v), the permeation of MT from HPMC formulation was significantly increased (125%, $p < .001$). However, the permeation was significantly reduced when CDs were used at relatively high concentrations (5 to 10% w/v concentration for HPbetaCD and 10% w/v concentration for RMbetaCD, $p < .001$). All the tissues were viable with good tissue integrity at the end of permeation experiments, as measured by methylthiazolotetrazolium assay and transepithelial electrical resistance measurements. In conclusion, formation of inclusion complex of MT with HPbetaCD and RMbetaCD was demonstrated in solution and solid state. Both HPbetaCD and RM betaCD at 1% w/v concentration were found to improve the nasal permeability of MT from HPMC gel formulations

Badr-Eldin S. M., Elkheshen S. A. and Ghorab M. M. (2008) Inclusion complexes of tadalafil with natural and chemically modified beta-cyclodextrins. I: Preparation and in-vitro evaluation. *Eur J Pharm. Biopharm(epublication)*

Abstract: The aim of this work was to investigate the inclusion complexation between tadalafil, a practically insoluble selective phosphodiesterase-5 inhibitor (PDE5), and two chemically modified beta-cyclodextrins: hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and heptakis-[2,6-di-O-methyl]-beta-cyclodextrin (DM-beta-CD), in comparison with the natural beta-cyclodextrin (beta-CD) in order to improve the solubility and the dissolution rate of the drug in an attempt to enhance its bioavailability. Inclusion complexation was investigated in both the solution and the solid state. The UV spectral shift method indicated guest-host complex formation between tadalafil and the three cyclodextrins (CDs). The phase solubility profiles with all the used CDs were classified as A(p)-type, indicating the formation of higher order complexes. The complexation efficiency values (CE), which reflect the solubilizing power of the CDs towards the drug, could be arranged in the following order: DM-beta-CD>HP-beta-CD>beta-CD. Solid binary systems of tadalafil with CDs were prepared by kneading and freeze-drying techniques at molar ratios of 1:1, 1:3 and 1:5 (drug to CD). Physical mixtures were prepared in the same molar ratios for comparison. Physicochemical characterization of the prepared systems at molar ratio of 1:5 was studied using differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and Fourier-transform infrared spectroscopy (FTIR). The results showed the formation of true inclusion complexes between the drug and both HP-beta-CD and DM-beta-CD using the freeze-drying method at molar ratio of 1:5. In contrast, crystalline drug was detectable in all other products. The dissolution of tadalafil from all the prepared binary systems was carried out to determine the most appropriate CD type, molar ratio, and preparation technique to prepare inclusion complexes to be used in the development of tablet formulation for oral delivery of tadalafil. The dissolution enhancement was increased on increasing the CD proportion in all the prepared systems. Both the CD type and the preparation technique played an important role in the performance of the system. Irrespective of the preparation technique, the systems prepared using HP-beta-CD and DM-beta-CD yielded better performance than the corresponding ones prepared using beta-CD. In addition, the freeze-drying technique showed superior dissolution enhancement than other methods especially when combined with the beta-CD derivatives

Bayomi M. A., Abanumay K. A., and Al Angary A. A. (2002) Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state. *Int J Pharm* **243**, 107-117.

Abstract: Nifedipine is a highly photosensitive drug that requires restricted protection from light during manufacturing, storage and handling of its dosage forms. Inclusion complexation of nifedipine with cyclodextrins (CDs) could be advantageous in protecting the drug against the effect of light. In this study,

solid inclusion complexes of nifedipine with beta-cyclodextrin (beta-CD), hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and dimethyl-beta-cyclodextrin (DM-beta-CD) were prepared using the coprecipitation method. The obtained solid inclusion complexes have been confirmed by differential scanning calorimetry (DSC), X-ray diffraction and infrared spectroscopy (IR). The IR spectra indicated partial inclusion of nifedipine molecules into CD cavities through the dihydropyridine ring. Inclusion complexation was also associated with a dramatic enhancement of drug dissolution with magnitudes depended on the type of CD. The effect of exposure to fluorescent lamp and sunlight on the photodegradation of uncomplexed and complexed nifedipine was tested. Photodegradation of nifedipine was monitored using a high performance liquid chromatographic (HPLC) assay method. Inclusion complexation of nifedipine showed to retard drug photodegradation as indicated by degradation rate constant lowering with values depended on light source and type of complexing agent. This effect was the least with beta-CD compared with that of modified beta-CD. It was also interesting to notice that inclusion complexation of nifedipine offered much higher protection against the effect of fluorescent lamp than that of sunlight. The obtained results suggests that the design of solid dosage forms of nifedipine such as a fast dissolving nifedipine tablets is possible with the advantages of low required light protection.

Bencini M., Ranucci E., Ferruti P., Trotta F., Donalisio M., Cornaglia M., Lembo D. and Cavalli R. (2008) Preparation and in vitro evaluation of the antiviral activity of the Acyclovir complex of a beta-cyclodextrin/poly(amidoamine) copolymer. *J Control Release* **126**, 17-25.

Abstract: A poly(amidoamine) (PAA) copolymer with beta-cyclodextrin was obtained by polyaddition reaction of 6-deoxy-6-amino-beta-cyclodextrin (beta-CD-NH(2)) and 2-methylpiperazine to 2,2-bis(acrylamido)acetic acid in aqueous medium. This beta-CD/PAA copolymer bears beta-CD units along the macromolecular chain, is water-soluble and non-cytotoxic. The complexing capacity of beta-CD/PAA was determined using an antiviral drug, Acyclovir, as a model of poorly water-soluble drug. Complex formation was confirmed by means of DSC and FTIR analyses. beta-CD/PAA can solubilize up to 11% w/w of Acyclovir notably increasing the aqueous solubility of the drug. The in vitro release studies showed the dependence of Acyclovir release rate on the solution pH. The antiviral activity of Acyclovir beta-CD/PAA complex was evaluated against herpes simplex virus type I in cell cultures. The Acyclovir beta-CD/PAA complex exhibited a higher antiviral activity than the free drug

Bentley M. V., Vianna R. F., Wilson S., and Collett J. H. (1997) Characterization of the influence of some cyclodextrins on the stratum corneum from the hairless mouse. *J Pharm Pharmacol* **49**, 397-402.

Abstract: Differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR) spectroscopy and transmission electron microscopy (TEM) have been used to determine the influence of beta-cyclodextrin (beta-CyD), hydroxypropyl-beta-CyD (HP-beta-CyD) and gamma-CyD on the structural properties of the stratum corneum from the hairless mouse. Some modest changes in the stratum corneum lipid transition temperature were induced by HP-beta-CyD and blue shifts were observed in the FTIR spectra of the C-H asymmetric and symmetric stretching of the lipids from the stratum corneum. Results from TEM studies indicated that HP-beta-CyD caused removal and possible disorganization of the lipid matrix that envelopes the corneocytes of the stratum corneum, whereas no effect was seen after treatment of the samples with beta-CyD and gamma-CyD. These results suggest that HP-beta-CyD can increase the permeability of the stratum corneum possibly as a result of extraction of lipids, and might thus enhance drug permeation through the skin.

Bergamasco R. C., Zanin G. M., and de Moraes F. F. (2005) Sulfluramid volatility reduction by beta-cyclodextrin. *J Agric Food Chem* **53**, 1139-1143.

Abstract: Sulfluramid is an expensive active principle of insecticidal baits that is lost by volatilization during the pelletization of baits. To increase the thermal stability of sulfluramid, we tested its molecular encapsulation in beta-cyclodextrin (beta-CD), using molar ratios of 1:1 and 1:2 (sulfluramid:beta-CD), using the complex preparation techniques of coprecipitation and kneading. The physical mixture of sulfluramid and beta-CD was also tested for comparison. The products of complexation were characterized by differential scanning calorimetry, thermogravimetry, and derivative thermogravimetry, indicating the formation of a sulfluramid/beta-CD complex and showing that the release of the complexed sulfluramid occurs in the range of 270-300 degrees C, a temperature range that is well above the temperature at which sulfluramid sublimates (40 degrees C). This result warrants a reduced sulfluramid loss in the preparation of

insecticidal baits. The preparation of the complex by kneading with molar ratio of 1:2 gave the highest yield of complex, about 64%, in relation to the theoretical maximum.

Bergonzi M. C., Bilia A. R., Di B. L., Mazzi G. and Vincieri F. F. (2007) Studies on the interactions between some flavonols and cyclodextrins. *Bioorg. Med. Chem Lett* **17**, 5744-5748.

Abstract: The interactions of some natural flavonols with alpha, beta- and gamma-Cds have been investigated. Guest molecules were galangin, kaempferol and quercetin. Inclusion complexes were prepared by kneading and freeze-drying. The complexes were characterized using different physico-chemical methods based on differential scanning calorimetry (DSC), infrared spectroscopy (IR) and NMR spectroscopy. In the proton and carbon spectra the effects of complexation on the chemical shifts of the internal and external protons of Cds in the presence of each flavonoid were observed. Moreover, the water-solubility of the flavonols in the presence of Cds was also evaluated. The increased solubility of quercetin and kaempferol in the presence of beta-Cd was evidenced. For all three guests, multidimensional NMR experiments in DMSO and water are consistent with dynamic binding processes, dominated by insertion of the B ring into the wider rim of the Cd cavity.

Bettinetti G., Mura P., Faucci M. T., Sorrenti M., and Setti M. (2002) Interaction of naproxen with noncrystalline acetyl beta- and acetyl gamma-cyclodextrins in the solid and liquid state. *Eur J Pharm Sci* **15**, 21-29.

Abstract: Randomly acetylated, amorphous beta-cyclodextrin (AcbetaCd) and gamma-cyclodextrin (AgammaCd), having an average substitution degree per anhydroglucose unit, respectively, of 1.1 and 0.95 (approximately 7.7 acetyl residues per macrocycle), were investigated for their interactions in the solid and liquid state with naproxen (NAP). Differential scanning calorimetry (DSC), supported by X-ray powder diffractometry (XRD), of NAP-AcbetaCd and NAP-AgammaCd blends revealed an apparent decrease in drug crystallinity which was related to a heating-induced solid-state interaction between the drug and each carrier. A solubility of approximately 0.40 NAP mass fraction in amorphous AcbetaCd and amorphous AgammaCd at room temperature was determined. Phase-solubility analysis at 25, 37, and 45 degrees C accounted for A(L)-type inclusion complexation of NAP with AcbetaCd ($K(1:1,25 \text{ degrees C})=4.5(4) \times 10^3 \text{ l mol}^{-1}$) and AgammaCd ($K(1:1,25 \text{ degrees C})=0.80(7) \times 10^3 \text{ l mol}^{-1}$) and revealed a solubilizing efficiency of AcbetaCd toward NAP approximately 4 times that of AgammaCd. Equimolar drug-carrier combinations prepared from the respective blends by grinding, kneading, coevaporation and freeze-drying were characterized by DSC and XRD and tested for dissolution rate of NAP using the dispersed amount and continuous flow through methods. The best performance in terms of dissolution rate enhancement (approximately 23 times and approximately 10 times the dissolution efficiency of pure drug in the dispersed amount and continuous flow through tests, respectively) was displayed by the NAP-AcbetaCd colyophilized product.

Bettinetti G. P., Sorrenti M., Rossi S., Ferrari F., Mura P., and Faucci M. T. (2002) Assessment of solid-state interactions of naproxen with amorphous cyclodextrin derivatives by DSC. *J Pharm Biomed Anal* **30**, 1173-1179.

Abstract: A microcalorimetric method based on differential scanning calorimetry (DSC) of drug-additive binary systems to assess kneading-induced interactions was applied to naproxen (NAP) in combinations with amorphous hydroxypropyl beta-cyclodextrin (HPbetaCd), beta-cyclodextrin sulfobutyl ether, sodium salt ((SBE)(7m)-betaCd), acetyl beta-cyclodextrin (AcbetaCd) and acetyl gamma-cyclodextrin (AgammaCd). Modifications of thermal parameters of NAP in DSC curves of physical mixtures indicate heating-induced interactions which resulted in a broadening of the NAP melting endotherm in the combinations with HPbetaCd, AcbetaCd and AgammaCd. The effect of kneading on the interaction was particularly pronounced for the NAP-HPbetaCd and NAP-(SBE)(7m)-betaCd systems, which show a similar drug-to-carrier interaction ratio (1:2 by weight) as that of the other systems. Drug-to-carrier ratios, calculated considering the amount of NAP which recrystallizes from the melted mixtures equivalent to NAP not bound to the carrier, show a distinctly lower affinity in solid-state of the drug for the anionically charged (SBE)(7m)-betaCd with respect to other neutral carriers. The similar affinity of NAP for AcbetaCd and AgammaCd demonstrates that the geometry of the cavity, which is a determinant factor for the inclusion complexation in liquid state, does not influence the interaction process in solid-state.

Bettinetti G., Sorrenti M., Catenacci L., Ferrari F., and Rossi S. (2006) Polymorphism, pseudopolymorphism, and amorphism of peracetylated alpha-, beta-, and gamma-cyclodextrins. *J Pharm Biomed Anal* **41**, 1205-1211.

Abstract: Polymorphism, pseudopolymorphism, and amorphism of hexakis(2,3,6-tri-O-acetyl)-alpha-cyclodextrin (TAalphaCyD), heptakis(2,3,6-tri-O-acetyl)-beta-cyclodextrin (TAbetaCyD), and octakis(2,3,6-tri-O-acetyl)-gamma-cyclodextrin (TAgammaCyD) were investigated using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffractometry (XRPD), Fourier transform infrared spectroscopy (FTIR) and optical microscopy. An anhydrous and a bi-hydrate crystalline forms of TAalphaCyD, two monotropic anhydrous polymorphs and three pseudopolymorphs (i.e. methanolate, hydrate, and isopropanolate-hydrate) of TAbetaCyD, as well as two monotropic anhydrous polymorphs and isostructural pseudopolymorphs (e.g. hydrate and isopropanolate-hydrate) of TAgammaCyD were isolated and characterized. The amorphous forms of each TACyD were also obtained. Thermal data for desolvation of TAalphaCyD.2H₂O and TAbetaCyD.CH₃OH were reconciled with their crystal packing features. Melting temperatures and enthalpies of the crystalline forms of each TACyD can be referred to for possible solid-state interactions with drugs.

Bilensoy E., Rouf M. A., Vural I., Sen M., and Hincal A. A. (2006) Mucoadhesive, thermosensitive, prolonged-release vaginal gel for clotrimazole:beta-cyclodextrin complex. *AAPS PharmSciTech* **7**, E38.

Abstract: The purpose of this study was to achieve a better therapeutic efficacy and patient compliance in the treatment for vaginitis. Clotrimazole (1%) has been formulated in a vaginal gel using the thermosensitive polymer Pluronic F127 (20%) together with mucoadhesive polymers such as Carbopol 934 and hydroxypropylmethylcellulose (0.2% for both). To increase its aqueous solubility, clotrimazole was incorporated as its inclusion complex with 1:1 molar ratio with beta-cyclodextrin. The inclusion complex was thoroughly characterized using various techniques, including ¹H NMR spectroscopy, FT IR spectrophotometry, differential scanning calorimetry, scanning electron microscopy, phase solubility studies, and determination of stability constant (k(1:1)). The gelation temperature and rheological behavior of different formulations at varying temperatures were measured. In vitro release profiles of the gels were determined in pH 5.5 citrate buffer. It was observed that complexation with cyclodextrin slowed down the release of clotrimazole considerably. Carbopol 934, on the other hand, was found to interact with beta-cyclodextrin, inducing precipitation. As far as rheological properties are concerned, thermosensitive in situ gelling was obtained with formulations containing drug:cyclodextrin complex rather than with free drug. Thus, the optimum formulation for a controlled-release thermosensitive and mucoadhesive vaginal gel was determined to be clotrimazole:beta-cyclodextrin 1% with 0.2% hydroxypropylmethylcellulose in Pluronic F127 gel (20%) providing continuous and prolonged release of active material above MIC values.

Bilensoy E., Gurkaynak O., Ertan M., Sen M. and Hincal A. A. (2008) Development of nonsurfactant cyclodextrin nanoparticles loaded with anticancer drug paclitaxel. *J Pharm. Sci* **97**, 1519-1529.

Abstract: In the current formulation of clinical use paclitaxel (PCX) is associated with solubilizers that may produce severe side effects. In this study, PCX was complexed to an amphiphilic cyclodextrin (CD), 6-O-CAPRO-beta-CD, capable of forming nanoparticles spontaneously in order to mask its physicochemical properties via the formation of inclusion complexes of the drug with amphiphilic CD before the nanoparticle is formed. Complexes have been characterized with various techniques such as ¹H NMR, Fourier Transform Infrared (FTIR), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) confirming the formation of inclusion complex between PCX and 6-O-CAPRO-beta-CD. Nanospheres and nanocapsules were prepared directly from the preformed PCX/6-O-CAPRO-beta-CD inclusion complex by the nanoprecipitation technique, showing a size from 150 to 250 nm for nanospheres and from 500 to 500 nm for nanocapsules. Zeta potentials of the nanospheres and nanocapsules indicate stable colloidal dispersions within the range of -18 to -39 mV. A 12-month physical stability was demonstrated for blank nanoparticles. PCX encapsulation was high with three-fold increase in loading when nanoparticles are prepared directly from preformed inclusion complexes of the drug with 6-O-CAPRO-beta-CD. In vitro liberation profiles of PCX from CD nanoparticles show a prolonged release profile for this drug up to 12 h for nanospheres and 24 h for nanocapsules

Bodor N., Drustrup J., and Wu W. (2000) Effect of cyclodextrins on the solubility and stability of a novel soft corticosteroid, loteprednol etabonate. *Pharmazie* **55**, 206-209.

Abstract: To increase the aqueous solubility and stability of the soft corticosteroid loteprednol etabonate

(LE), drug complexation using various cyclodextrins (CDs), such as gamma-cyclodextrin (gamma-CD), 2-hydroxypropyl-beta-cyclodextrin (HPBCD), maltosyl-beta-cyclodextrin (MBCD), mixture of glucosyl/maltosyl-alpha-, beta-, and gamma-cyclodextrin (GMCD), and heptakis (2,6-di-O-methyl)-beta-cyclodextrin (DMCD), were attempted. The solubilizing and stabilizing effects of CD by itself or combined with various co-solvents were also investigated. Micronized (5 micron) LE was mixed in various aqueous CD or CD with cosolvent solutions. After equilibration and filtration at 23 degrees C, the solubility of LE was determined by HPLC. Subsequently, the stability of LE in the solutions was also determined by following the LE concentration change in the solution for an appropriate period. CD complexation significantly increased the aqueous solubility and stability of LE. The increase in solubility displayed a concentration dependency on CDs (0-50%). Among the five CDs used, DMCD showed the highest effects on the solubility (4.2-18.3 mg/ml in 10-50% DMCD) and stability ($t_{90} > 4$ years at 4 degrees C, when LE 0.5 mg/ml was dissolved in 10% DMCD solution) of LE. By adding co-solvents, such as glycerol, propylene glycol (PG), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP-10), the solubility of LE in DMCD solutions was further increased. Degradation of LE to the corresponding metabolites, delta 1-cortienic acid etabonate (AE) and delta 1-cortienic acid (A), in aqueous CD solutions appeared to be a predicted, two-step kinetics. Differential Scanning Calorimetry (DSC) was used to assist explaining the solubilizing and stabilizing activity differences between CDs. LE/CD mixture or lyophilized LE/CD complex was scanned at a rate of 20 degrees C/min. The exothermic peak found in the DSC diagram with LE/DMCD sample, but not with LE/HPBCD samples, suggests a stronger complex formed between LE and DMCD, resulting in higher solubility and stability of LE in DMCD than in HPBCD.

Bongiorno D., Ceraulo L., Mele A., Panzeri W., Selva A., and Turco L., V (2002) Structural and physicochemical characterization of the inclusion complexes of cyclomaltooligosaccharides (cyclodextrins) with melatonin. *Carbohydr Res* **337**, 743-754.

Abstract: The stoichiometry, geometry, stability, and solubility of the inclusion complexes of melatonin (MLT) with native cyclomaltooligosaccharides (alpha-, beta- or gamma-cyclodextrins, CDs) are determined experimentally by high-resolution NMR spectroscopy, calorimetric and solubility measurements, and mass spectrometry. The observed differences are discussed in terms of molecular recognition expression of the host-guest (h-g) interactions within the hydrophobic CDs cavities of different size. The 1:1 h-g stoichiometry in water solution prevails at low CD concentrations; the trend to form higher order associations is observed at increasing CD concentrations. The stability order beta-CD>gamma-CD>alpha-CD for the complexes in water solution and beta-CD>alpha-CD>gamma-CD for the protonated or alkali-cationated complexes in the gas phase are rationalized on the grounds of the structural data from NMR spectroscopy and of the thermodynamic parameters from calorimetric measurements.

Boudad H., Legrand P., Lebas G., Cheron M., Duchene D., and Ponchel G. (2001) Combined hydroxypropyl-beta-cyclodextrin and poly(alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir. *Int J Pharm* **218**, 113-124.

Abstract: The aim of this study was to prepare and characterize an hydroxypropyl-beta-cyclodextrin-saquinavir inclusion complex with the purpose of incorporating this complex into poly(alkylcyanoacrylate) nanoparticles in order to increase the drug loading. Hydroxypropyl-beta-cyclodextrin-saquinavir complex was characterized by thermal (differential scanning calorimetry), crystallographic (X-ray diffractography) and spectroscopic methods (circular dichroism, H1-NMR). Nanoparticles were prepared by polymerization of alkylcyanoacrylate monomers (isobutyl- and isohexylcyanoacrylate) in a water solution of the complex and further characterized. The apparent solubility of saquinavir was increased 400-fold at pH 7.0 in presence of hydroxypropyl-beta-cyclodextrin owing to the formation of a drug-cyclodextrin complex as demonstrated mainly by ¹H NMR and confirmed by other techniques. Saquinavir-loaded nanoparticles could be easily prepared in the presence of a drug-cyclodextrin complex. It was found that large amounts of cyclodextrins remained associated with the particles, resulting in a 20-fold increase in saquinavir loading compared to nanoparticles prepared in the absence of cyclodextrins. This study has shown that the loading in saquinavir of poly(alkylcyanoacrylate) nanospheres could be dramatically improved by simultaneously increasing the apparent solubility of the drug in the preparation medium and the amount of cyclodextrin associated with the particles, making these nanospheres a promising system for oral application.

Branchu S., Forbes R. T., York P., Petren S., Nyqvist H., and Camber O. (1999) Hydroxypropyl-beta-cyclodextrin inhibits spray-drying-induced inactivation of beta-galactosidase. *J Pharm Sci* **88**, 905-911.

Abstract: The single-step, fast spray-drying process may represent a valuable alternative to the multistep, time-consuming freeze-drying process in the area of formulation and processing of biopharmaceuticals. In this study, we tested the use of sucrose and hydroxypropyl-beta-cyclodextrin (HP-beta-CD) as stabilizing excipients in the spray-drying of a model protein, beta-galactosidase. The solutions were processed using a Buchi 190 cocurrent Mini Spray Dryer at an outlet temperature of 61 +/- 2 degrees C. The powders were redissolved and analyzed for catalytic activity, aggregation, chemical decomposition, and thermal susceptibility as observed by high-resolution calorimetry. Spray-drying significantly inactivated beta-galactosidase. Spray-drying beta-galactosidase in the presence of sucrose did not prevent inactivation. However, after spray-drying beta-galactosidase in the presence of HP-beta-CD, or HP-beta-CD and sucrose, full catalytic activity was exhibited on reconstitution. Furthermore, the reconstituted product was unchanged in terms of molecular weight, charge, and thermal stability. These findings are consistent with a hypothesis that the change responsible for inactivation of beta-galactosidase was mainly a monomolecular, noncovalent change, i. e., the formation of incorrect structures, that arose from surface denaturation. This study clearly demonstrates that cyclodextrins can be useful stabilizing excipients in the preparation of spray-dried protein pharmaceuticals.

Bu H., Naess S. N., Beheshti N., Zhu K., Knudsen K. D., Kjoniksen A. L., Elgsaeter A., and Nystrom B. (2006) Characterization of thermally sensitive interactions in aqueous mixtures of hydrophobically modified hydroxyethylcellulose and cyclodextrins. *Langmuir* **22**, 9023-9029.

Abstract: Effects of beta-cyclodextrin (beta-CD) or hydroxypropyl-beta-cyclodextrin (HP-beta-CD) addition and temperature on thermodynamic, rheological, and structural features of semidilute solutions of hydroxyethylcellulose (HEC) and its hydrophobically modified analogue (HM-HEC) are reported. Differential scanning calorimetric (DSC) measurements revealed a thermally induced crystal melting transition of beta-CD at high concentrations in solutions of HEC and HM-HEC. No transition with HP-beta-CD was observed in aqueous solution. Viscosity results indicated that at a cosolute concentration of 2 mM, the beta-CD units are threaded onto hydrophobic tails of HM-HEC (C16 groups) to form columnar structures. This arrangement is more effective in the encapsulation of the hydrophobic chains than the monomer hydrophobic deactivation accomplished by the HP-beta-CD units. At cosolute concentrations above 8 mM, no further decoupling of the hydrophobic interactions occurs for any of the cosolutes. Small-angle neutron scattering (SANS) experiments on HM-HEC/beta-CD mixtures suggest that the large-scale association structures in HM-HEC/D(2)O solutions are reduced upon addition of beta-CD, and an interesting temperature effect is observed at 2 mM beta-CD addition. At high beta-CD concentrations and low temperatures, the formation of large beta-CD clusters or crystallites generates cross-links in the HEC and HM-HEC networks, resulting in a viscosity enhancement of several orders of magnitude. This strong temperature effect is not reflected in the structural features probed by SANS.

Cafaggi S., Vallarino M., Caviglioli G., Parodi B., and Bignardi G. (1998) Study of the interaction of dithranol with heptakis(2,3,6-tri-O-methyl)-beta-cyclodextrin in solution and in the solid state. *J Pharm Pharmacol* **50**, 257-264.

Abstract: The interaction between dithranol and heptakis(2,3,6-tri-O-methyl)-beta-cyclodextrin (TMBCyD) has been investigated in aqueous solution containing isoascorbic acid (0.2% w/v) as antioxidant and in the solid state. The interaction in the solid state was studied by differential scanning calorimetry (DSC), infrared spectroscopy (IR), X-ray powder diffractometry (XPD) and a dissolution-rate method. The extent of complexation between the two substances was poor, as indicated by the low value of the slope of the linear part of the solubility curve. A phase diagram was constructed by measuring the thermal behaviour of various re-solidified physical mixtures of dithranol and of TMBCyD previously subjected to heating until melting of the TMBCyD. The loss of dithranol, owing to sublimation and degradation caused by the thermal treatment used, was less than 10%. In keeping with XPD and IR data, the phase diagram indicated that a complex was formed containing 13.7% dithranol (molar ratio 1:1) which had a congruent melting point at 164 degrees C. The drug dissolution rate from the 1:1 complex was measurable, unlike that of the corresponding physical mixture, and was significantly increased when the complex was dispersed in the glassy matrix of TMBCyD, as it was in re-solidified mixtures containing 2-7% dithranol. The results show that the solubility of dithranol is increased significantly as a consequence of its interaction with TMBCyD, despite the low extent of complexation between the two substances.

Calabro M. L., Tommasini S., Donato P., Raneri D., Stancanelli R., Ficarra P., Ficarra R., Costa C., Catania S., Rustichelli C., and Gamberini G. (2004) Effects of alpha- and beta-cyclodextrin complexation on the physico-chemical properties and antioxidant activity of some 3-hydroxyflavones. *J Pharm Biomed Anal* **35**, 365-377.

Abstract: Inclusion complexes of some flavonols (3-hydroxyflavone, morin and quercetin) have been obtained with alpha- and beta-cyclodextrins, by the co-evaporation method. Different analytical techniques (DSC, XRPD, FT-IR, ¹H-NMR, UV-Vis) have been employed for a throughout investigation of the structural characteristics of such supramolecular aggregates, which exhibited distinct spectroscopic features and properties from both "guest" and "host" molecules. The stoichiometric ratios and stability constants describing the extent of formation of the complexes have been determined by phase-solubility studies; in all cases type-AL diagrams have been obtained (soluble 1:1 complexes). The effect of molecular encapsulation on the flavonols antioxidant activity has been afterwards evaluated, by means of different biological assays (Bathophenanthroline test; Comet assay; Lipid peroxidation). Complexation with cyclodextrins further improved the antioxidant activity, increasing drugs solubility in the biological moiety.

Castillo J. A., Palomo-Canales J., Garcia J. J., Lastres J. L., Bolas F., and Torrado J. J. (1999) Preparation and characterization of albendazole beta-cyclodextrin complexes. *Drug Dev Ind Pharm* **25**, 1241-1248.

Abstract: Albendazole (ABZ), mebendazole (MBZ), and ricobendazole (RBZ) are low-soluble anthelmintic benzimidazole carbamate drugs. To increase their aqueous solubility, three different types of beta-cyclodextrins (CyDs): beta-cyclodextrin (CD), hydroxypropyl-beta-cyclodextrin (HPCD), and methyl-beta-cyclodextrin (MCD) were used. Solubility depended on the type of CyDs. Increased solubility was obtained when the more substituted CyDs (HPCD or MCD) were used instead of nonsubstituted CD. Stability constants were calculated assuming a 1:1 stoichiometry. Calculated stability constant values depended on initial solubility of drug and pH of the medium. Solid ABZ complexes were prepared by coprecipitation and freeze-drying methods. These products were compared with physical mixtures of ABZ and CyDs. The characterization of these products was made by differential scanning calorimetry (DSC) and drug release studies. True inclusion complexes were obtained only by the freeze-drying method. Drug release studies showed that the freeze-dried inclusion complexes increased the solubility rate of ABZ, although a supersaturation effect was observed when drug release studies were performed in nonsink conditions. A bioavailability study on mice was done with a formulation of ABZ:HPCD complex and was compared to a conventional ABZ suspension. A significantly ($p < .05$) shorter T_{max} of absorption was obtained by using the complex formulation. Greater and significant ($p < .05$) differences for AUC and C_{max} were observed.

Cavalli R., Peira E., Caputo O., and Gasco M. R. (1999) Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with beta-cyclodextrins. *Int J Pharm* **182**, 59-69.

Abstract: Inclusion complexes of hydrocortisone and progesterone were formed with beta-cyclodextrin or 2-hydroxypropyl-beta-cyclodextrin. The formation of the complexes was confirmed by differential scanning calorimetry (DSC). The inclusion complexes were incorporated in two types of solid lipid nanoparticles (SLN). In the presence of the complexes the sizes of SLN remained below 100 nm. DSC analysis showed that hydrocortisone and progesterone are dispersed in SLN in an amorphous state. Using the beta-cyclodextrin complexes the incorporation of the more hydrophilic drug, hydrocortisone, was higher than that of progesterone. Release of hydrocortisone and progesterone from SLN was lower when they were incorporated as inclusion complexes than as free molecules. Copyright.

Cerchiara T., Luppi B., Bigucci F., and Zecchi V. (2003) Effect of chitosan on progesterone release from hydroxypropyl-beta-cyclodextrin complexes. *Int J Pharm* **258**, 209-215.

Abstract: An inclusion complex composed of progesterone (Prog) and hydroxypropyl-beta-cyclodextrin (HPbetaCD) was prepared by the spray-drying and freeze-drying methods. Prog alone and its inclusion complex with HPbetaCD were incorporated into chitosan by spray-drying and freeze-drying. The inclusion complex was characterized by IR and DSC. The inclusion complex was investigated in solution by phase solubility diagrams and stability constant was determined at pH 7.4 and at different temperatures (10, 25 and 37 degrees C) to obtain the thermodynamic parameters of inclusion. The results indicate that the Prog-HPbetaCD inclusion complex is more water soluble than Prog alone. Release data from all samples showed significant improvement of the dissolution rate of Prog and a controlled release is obtained in the presence of chitosan.

Chadha R., Kashid N., Kumar A., and Jain D. V. (2002) Calorimetric studies of diclofenac sodium in aqueous solution of cyclodextrin and water-ethanol mixtures. *J Pharm Pharmacol* **54**, 481-486.

Abstract: The technique of solution calorimetry has been employed to study the interaction between diclofenac sodium and beta-cyclodextrin by determining the enthalpies of solution of the drug in water and in aqueous beta-cyclodextrin solution. Thermodynamic parameters characterizing the binding process such as enthalpy ΔH^0 , equilibrium constant K , free energy ΔG^0 and entropy ΔS^0 have been calculated to be $12.00 \text{ kJ mol}^{-1}$, $1670 \text{ dm}^3 \text{ mol}^{-1}$, $-19.03 \text{ kJ mol}^{-1}$ and $22.98 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. Enthalpies of solution of diclofenac sodium have also been determined in water-ethanol mixtures.

Chao J., Li J., Meng D., and Huang S. (2003) Preparation and study on the solid inclusion complex of sparfloxacin with HP-beta-cyclodextrin. *Spectrochim Acta A Mol Biomol Spectrosc* **59**, 705-711.

Abstract: The interaction of sparfloxacin with HP-beta-cyclodextrin (HP-beta-CD) has been studied by several analytical techniques, including $^1\text{H-NMR}$, fluorescence spectroscopy, infrared spectroscopy, thermal analysis and scanning electron microscopy. In this paper, solid inclusion complex of sparfloxacin with HP-beta-CD was synthesized by the coprecipitation method. In addition, the characterization of the inclusion complex has been proved by fluorimetry, infrared, differential scanning calorimetry and 1D, 2D NMR. The experimental results confirmed the existence of 1:1 inclusion complex of sparfloxacin with HP-beta-CD. The formation constant of complex was determined by the fluorescence method and $^1\text{H-NMR}$. Spatial configuration of complex has been proposed on 2D NMR technique.

Chao J. B., Tong H. B., Huang S. P., and Liu D. S. (2004) Preparation and study on the solid inclusion complex of sparfloxacin with beta-cyclodextrin. *Spectrochim Acta A Mol Biomol Spectrosc* **60**, 161-166.

Abstract: The interaction of sparfloxacin with beta-cyclodextrin (beta-CD) has been studied by several analytical techniques, including $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, fluorescence spectroscopy, infrared spectroscopy, thermal analysis, and scanning electron microscope. In this paper, solid inclusion complex of sparfloxacin with beta-CD was synthesized by the coprecipitation method. In addition, the characterization of the inclusion complex has been proved by fluorimetry, Infrared, differential scanning calorimetry and 1D, 2D NMR. The experimental results confirmed the existence of 1:1 inclusion complex of sparfloxacin with beta-CD. The formation constant of complex was determined by fluorescence method and $^1\text{H-NMR}$. Spatial configuration of complex has been proposed on 2D NMR techniques.

Choi H. G., Lee B. J., Han J. H., Lee M. K., Park K. M., Yong C. S., Rhee J. D., Kim Y. B., and Kim C. K. (2001) Terfenadine-beta-Cyclodextrin inclusion complex with antihistaminic activity enhancement. *Drug Dev Ind Pharm* **27**, 857-862.

Abstract: Terfenadine, an antihistaminic drug, has relatively low bioavailability after oral administration due to its limited solubility in water. To enhance the antihistaminic activity of terfenadine, the terfenadine-beta-cyclodextrin (1:2) inclusion complex was prepared by the neutralization method. The solubility and dissolution of the inclusion complex were carried out, and its antihistaminic activity was then evaluated and compared with terfenadine powder by the passive subcutaneous anaphylaxis method in rats. The formation constant of the inclusion complex was higher at lower pH, while its formation ratio was 1:2 irrespective of pH. For terfenadine, it improved the solubility 200 times and the dissolution rate 5 times. It gave a low histamine level at 30 min, followed by a sustained low level until 60 min, while terfenadine powder gave a low histamine level at 60 min, suggesting that it had faster and more effective antihistaminic activity than terfenadine powder in rats due to fast dissolution and absorption of terfenadine. It is concluded that this inclusion complex enhanced the antihistaminic activity of terfenadine following the enhanced solubility and dissolution of terfenadine.

Choi H. G., Kim D. D., Jun H. W., Yoo B. K., and Yong C. S. (2003) Improvement of dissolution and bioavailability of nitrendipine by inclusion in hydroxypropyl-beta-cyclodextrin. *Drug Dev Ind Pharm* **29**, 1085-1094.

Abstract: A significant increase in solubility and dissolution rate of nitrendipine, a slightly soluble calcium channel blocker, was achieved by inclusion complexation with hydroxypropyl-beta-cyclodextrin (HP-beta-CD). The inclusion complex was prepared by solvent evaporation method and characterized by phase solubility method, x-ray diffractometry, infrared spectroscopy, and differential scanning calorimetry. The solubility of nitrendipine increased linearly as a function of HP-beta-CD concentration, resulting in AL-type phase solubility diagram which revealed a formation of inclusion complex in a molar ratio of 1:1, with

the apparent association constant of $108.3M^{-1}$. The in vitro dissolution rate of nitrendipine in pH 7.4 phosphate buffer was in the order of inclusion complex, physical mixture, and nitrendipine powder. These three different forms of nitrendipine were administered orally to rats with a dose of 10 mg/kg equivalent to nitrendipine. The AUC of inclusion complex was significantly larger than that of nitrendipine powder. T_{max} of inclusion complex was significantly shorter and C_{max} was significantly higher than those of nitrendipine powder. C_{max} of physical mixture was higher than that of nitrendipine powder. T_{max} of physical mixture, however, remained the same. The results indicated that the bioavailability of nitrendipine could be improved markedly by inclusion complexation, possibly due to an increased dissolution rate.

Cirri M., Rangoni C., Maestrelli F., Corti G., and Mura P. (2005) Development of fast-dissolving tablets of flurbiprofen-cyclodextrin complexes. *Drug Dev Ind Pharm* **31**, 697-707.

Abstract: The present study was aimed at developing a tablet formulation based on an effective flurbiprofen-cyclodextrin system, able to allow a rapid and complete dissolution of this practically insoluble drug. Three different cyclodextrins were evaluated: the parent beta-cyclodextrin (previously found to be the best partner for the drug among the natural cyclodextrins), and two amorphous, highly soluble beta-cyclodextrin derivatives, i.e., methyl-beta-cyclodextrin and hydroxyethyl-beta-cyclodextrin. Equimolar drug-cyclodextrin binary systems prepared according to five different techniques (physical mixing, kneading, sealed-heating, coevaporation, and colyophilization) were characterized by Differential Scanning Calorimetry, x-ray powder diffractometry, infrared spectroscopy, and optical microscopy and evaluated for solubility and dissolution rate properties. The drug solubility improvement obtained by the different binary systems varied from a minimum of 2.5 times up to a maximum of 120 times, depending on both the cyclodextrin type and the system preparation method. Selected binary systems were used for preparation of direct compression tablets with reduced drug dosage (50 mg). Chitosan and spray-dried lactose, alone or in mixture, were used as excipients. All formulations containing drug-cyclodextrin systems gave a higher drug dissolved amount than the corresponding ones with drug alone (also at a dose of 100 mg); however, the drug dissolution behavior was strongly influenced by formulation factors. For example, for the same drug-cyclodextrin product the time to dissolve 50% drug varied from less than 5 minutes to more than 60 minutes, depending on the excipient used for tableting. In particular, only tablets containing the drug kneaded with methyl-beta-cyclodextrin or colyophilized with beta-cyclodextrin and spray-dried lactose as the only excipient satisfied the requirements of the Food and Drug Administration (FDA) for rapid dissolving tablets, allowing more than 85% drug to be dissolved within 30 minutes. Finally, it can be reasonably expected that the obtained drug dissolution rate improvement will result in an increase of its bioavailability, with the possibility of reducing drug dosage and side effects.

Correa D. H., Melo P. S., de Carvalho C. A., de Azevedo M. B., Duran N., and Haun M. (2005) Dehydrocrotonin and its beta-cyclodextrin complex: cytotoxicity in V79 fibroblasts and rat cultured hepatocytes. *Eur J Pharmacol* **510**, 17-24.

Abstract: Trans-dehydrocrotonin has antiulcerogenic and antitumor activities. A complex of beta-cyclodextrin with dehydrocrotonin was developed to improve the delivery of dehydrocrotonin. Complex in solid state was evaluated using X-ray diffraction (XRD), differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA) and scanning electron microscopy (SEM). X-ray diffraction and scanning electron microscopy studies showed that dehydrocrotonin exists in a semicrystalline state in the complexed form with beta-cyclodextrin. Differential scanning calorimetry studies showed the existence of a complex of dehydrocrotonin with beta-cyclodextrin. The thermal gravimetric analysis studies confirmed the differential scanning calorimetry results of the complex. Free dehydrocrotonin and the dehydrocrotonin/beta-cyclodextrin inclusion complex were assayed in freshly isolated rat hepatocytes and in V79 cells. Cytotoxicity was determined using nucleic acid content, methylthiazolotetrazolium (MTT) reduction and neutral red uptake assays. In all assays, there was a large reduction (3.5-16.1-fold) in the cytotoxicity of dehydrocrotonin in hepatocytes when complexed with beta-cyclodextrin, whereas for V79 cells the decrease in cytotoxicity was 1.7- and 1.87-fold for MTT reduction and nucleic acid content assays, respectively. The lower cytotoxicity of the dehydrocrotonin/beta-cyclodextrin complex compared to free dehydrocrotonin in rat hepatocytes and V79 cells suggests that such a complex may be useful for the administration of dehydrocrotonin in vivo.

Cwiertnia B., Hladon T., and Stobiecki M. (1999) Stability of diclofenac sodium in the inclusion complex with beta-cyclodextrin in the solid state. *J Pharm Pharmacol* **51**, 1213-1218.

Abstract: The aim of this study was to characterize the thermal stability of diclofenac sodium both alone and in the inclusion complex with beta-cyclodextrin in the solid state, by determination of the number of the products of its decomposition, which were identified by GC-MS. The molar ratio of diclofenac sodium in the inclusion complex with beta-cyclodextrin was 1:1. The decomposition of diclofenac sodium both alone and in inclusion complex with beta-cyclodextrin occurred according to the first-order reaction. The HPLC of the samples thermostated at 80 degrees C gave five products of decomposition, which were identified by GC-MS. Diclofenac sodium in the inclusion complex with beta-cyclodextrin was more thermally stable. Thermal decomposition of diclofenac sodium leads to formation of five products, of which 4-chloro-10H-9-acridinone had not been reported previously in the literature.

Denadai A. M., Santoro M. M., Lopes M. T., Chenna A., de Sousa F. B., Avelar G. M., Gomes M. R., Guzman F., Salas C. E., and Sinisterra R. D. (2006) A supramolecular complex between proteinases and beta-cyclodextrin that preserves enzymatic activity: physicochemical characterization. *BioDrugs* **20**, 283-291.

Abstract: BACKGROUND: Cyclodextrins are suitable drug delivery systems because of their ability to subtly modify the physical, chemical, and biological properties of guest molecules through labile interactions by formation of inclusion and/or association complexes. Plant cysteine proteinases from Caricaceae and Bromeliaceae are the subject of therapeutic interest, because of their anti-inflammatory, antitumoral, immunogenic, and wound-healing properties. METHODS: In this study, we analyzed the association between beta-cyclodextrin (betaCD) and fraction P1G10 containing the bioactive proteinases from *Carica candamarcensis*, and described the physicochemical nature of the solid-state self-assembled complexes by Fourier transform infrared (FTIR) spectroscopy, thermogravimetry (TG), differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and nuclear magnetic resonance (NMR), as well as in solution by circular dichroism (CD), isothermal titration calorimetry (ITC), and amidase activity. RESULTS AND DISCUSSION: The physicochemical analyses suggest the formation of a complex between P1G10 and betaCD. Higher secondary interactions, namely hydrophobic interactions, hydrogen bonding and van der Waals forces were observed at higher P1G10 : betaCD mass ratios. These results provide evidence of the occurrence of strong solid-state supramolecular non-covalent interactions between P1G10 and betaCD. Microcalorimetric analysis demonstrates that complexation results in a favorable enthalpic contribution, as has already been described during formation of similar betaCD inclusion compounds. The amidase activity of the complex shows that the enzyme activity is not readily available at 24 hours after dissolution of the complex in aqueous buffer; the proteinase becomes biologically active by the second day and remains stable until day 16, when a gradual decrease occurs, with basal activity attained by day 29. CONCLUSION: The reported results underscore the potential for betaCDs as candidates for complexing cysteine proteinases, resulting in supramolecular arrays with sustained proteolytic activity.

Dias M. M., Raghavan S. L., Pellett M. A., and Hadgraft J. (2003) The effect of beta-cyclodextrins on the permeation of diclofenac from supersaturated solutions. *Int J Pharm* **263**, 173-181.

Abstract: Supersaturation is a very useful method of enhancing the permeation of drugs across membranes such as skin, because unlike other methods, it does not interfere with the ultrastructure of the stratum corneum. Many drugs are able to form inclusion complexes with beta-cyclodextrins (beta-CDs) and this study investigates the anti-nucleating effects of these compounds on supersaturated solutions of diclofenac. The ability of various betaCDs to form inclusion complexes with diclofenac was assessed by measuring their saturated solubilities. Solutions containing hydroxypropyl beta-cyclodextrin (HPbeta-CD, with a molar substitution of 0.9) produced a 7.5-fold increase in the solubility of diclofenac, which suggested that a strong complex was formed between the two compounds. This association was characterized using differential scanning calorimetry. Permeation across silicone membranes of these saturated solutions of diclofenac in the presence of the different betaCDs produced similar flux values suggesting that the overall activity was also similar. The effect of different molar ratios of HPbeta-CD and diclofenac, and the anti-nucleating effect of HPbeta-CD (both on its own and in combination with a known anti-nucleant, hydroxypropylmethyl cellulose (HPMC)) on the diffusion of diclofenac across silicone membranes was investigated. HPbeta-CD appears to have a stabilizing effect on supersaturated solutions of diclofenac as a co-ingredient with HPMC.

Dilova V., Zlatarova V., Spirova N., Filcheva K., Pavlova A., and Grigorova P. (2004) Study of insolubility problems of dexamethasone and digoxin: cyclodextrin complexation. *Boll Chim Farm* **143**, 20-23.

Abstract: Cyclodextrins are able to form inclusion complexes with a number of drugs if their molecular dimensions correspond to those of the cyclodextrin cavity which leads to change of physicochemical and biopharmaceutical properties of drugs. 2-Hydroxypropyl beta cyclodextrin (HP beta CD) is suitable for parenteral application because of its considerable solubility in water and low hemolytic activity. Digoxin is insoluble in water, sensitive to light and is a subject of acidic hydrolysis, it is a challenge to the technologists of parenteral dosage forms. Dexamethasone (Dex) has a very small solubility in water (0.1 mg/ml), which caused troubles by preparing liquid medicine forms. The inclusion of hydroxy acids in CD-complexes in the necessary molar proportions leads to considerable increase in the solubility of a medicine and to several times decrease of the amount of CD used. Inclusion complexation was confirmed by the results from the studies of Differential Scanning Calorimetry. The present investigation demonstrated that Digoxin/CD complex shows stability in water medium and the optimum molar ratio Digoxin/HP beta CD is 1:6. The same results can be achieved through HP beta CD, by including Dex in a multicomponent composition containing HP beta CD and citric acid in a molar ratio of 1:4:1.

Dong T., He Y., Shin K. M., and Inoue Y. (2004) Formation and Characterization of Inclusion Complexes of Poly(butylene succinate) with alpha- and gamma-Cyclodextrins. *Macromol Biosci* **4**, 1084-1091.

Abstract: The inclusion complexes (ICs) of alpha- and gamma-cyclodextrins (CDs) with high-molecular-weight poly(butylene succinate) (PBS) were prepared and characterized by differential scanning calorimetry, Fourier-transform infrared spectroscopy (FT-IR), wide-angle X-ray diffraction, solid-state ¹³C nuclear magnetic resonance (NMR) spectroscopy, and solution ¹H NMR spectroscopy. The resultant ICs were found to have channel structures. FT-IR data suggested that the ICs were stabilized by hydrogen bonds between the host CD molecules and the guest PBS chains. Through the formation of ICs, the PBS chain possibly adopts the kink conformation in the included state, as indicated by NMR analysis. Experimental and curve-fitting FT-IR spectrum of alpha-CD-PBS IC in the carbonyl region ($\nu(\text{C}=\text{O})$).

Echezarreta-Lopez M., Torres-Labandeira J. J., Castineiras-Seijo L., Santana-Penin L., and Vila-Jato J. L. (2000) Complexation of the interferon inducer, bropirimine, with hydroxypropyl-beta-cyclodextrin. *Eur J Pharm Sci* **9**, 381-386.

Abstract: Bropirimine (ABPP) is an orally active immunomodulator that increases endogenous alpha-interferon and other cytokines used clinically against carcinoma in situ of the bladder. The oral absorption of ABPP is poor because its low solubility in water. The purpose of this study is to develop a technological procedure useful to increase the water solubility of ABPP. To this end, the interaction of ABPP with several cyclodextrin derivatives-alpha-, beta-, gamma- and hydroxypropyl-beta-cyclodextrin with a degree of substitution 2.7 (HPbetaCD) was studied and the effect of the complexation process on the water solubility of the drug was evaluated. The best results were obtained with the hydroxypropyl derivative, HPbetaCD, that interacts in a 1:1 drug:cyclodextrin molar ratio. The inclusion complex ABPP-HPbetaCD was characterized in solution by nuclear magnetic resonance (¹H-NMR). The solid inclusion complex was obtained by freeze-drying and characterized by differential scanning calorimetry (DSC), X-ray diffractometry and mass spectrometry. The dissolution rate of ABPP from the HPbetaCD solid inclusion complex was increased compared to the powdered drug but not differences were found between the complex and a physical mixture with a similar molar ratio. The increase of the dissolution rate of the drug can be attributed to the breakdown in solution of the drug dimers in the presence of the cyclodextrin and to the complex formation.

Fatouros D. G., Hatzidimitriou K., and Antimisariis S. G. (2001) Liposomes encapsulating prednisolone and prednisolone-cyclodextrin complexes: comparison of membrane integrity and drug release. *Eur J Pharm Sci* **13**, 287-296.

Abstract: Inclusion complexes of prednisolone (PR) with beta-cyclodextrin (beta-CD) and hydropropyl-beta-cyclodextrin (HPbeta-CD) were formed by the solvation method, and were characterized by DSC, X-ray diffractometry and FT-IR spectroscopy. PC liposomes incorporating PR as plain drug or inclusion complex were prepared using the dehydration-rehydration method and drug entrapment as well as drug release were estimated for all liposome types prepared. The highest PR entrapment value (80% of the starting material) was achieved for PC/Chol liposomes when the HPbeta-CD-PR (2:1, mol/mol) complex was entrapped. The leakage of vesicle encapsulated 5,6-carboxyfluorescein (CF) was used as a measure of the vesicle membrane integrity. As judged from our experimental results liposomes which encapsulate

beta-CD-PR complexes are significantly less stable (when their membrane integrity is considered) compared to liposomes of identical lipid compositions which incorporate plain drug or even (in some cases) non-drug incorporating liposomes, which were prepared and studied for comparison. Interestingly, liposomes which encapsulate HPbeta-CD-PR complexes, have very low initial CF latency values, indicating that the leakage of CF is a process of very high initial velocity. Interactions between lipid and cyclodextrin molecules may be possibly resulting in rapid reorganization of the lipid membrane with simultaneous fast release of CF molecules. The release of PR from liposomes was highest when the drug was entrapped in the form of a complex with beta-CD. Nevertheless, the very high entrapment ability of PR in the form of HPbeta-CD-PR complexes in comparison to plain drug is a indubitable advantage of this approach.

Felton L. A., Wiley C. J., and Godwin D. A. (2002) Influence of hydroxypropyl-beta-cyclodextrin on the transdermal permeation and skin accumulation of oxybenzone. *Drug Dev Ind Pharm* **28**, 1117-1124.

Abstract: The objective of the present study was to determine the effects of hydroxypropyl-beta-cyclodextrin (HPCD) concentration on the transdermal permeation and skin accumulation of a model ultraviolet (UV) absorber, oxybenzone. The concentration of oxybenzone was held constant at 2.67 mg/mL for all formulations, while the HPCD concentrations varied from 0 to 20% (w/w). Complexation of oxybenzone by HPCD was demonstrated by differential scanning calorimetry. A modified Franz cell apparatus was used in the transdermal experiments, with aliquots of the receptor fluid assayed for oxybenzone by high-performance liquid chromatography. From the permeation data, flux of the drug was calculated. Skins were removed from the diffusion cells at specified time points over a 24-hr period and the oxybenzone content in the skin determined. The aqueous solubility of oxybenzone increased linearly with increasing HPCD concentration, following a Higuchi AL-type complexation. The stability constant of the reaction was calculated from the phase-solubility diagram and found to be 2047 M⁻¹. As the concentration of HPCD was increased from 0 to 10%, transdermal permeation and skin accumulation of oxybenzone increased. Maximum flux occurred at 10% HPCD, where sufficient cyclodextrin was added to completely solubilize all oxybenzone. When the concentration of HPCD was increased to 20%, both transdermal permeation and skin accumulation decreased. These data suggest the formation of a drug reservoir on the surface of the skin.

Fernandes C. M., Teresa V. M., and Veiga F. J. (2002) Physicochemical characterization and in vitro dissolution behavior of nicardipine-cyclodextrins inclusion compounds. *Eur J Pharm Sci* **15**, 79-88.

Abstract: Inclusion complexation between nicardipine hydrochloride (NC), a calcium-channel antagonist, and beta-cyclodextrin (beta-CD) or hydroxypropyl-beta-cyclodextrin (HPbetaCD) was evaluated in aqueous environment and in solid state. The phase solubility profiles with both cyclodextrins (CDs) were classified as A(L)-type, indicating the formation of 1:1 stoichiometric inclusion complexes. Stability constants (K_s) were calculated from the phase solubility diagrams and were found to be pH dependent. More stable NC:CDs complexes were formed in alkaline medium in which the drug is in its non-ionized form. Binary systems of NC with CDs, prepared experimentally by different techniques (kneading, evaporation, freeze-drying and spray-drying), were investigated by differential scanning calorimetry, Fourier transformation-infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. From this analysis, evaporation, freeze-drying and spray-drying were found to produce inclusion complexes. In contrast, crystalline drug was still clearly detectable in the kneaded products. The dissolution profiles of the obtained powders were studied in order to define the most appropriate CD and preparation method to originate inclusion complexes, which will be used in the development of a new controlled release formulation of NC. Both the preparation and nature of carrier played an important role in the dissolution performance of the system. However, independently of the preparation technique, all the combinations with HPbetaCD were more effective in achieving the enhancement of the NC dissolution rate, yielding better performances than the corresponding ones with betaCD.

Fernandes C. M. and Veiga F. J. (2002) Effect of the hydrophobic nature of triacetyl-beta-cyclodextrin on the complexation with nicardipine hydrochloride: physicochemical and dissolution properties of the kneaded and spray-dried complexes. *Chem Pharm Bull (Tokyo)* **50**, 1597-1602.

Abstract: The inclusion ability of triacetyl-beta-cyclodextrin (TAbetaCD), a hydrophobic cyclodextrin (CD) derivative was examined, using nicardipine hydrochloride (NC) as model drug. The binary compounds were prepared in a 1 : 1 molar ratio by the kneading and the spray-drying techniques. In order

to confirm the complexation between NC and TAbetaCD in the solid state, differential scanning calorimetry, X-ray diffractometry, Fourier transformation-infrared spectroscopy and scanning electron microscopy were carried out and the results were compared with the corresponding physical mixture in the same molar ratio. The kneaded product presented only slight modifications on the drug physicochemical and morphological properties, which could mean that no complex formation occurred during this process. In contrast, spray-drying was found to produce inclusion complexes with amorphous nature. In vitro dissolution studies were carried out in simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids, according to the United States Pharmacopoeia (USP) basket method. The NC in vitro release from the kneaded and spray-dried products was markedly retarded in both dissolution media. However, this retarding effect was significantly more evident for the spray-dried compound. It was concluded that the formation of real inclusion complexes could only be achieved by the spray-drying method.

Ficarra R., Ficarra P., Di Bella M. R., Raneri D., Tommasini S., Calabro M. L., Gamberini M. C., and Rustichelli C. (2000) Study of beta-blockers/beta-cyclodextrins inclusion complex by NMR, DSC, X-ray and SEM investigation. *J Pharm Biomed Anal* **23**, 33-40.

Abstract: The formation of inclusion complexes between beta-cyclodextrin with the two beta-blockers, atenolol and celiprolol, have been studied in the aqueous environment and in the solid state by nuclear magnetic resonance (NMR) spectroscopy, X-ray, differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) techniques. The magnitude of the chemical shifts of the interior and exterior beta-cyclodextrin protons in the presence of each beta-blocker indicated that these are included within the beta-cyclodextrin cavity. In aqueous solution they form 1:1 complexes. In the solid state the formation of the beta-cyclodextrin/atenolol (celiprolol) complexes is confirmed by X-ray, DSC and SEM, also employed to characterize pure substances and their physical mixtures.

Ficarra R., Tommasini S., Raneri D., Calabro M. L., Di Bella M. R., Rustichelli C., Gamberini M. C., and Ficarra P. (2002) Study of flavonoids/beta-cyclodextrins inclusion complexes by NMR, FT-IR, DSC, X-ray investigation. *J Pharm Biomed Anal* **29**, 1005-1014.

Abstract: Flavonoids are natural substances with a lot of biological activities, including the antioxidant one. Their use in pharmaceutical field is, however, limited by their aqueous insolubility. As the formation of the inclusion complexes can improve their solubility in water, the flavonoids hesperetin, hesperidin, naringenin and naringin have been complexed with beta-cyclodextrin (beta-CD) by the coprecipitation method and studied in solution and in solid state by NMR, FT-IR, differential scanning calorimetry and X-ray techniques. The effects of complexation on the chemical shifts of the internal and external protons of beta-CD in the presence of each flavonoid were observed.

Filipovic-Grcic J., Voinovich D., Moneghini M., Becirevic-Lacan M., Magarotto L., and Jalsenjak I. (2000) Chitosan microspheres with hydrocortisone and hydrocortisone-hydroxypropyl-beta-cyclodextrin inclusion complex. *Eur J Pharm Sci* **9**, 373-379.

Abstract: In the present study, an inclusion complex composed of hydrocortisone acetate (HC) and hydroxypropyl-beta-cyclodextrin (HPbetaCD) was prepared by the spray-drying method. HC alone, HC inclusion complex or HC with HPbetaCD as a physical mixture were incorporated into chitosan microspheres by spray-drying. The inclusion complex and microspheres were characterized by X-ray powder diffractometry and differential scanning calorimetry (DSC). Microspheres were studied with respect to particle size distribution, drug content and in vitro drug release. The results indicate that the HCHPbetaCD inclusion complex is more water soluble than HC alone. The HC release rates from chitosan microspheres were influenced by the drug/polymer ratio in the manner that an increase in the release rate was observed when the drug loading was decreased. However, release data from all samples showed significant improvement of the dissolution rate for HC, with 25-40% of the drug being released in the first hour compared with about 5% for pure HC. The complexation method and microsphere preparation method (spray-drying) is simple with great potential for industrial production.

Gan Y., Pan W., Wei M., and Zhang R. (2002) Cyclodextrin complex osmotic tablet for glipizide delivery. *Drug Dev Ind Pharm* **28**, 1015-1021.

Abstract: Poorly soluble glipizide was selected as the model drug to prepare osmotic pump tablets (OPT) with proper accessorial material after it was made an inclusion complex by kneading method in order to increase solubility. Polyethylene glycol 4000 (PEG4000) and cellulose acetate (CA) were selected as the

coating materials, and acetone-water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push-pull osmotic tablet. The results indicated that glipizide-cyclodextrin inclusion complex OPT had excellent zero-order release characteristics in vitro.

Gladys G., Claudia G., and Marcela L. (2003) The effect of pH and triethanolamine on sulfisoxazole complexation with hydroxypropyl-beta-cyclodextrin. *Eur J Pharm Sci* **20**, 285-293.

Abstract: A novel complexation of sulfisoxazole with hydroxypropyl-beta-cyclodextrin (HP-beta-CD) was studied. Two systems were used: binary complexes prepared with HP-beta-CD and multicomponent system (HP-beta-CD and the basic compound triethanolamine (TEA)). Inclusion complex formation in aqueous solutions and in solid state were investigated by the solubility method, thermal analysis (differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)), Fourier-transform infrared spectroscopy (FT-IR) and dissolution studies. The solid complexes of sulfisoxazole were prepared by freeze-drying the homogeneous concentrated aqueous solutions in molar ratios of sulfisoxazole:HP-beta-CD 1:1 and 1:2, and sulfisoxazole:TEA:HP-beta-CD 1:1:2. FT-IR and thermal analysis showed differences among sulfisoxazole:HP-beta-CD and sulfisoxazole:TEA:HP-beta-CD and their corresponding physical mixtures and individual components. The HP-beta-CD solubilization of sulfisoxazole could be improved by ionization of the drug molecule through pH adjustments. However, larger improvements of the HP-beta-CD solubilization are obtained when multicomponent systems are used, allowing to reduce the amount of CD necessary to prepare the target formulation.

Godwin D. A., Wiley C. J., and Felton L. A. (2006) Using cyclodextrin complexation to enhance secondary photoprotection of topically applied ibuprofen. *Eur J Pharm Biopharm* **62**, 85-93.

Abstract: Each year millions of people are overexposed to the sun resulting in photodamage of the skin. Secondary photoprotection is the application of medicinal agents to the body after sun exposure to reduce this damage. The objective of this study was to determine the affects of hydroxypropyl-beta-cyclodextrin (HPCD) complexation on the secondary photoprotective properties of topically applied ibuprofen. Complexation of ibuprofen by HPCD was demonstrated by differential scanning calorimetry, while solubilities were determined using HPLC. A linear ($r(2) > 0.999$) relationship was found between ibuprofen solubility and HPCD concentration. For subsequent experiments, the concentration of ibuprofen was held constant at the solubility in 10% HPCD (10.6mg/ml), while the HPCD concentration varied from 0 to 20% (w/w). In vitro transdermal permeation experiments demonstrated a parabolic relationship between transdermal kinetic parameters and HPCD concentration, with maximum values for both flux and skin accumulation occurring with the 10% HPCD formulation. In vivo experiments were performed by exposing hairless mice to UV radiation and applying ibuprofen-HPCD formulations topically at various times following UV exposure. Edema and epidermal lipid damage data demonstrated that application of ibuprofen-HPCD formulations within 1h of UV exposure provided significant photoprotection.

Gowrishankar P., Ali M. and Baboota S. (2007) Preparation and properties of valdecoxib-hydroxypropyl beta-cyclodextrin inclusion complex. *PDA. J Pharm. Sci Technol.* **61**, 175-182.

Abstract: Valdecoxib is a non-steroidal anti-inflammatory drug used in the treatment of rheumatoid and osteoarthritis. It is practically insoluble in water. Incidence of adverse events such as nausea has been reported in some trials. Therefore, an attempt was made to improve the aqueous solubility of the drug by making an inclusion complex using hydroxypropyl beta-cyclodextrin (HPbeta-CD). The complexes were prepared by physical mixture and freeze-drying methods. The different methods employed for evaluation--including differential scanning calorimetry, Fourier transform infrared spectral analysis, and scanning electron microscopy studies--indicated complete formation of the complex by the freeze-drying method in a molar ratio of 1:1. The prepared complexes showed an improved in vitro dissolution profile and better anti-inflammatory activity as compared to the pure drug.

Granero G. and Longhi M. (2002) Thermal analysis and spectroscopic characterization of interactions between a naphthoquinone derivative with HP-beta-CD or PVP. *Pharm Dev Technol* **7**, 381-390.

Abstract: The purpose of the present study was to investigate the interaction between both hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and PVP-K30 with 2-hydroxy-N-(3-methyl-5-ethyl-4-isoxazolyl)-1,4-naphthoquinone-4-imina (I), a synthetic derivative of isoxazolynaphthoquinones that has demonstrated to

exhibit important biological activity against *S. aureus* and *T. cruzi*. The continuous variation plot for I-HP-beta-CD system showed a 1:1 stoichiometry for the complex. Ultraviolet absorption spectroscopy indicates that the isoxazole moiety of I is preferably incorporated in the cavity. Furthermore, proton nuclear magnetic resonance spectroscopy suggests that this incorporation is made from the primary hydroxyl group side of the cyclodextrin. The validation of this incorporation is further evidenced by thermal analysis (DSC and TGA) and infrared spectroscopy. I-PVP-K30 interactions in solid state were demonstrated by combining the infrared spectroscopy data with the results of thermal analysis (DSC, TGA). These methods suggest that drug-polymer interaction probably occurs via intermolecular hydrogen bonding between the drug hydroxyl and polymer carbonyl groups.

Haiyun D., Jianbin C., Guomei Z., Shaomin S., and Jinhao P. (2003) Preparation and spectral investigation on inclusion complex of beta-cyclodextrin with rutin. *Spectrochim Acta A Mol Biomol Spectrosc* **59**, 3421-3429.

Abstract: Solid inclusion complex of rutin with beta-cyclodextrin (beta-CD) was prepared by coprecipitate method. The formation of inclusion complex was confirmed by differential scanning calorimetry (DSC) and X-ray diffraction. The formation constant was obtained by steady-state fluorescence measurements and the result suggested the complex preferred 1:1 (rutin:CD) stoichiometry. Furthermore, the spatial configuration of the complex has been proposed based on NMR and molecular modeling.

Hao X., Liang C., and Jian-Bin C. (2002) Preparation and spectroscopic studies of an inclusion complex of adenine with beta-cyclodextrin in solution and in the solid state. *Analyst* **127**, 834-837.

Abstract: The interaction between adenine and beta-CD has been investigated in solution and in the solid state by several analytical techniques, primarily by ¹H-NMR, 2D ROESY and fluorescence spectra, and secondarily by other important techniques, for example, Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC). The association constant and 1:1 nature of the complex between adenine and beta-CD in solution were determined by fluorescence spectroscopy. A spatial configuration for the complex in solution is proposed from analysis of the ¹H-NMR and 2D ROESY data. The Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC) data are consistent with the formation of an inclusion complex. In addition, a solid inclusion complex of adenine with beta-CD was synthesized by the coprecipitation method.

Ikeda Y., Kimura K., Hirayama F., Arima H., and Uekama K. (2000) Controlled release of a water-soluble drug, captopril, by a combination of hydrophilic and hydrophobic cyclodextrin derivatives. *J Control Release* **66**, 271-280.

Abstract: Parent beta-cyclodextrin (beta-CyD) and 2-hydroxypropyl-beta-CyD (HP-beta-CyD) form 1:1 solid complexes with an orally active angiotensin-converting enzyme inhibitor, captopril, while hydrophobic perbutanoyl-beta-CyD (TB-beta-CyD) forms a solid dispersion or solid solution with the drug. The binary system of captopril/HP-beta-CyD or captopril/TB-beta-CyD and the ternary system of captopril/TB-beta-CyD/HP-beta-CyD in different molar ratios were prepared by the kneading method, and the release behavior of the drug was investigated. The release rate of captopril from the binary HP-beta-CyD system was rather fast, whereas that from the binary TB-beta-CyD system was comparatively slower, the retarding effect being dependent on the amounts of TB-beta-CyD. The release rate from the ternary captopril/TB-beta-CyD/HP-beta-CyD system was slowed down by the addition of small amounts of HP-beta-CyD, whereas the rate became faster as the molar ratio of HP-beta-CyD further increased (>.25 molar ratio). Both water penetration studies and microscopic observation suggested that the retarding effect is attributable to a gel formation of HP-beta-CyD in the TB-beta-CyD hydrophobic matrix. It was difficult to prolong plasma levels of captopril by administering orally either the binary HP-beta-CyD or TB-beta-CyD system in dogs. On the other hand, the ternary captopril/TB-beta-CyD/HP-beta-CyD system (molar ratio of 1:0.5:0.5) gave a plasma profile comparable to that of a commercially available sustained release preparation (Captopril R). Therefore, a combination of HP-beta-CyD and TB-beta-CyD is useful for the controlled release of water-soluble drugs such as captopril.

Ionita G., Meltzer V., Pincu E. and Chechik V. (2007) Inclusion complexes of cyclodextrins with biradicals linked by a polyether chain--an EPR study. *Org. Biomol. Chem* **5**, 1910-1914.

Abstract: Complexation of beta-cyclodextrin with flexible nitroxide biradicals linked by a polyethylene glycol chain was monitored by EPR spectroscopy. The EPR spectra of the uncomplexed biradicals show an

exchange interaction due to the flexibility of the polyethylene glycol chain. Complexation with cyclodextrin leads to the disappearance of the exchange interaction in the EPR spectra. The complexation can be reversed by the addition of competing guests (e.g., adamantane derivatives). At high concentration, the inclusion complexes precipitate, and differential scanning calorimetry (DSC) of the precipitates proved the formation of complexes. Elemental analysis data revealed that the complexes contain several cyclodextrin units per biradical but that the composition was not stoichiometric.

Jain A. C. and Adeyeye M. C. (2001) Hygroscopicity, phase solubility and dissolution of various substituted sulfobutylether beta-cyclodextrins (SBE) and danazol-SBE inclusion complexes. *Int J Pharm* **212**, 177-186.

Abstract: The aim of the present work was to characterize hygroscopicity, phase solubility and dissolution properties for various substituted sulfobutylether beta-cyclodextrins (SBEs) and danazol-SBE inclusion complexes. Moisture sorption was measured using a symmetric gravimetric analyzer. The complexes were characterized by powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Moisture sorption isotherms for the SBEs and the complexes showed low moisture sorption at RH <60%. The moisture absorption-desorption isotherms for the various SBEs showed very little hysteresis, indicating almost complete desorption. Moisture adsorbed by the various SBE was in the order SBE 7>SBE 4>SBE 5 at 95% RH. Powder XRD data for complexes showed the disappearance of characteristic crystalline peaks for danazol or the formation of amorphous entities and DSC showed the disappearance of the peak of fusion of danazol indicating complex formation. Phase solubility of danazol with various substituted SBEs indicated 1:1 stoichiometry of complexes. The apparent stability constant, as determined by the method of Higuchi and Connors, increased as the degree of substitution of SBEs increased and decreased as the temperature increased. The dissolution of the complexes was significantly greater than that of the corresponding physical mixtures indicating that the formation of amorphous complex increased the solubility of poorly soluble danazol. More than 85% of danazol was released in <10 min, compared to 15% danazol release from the physical mixtures.

Jambhekar S., Casella R., and Maher T. (2004) The physicochemical characteristics and bioavailability of indomethacin from beta-cyclodextrin, hydroxyethyl-beta-cyclodextrin, and hydroxypropyl-beta-cyclodextrin complexes. *Int J Pharm* **270**, 149-166.

Abstract: In an effort to improve the bioavailability of the insoluble drug indomethacin, three complexes were prepared with indomethacin and the soluble complexing agents beta-, hydroxyethyl-beta-, and hydroxypropyl-beta-cyclodextrin. The indomethacin content was similar among the complexes ($P \leq 0.05$). To confirm complex formation, each complex was characterized by ultraviolet, infrared, nuclear-magnetic resonance, powder X-ray diffraction, and differential-scanning calorimetry techniques. Powder diffraction studies show the beta-cyclodextrin complex was polycrystalline, and the hydroxyethyl- and hydroxypropyl-beta-cyclodextrin complexes were amorphous. Phase-solubility analysis confirmed the formation of complexes and suggested the three complexes were bound similarly. Solubility studies show complexation increased indomethacin solubility, and the hydroxyethyl- and hydroxypropyl-beta-cyclodextrin complexes were more soluble than the beta-cyclodextrin complex in 0.1 N hydrochloric acid and distilled water. Dosage forms were prepared by encapsulating the complexes without the addition of excipients. Dissolution studies show the encapsulated beta- and hydroxyethyl-beta-cyclodextrin complexes had superior dissolution when compared to the hydroxypropyl-beta-cyclodextrin and Indocin (50 mg) capsules. Bioavailability studies were performed by administering the indomethacin complex or Indocin capsules to male-albino, New Zealand rabbits. Indomethacin plasma-time concentration data fit best to a compartment-independent model for all capsule formulations. Bioavailability comparisons by ANOVA show no significant difference ($P \leq 0.10$) in the peak-plasma time and peak concentration among the capsule formulations. The area-under-the-curve for the beta-cyclodextrin complex capsules was found to be significantly higher ($P \leq 0.10$) than all other capsule formulations. In conclusion, the bioavailability of indomethacin was improved by complexation with only beta-cyclodextrin. No correlations were found among the bioavailability, solubility, and dissolution results.

Jianbin C., Liang C., Hao X., and Dongpin M. (2002) Preparation and study on the solid inclusion complex of ciprofloxacin with beta-cyclodextrin. *Spectrochim Acta A Mol Biomol Spectrosc* **58**, 2809-2815.

Abstract: The interaction of ciprofloxacin with beta-cyclodextrin (betaCD) has been studied by several analytical techniques, including ¹H-NMR (nuclear magnetic resonance), ¹³C-NMR, fluorescence

spectroscopy, infrared (IR) spectroscopy, thermal analysis, and scanning electron microscope. In this paper, solid inclusion complex of ciprofloxacin with beta-CD was synthesized by the coprecipitation method. In addition, the characterization of the inclusion complex has been proved by fluorimetry, IR, differential scanning calorimetry and 1D, 2D NMR. The experimental results confirmed the existence of 1:1 inclusion complex of ciprofloxacin with beta-CD. The formation constant of complex was determined by fluorescence method and ¹H-NMR. Spatial configuration of complex has been proposed on two dimensional NMR technique.

Johnson J. L., He Y., Jain A., and Yalkowsky S. H. (2006) Improving cyclodextrin complexation of a new antihepatitis drug with glacial acetic acid. *AAPS PharmSciTech* **7**, E18.

Abstract: The purpose of this study was to develop and evaluate a solid nonaqueous oral dosage form for a new hepatitis C drug, PG301029, which is insoluble and unstable in water. Hydroxypropyl-beta-cyclodextrin (HPbetaCD) and PG301029 were dissolved in glacial acetic acid. The acetic acid was removed by rotoevaporation such that the drug exists primarily in the complexed form. The stability of formulated PG301029 was determined upon dry storage and after reconstitution in simulated intestinal fluid (SIF), simulated gastric fluid (SGF), and water. Formulated PG301029 was found to be stable upon storage and can be reconstituted with water to a concentration 200 times that of the intrinsic solubility. Once reconstituted, the powder dissolves rapidly and PG301029 remains stable for 21 hours in SGF, SIF, and water. The unique use of acetic acid and HPbetaCD results in a solid dosage form of PG301029 that is both soluble and stable in water.

Kale R., Tayade P., Saraf M. and Juvekar A. (2008) Molecular encapsulation of thalidomide with sulfobutyl ether-7 beta-cyclodextrin for immediate release property: enhanced in vivo antitumor and antiangiogenesis efficacy in mice. *Drug Dev. Ind. Pharm.* **34**, 149-156.

Abstract: Thalidomide's reported ability to inhibit tumor angiogenesis has led to clinical trials determining its effectiveness in combating various types of cancer. Since thalidomide exhibits low oral bioavailability due to limitations in solubility, inclusion complexation using sulfobutyl ether-7 beta-cyclodextrin was used to improve the delivery of thalidomide. Our main goals were to increase the solubility, bioavailability as well as chemical stability of thalidomide through complexation with anionic beta-cyclodextrin, to characterize the complex in solid state using differential scanning calorimetry, X-ray powder diffractometry, and to explore thalidomide's antitumorigenic and antiangiogenesis potential when administered orally as free and in combination with cyclodextrin to experimental animals. The aqueous solubility and aqueous alkaline stability of thalidomide was markedly increased by the SBE7betaCD complexation. Thalidomide administered orally in combination with SBE7betaCD, led to a significant delay in tumor formation as a result of improved cellular drug absorption, distribution through solubilization in experimental animals. The improved pharmacological efficacy of the thalidomide-cyclodextrin complex compared to free thalidomide in mouse melanoma model suggest that such a delivery system may be useful for the improved therapeutics of thalidomide, in vivo

Kataoka T., Kidowaki M., Zhao C., Araki J., Ikehara T. and Ito K. (2007) Thermal properties and microstructures of methylated polyrotaxane solutions. *Curr. Drug Discov. Technol.* **4**, 275-281.

Abstract: Aqueous solutions of polyrotaxanes consisting of poly(ethylene glycol) and methylated alpha-cyclodextrins (alpha-CD) were studied by means of differential scanning calorimetry (DSC), dynamic light scattering, and X-ray diffraction in order to investigate the effect of the degree of methylation on thermoresponsive behavior. Polyrotaxanes with a degree of methylation higher than 50% had a lower critical solution temperature (LCST) and showed reversible associations and dissociations in water. In the transmittance measurements, the cloud point of methylated polyrotaxanes (MePR) shifted to a lower temperature with an increase in the degree of methylation. The heating curve obtained by DSC for the nearly permethylated polyrotaxane showed one broad endothermic peak that was associated with the microcrystallization of methylated CDs by hydrophobic interactions. On the other hand, the DSC profiles for partially methylated polyrotaxanes had several endothermic peaks, indicating multiple phase transitions of the MePR solutions. The results imply that the thermal properties of the MePR-water system are significantly affected by not only the methyl groups on alpha-CDs but also by the remaining hydroxyl groups.

Koester L. S., Guterres S. S., Le Roch M., Eifler-Lima V. L., Zuanazzi J. A., and Bassani V. L. (2001) Ofloxacin/beta-cyclodextrin complexation. *Drug Dev Ind Pharm* **27**, 533-540.

Abstract: Ofloxacin (OFX) is a fluorquinolone characterized by photochemical instability. With the goal to improve its photostability in aqueous solutions, the complexation of ofloxacin with beta-cyclodextrin was investigated. The complexes showed a water solubility enhancement of approximately 2.6 times; nevertheless, the photodegradation of ofloxacin was not reduced. The complexes obtained were characterized by thermal and ¹H nuclear magnetic resonance (NMR) analysis, which revealed an interaction between ofloxacin and beta-cyclodextrin. The last analysis indicated that only partial inclusion of the N-methylpiperazinyl moiety occurred, which can explain the fact that photostabilization was not improved. This partial inclusion phenomenon could be explained also by computer-aided molecular modeling.

Koester L. S., Mayorga P., Pereira V. P., Petzhold C. L., and Bassani V. L. (2003) Carbamazepine/betaCD/HPMC solid dispersions. II. Physical characterization. *Drug Dev Ind Pharm* **29**, 145-154.

Abstract: Solid dispersions containing carbamazepine (CBZ) associated with beta-cyclodextrin (betaCD) and/or hydroxypropyl methylcellulose were prepared by two different methods, spray-drying or physical mixture, and characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and x-ray powder diffraction analysis (XRPD) studies. Scanning electron microscopy pictures showed that spray-drying produced a mixture of hollow, spherical, and partially shrunken microparticles of homogeneous materials, whereas the physical mixtures yielded heterogeneous systems in which all individual components could be identified. Thermal and IR analyses suggest the existence of a strong interaction between CBZ and excipients in spray-dried solid dispersions, but no CBZ polymorphic transition was detected by either IR spectroscopy or XRPD analysis after the spray-drying process.

Koester L. S., Xavier C. R., Mayorga P., and Bassani V. L. (2003) Influence of beta-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. *Eur J Pharm Biopharm* **55**, 85-91.

Abstract: The in vitro release profiles of carbamazepine and beta-cyclodextrin either complexed or simply mixed and subsequently incorporated in hydrophilic matrix tablets containing 15 or 30% hydroxypropyl methylcellulose were evaluated. Solubility studies revealed a linear relationship between the increase in carbamazepine solubility and the increase in beta-cyclodextrin concentration. Drying methods (spray-drying and freeze-drying) were used to obtain carbamazepine/beta-cyclodextrin solid complexes in order to prepare tablets. The results demonstrated that matrix tablets containing carbamazepine/beta-cyclodextrin solid complexes displayed faster carbamazepine and beta-cyclodextrin release compared to that containing simple physical mixture. Gelling and matrix formation was impaired in formulation containing 15% hydroxypropyl methylcellulose and spray-dried complex. The comparison of spray-drying and freeze-drying revealed no significant influence of both drying methods on carbamazepine and beta-cyclodextrin dissolution rate when carbamazepine/beta-cyclodextrin complexes were incorporated in 30% hydroxypropyl methylcellulose matrix tablets. The results point to the possibility of modulating carbamazepine release using a hydroxypropyl methylcellulose matrix associated to the drug complexed with beta-cyclodextrin.

Kumar A., Agarwal S. P., and Khanna R. (2003) Modified release bi-layered tablet of melatonin using beta-cyclodextrin. *Pharmazie* **58**, 642-644.

Abstract: A modified release bi-layered tablet of melatonin incorporating a fast release fraction consisting of melatonin-beta-cyclodextrin inclusion complex and a slow release fraction containing melatonin in HPMC K15M and Carbopol 971 P matrices was prepared. The formulation developed showed an initial burst followed by a near zero order release pattern for a period of 8 h. The drug content, physical characteristics and the release profile were unaffected after 3 months of an accelerated stability study at 40 degrees C and 75% relative humidity.

Lahiani-Skiba M., Barbot C., Bounoure F., Joudieh S., and Skiba M. (2006) Solubility and dissolution rate of progesterone-cyclodextrin-polymer systems. *Drug Dev Ind Pharm* **32**, 1043-1058.

Abstract: This contribution focused on the solubility improvement of the poorly water-soluble steroid

hormone progesterone which, in its natural state, presents a reduced oral bioavailability. In the first part of this study, two simple, reproducible methods that were candidates for use in the preparation of inclusion complexes with cyclodextrins were investigated. Solubility capacities of the progesterone complex with hydroxypropyl-beta-CD (HPbeta-CD), hydroxypropyl-gamma-CD (HPgamma-CD), permethyl-beta-CD (PMbeta-CD), and sulfobutylether-beta-CD (SBEbeta-CD), prepared by the freeze-drying and precipitation methods, were evaluated by Higuchi phase solubility studies. The results showed that HPbeta-CD and PMbeta-CD were the most efficient among the four cyclodextrins for the solubilization of progesterone, with the highest apparent stability constants. Therefore, dissolution studies were conducted on these latest progesterone/cyclodextrin complexes and physical mixtures. Two additional natural cyclodextrins, beta-CD and gamma-CD, were taken as references. Hence, the influence of more highly soluble derivatives of beta-CD (HPbeta-CD, PMbeta-CD) on the progesterone dissolution rate, in comparison to pristine beta-CD, alongside an increase in the cavity width for gamma-CD versus beta-CD, were investigated. The dissolution kinetics of progesterone dissolved from HPbeta-CD, PMbeta-CD, and gamma-CD revealed higher constant rates in comparison to beta-CD. Therefore, the aim of the second part of this study was to investigate the possibility of improving the dissolution rate of progesterone/beta-CD binary systems upon formation of ternary complexes with the hydrophilic polymer, PEG 6000, as beta-CD had the smallest progesterone solubility and dissolution capacity among the four cyclodextrins studied (beta-CD, HPbeta-CD, HPgamma-CD and PMbeta-CD). The results indicated that dissolution constant rates were considerably enhanced for the 5% and 10% progesterone/beta-CD complexes in PEG 6000. The interaction of progesterone with the cyclodextrins of interest on the form of the binary physical mixtures, complexes, or ternary complexes were investigated by differential scanning calorimetry (DSC) and Fourier transformed-infrared spectroscopy (FT-IR). The results proved that progesterone was diffused into the cyclodextrin cavity, replacing the water molecules and, in case of ternary systems, that the progesterone beta-cyclodextrin was well dispersed into PEG, thus improving progesterone bioavailability for subsequent oral delivery in the same way as derivatized cyclodextrins. The present work proves that ternary complexes are promising systems for drug encapsulation.

Larrucea E., Arellano A., Santoyo S., and Ygartua P. (2001) Interaction of tenoxicam with cyclodextrins and its influence on the in vitro percutaneous penetration of the drug. *Drug Dev Ind Pharm* **27**, 251-260. **Abstract:** Solid complexes of tenoxicam (TEN) with cyclodextrins (CDs), in a 1:1 molar ratio, were obtained by the coprecipitation method and characterized by x-ray diffractometry, infrared spectroscopy, and differential scanning calorimetry. The binding capacity of the CDs with TEN was also demonstrated in aqueous solution and in water-propylene glycol mixtures. The purpose of this study was to determine the effect of CDs on the in vitro percutaneous penetration of TEN from carbopol gels, taking into account the role of the CD cavity size and the nature of the substituents. The effect of pretreatment was studied too. In vitro permeation experiments were carried out on Franz diffusion cells using cellulose nitrate membranes and abdominal rat skin. In these results, the release rates of the drug scarcely decreased when the CDs were added, probably because of a lower concentration of the free drug and an increased gel viscosity. However, it was also found that CDs, particularly gamma-CD and M-beta-CD, can improve slightly TEN absorption through the skin. Pretreatment studies with CDs, however, provided no effects on TEN permeation, but lag time was markedly reduced, suggesting a faster partitioning of TEN into the skin. Therefore, the use of pretreatment with CDs would be interesting when a quick action of the drug is desired.

Latrofa A., Trapani G., Franco M., Serra M., Muggironi M., Fanizzi F. P., Cutrignelli A., and Liso G. (2001) Complexation of phenytoin with some hydrophilic cyclodextrins: effect on aqueous solubility, dissolution rate, and anticonvulsant activity in mice. *Eur J Pharm Biopharm* **52**, 65-73. **Abstract:** The main objective of this study was to evaluate the influence of hydroxypropylated beta- and gamma-cyclodextrins and Me-beta-cyclodextrin (HP-beta-CD, HP-gamma-CD, and Me-beta-CD, respectively) on the dissolution rate and bioavailability of the antiepileptic agent, phenytoin (DPH). The corresponding solid complexes were prepared by a freeze-drying method and characterized by infrared spectroscopy, X-ray powder diffraction, and differential scanning calorimetry studies. Evidence of inclusion complex formation in the case of HP-beta-CD was obtained by (1)H- and (13)C-nuclear magnetic resonance spectroscopy. Drug solubility and dissolution rate in 0.05 M potassium phosphate buffer (pH 6) were notably improved by employing the beta-CDs. Thus a 45% w/v HP-beta-CD or Me-beta-CD solution gave rise to an increase of dissolved drug of 420- and 578-fold, respectively. The Q(10) (i.e. percentage of dissolved DPH at 10 min) was 5.2% for the pure drug and 93, 98, and 96% for DPH/HP-beta-CD,

DPH/HP-gamma-CD, and DPH/Me-beta-CD complexes, respectively. Moreover, it was found that in the maximal electroshock seizure test in mice the DPH/Me-beta-CD complex exhibited anticonvulsant activity similar to DPH sodium salt (NaDPH).

Lee K. P., Choi S. H., Ryu E. N., Ryoo J. J., Park J. H., Kim Y., and Hyun M. H. (2002) Preparation and characterization of cyclodextrin polymer and its high-performance liquid-chromatography stationary phase. *Anal Sci* **18**, 31-34.

Abstract: Cyclodextrin (CD) polymers were synthesized from the reaction of native CDs with a hexamethylene diisocyanate (HDI) compound in a dried DMF solution. The obtained CD polymer contained a range of 8-14% N due to HDI by elemental analysis. The physical and chemical properties of the CD polymers were characterized by IR, solid state ¹³C NMR, TGA, and DSC, respectively. An HPLC column was prepared using the CD polymer with a carbamate linker by a slurry method. Separation of the phenol isomers was conducted using the CD polymer stationary phase and CD by HPLC. Furthermore, an inclusion complex of the phenol isomer was studied by FT-Raman spectroscopy. From the HPLC and FT-Raman results, inclusion phenomena of o-, m-, and p-nitrophenol onto CD and CD polymers were analyzed.

Li J., Guo Y., and Zografi G. (2002) The solid-state stability of amorphous quinapril in the presence of beta-cyclodextrins. *J Pharm Sci* **91**, 229-243.

Abstract: The major objective of this study was to investigate the effects of beta-cyclodextrin (beta-CD) and hydroxypropyl-beta-cyclodextrin (HP-beta-CD) on the solid-state chemical reactivity of the drug, quinapril, when amorphous samples are prepared by colyophilization of quinapril and each of these beta-CDs. For comparison, a physical mixture with beta-CD and colyophilized mixtures with trehalose and dextran were also prepared and subjected to a similar chemical stability test at 80 degrees C followed by HPLC analysis. Significant inhibition of degradation was observed only for colyophilized miscible mixtures with beta-CD and HP-beta-CD at molar ratios in excess of 1:1. Colyophilized mixtures with trehalose and dextran, shown to have phase separated, and the physical mixture with beta-CD exhibited no inhibiting effects. This suggests that specific molecular complexation is responsible for the significant inhibition by the beta-CDs. The tendency of quinapril to form molecular complexes in solution with the beta-CDs was measured by (1)H solution NMR, by estimating complexation constants from the chemical shift of specific groups on quinapril. Supporting evidence for solid-state complexation was provided by FTIR analysis. DSC and TSC measurements indicated that the beta-CDs do not have high enough glass transition temperatures to reduce reactivity by reducing molecular mobility.

Li J., Ni X., Zhou Z., and Leong K. W. (2003) Preparation and characterization of polypseudorotaxanes based on block-selected inclusion complexation between poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) triblock copolymers and alpha-cyclodextrin. *J Am Chem Soc* **125**, 1788-1795.

Abstract: A series of new polypseudorotaxanes were synthesized in high yields when the middle poly(ethylene oxide) (PEO) block of poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide) (PPO-PEO-PPO) triblock copolymers was selectively recognized and included by alpha-cyclodextrin (alpha-CD) to form crystalline inclusion complexes (ICs), although the middle PEO block was flanked by two thicker PPO blocks, and a PPO chain had been previously thought to be impenetrable to alpha-CD. X-ray diffraction studies demonstrated that the IC domains of the polypseudorotaxanes assumed a channel-type structure similar to the necklace-like ICs formed by alpha-CD and PEO homopolymers. Solid-state CP/MAS (¹³C NMR) studies showed that the alpha-CD molecules in the polypseudorotaxanes adopted a symmetrical conformation due to the formation of ICs. The compositions and stoichiometry of the polypseudorotaxanes were studied using (1)H NMR, and a 2:1 (ethylene oxide unit to alpha-CD) stoichiometry was found for all polypseudorotaxanes although the PPO-PEO-PPO triblock copolymers had different compositions and block lengths, suggesting that only the PEO block was closely included by alpha-CD molecules, whereas the PPO blocks were uncovered. The hypothesis was further supported by the differential scanning calorimetry (DSC) studies of the polypseudorotaxanes. The glass transitions of the PPO blocks in the polypseudorotaxanes were clearly observed because they were uncovered by alpha-CD and remained amorphous, whereas the glass-transition temperatures increased, because the molecular motion of the PPO blocks was restricted by the hard crystalline phases of the IC domains formed by alpha-CD and the PEO blocks. The thermogravimetric analysis (TGA) revealed that the polypseudorotaxanes had better thermal stability than their free components due to the inclusion complexation. Finally, the kinetics

of the threading process of alpha-CD onto the copolymers was also studied. The findings reported in this article suggested interesting possibilities in designing other cyclodextrin ICs and polypseudorotaxanes with block structures.

Li N., Zhang Y. H., Wu Y. N., Xiong X. L., and Zhang Y. H. (2005) Inclusion complex of trimethoprim with beta-cyclodextrin. *J Pharm Biomed Anal* **39**, 824-829.

Abstract: The complexation of trimethoprim (TMP) with beta-cyclodextrin (beta-CD) was studied. UV-spectrophotometry and phase-solubility techniques were employed to investigate the complexation behaviour in liquid medium, and to demonstrate that the aqueous solubility of TMP increased 2.2-fold due to complexation with beta-CD. Solid samples prepared by co-evaporation (in 2 wt% acetic acid solution) have also been studied, using differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD), to assess the formation of the inclusion complex. The water content of the complex and beta-CD was determined using thermo gravimetric analysis (TGA). In vitro dissolution analysis indicated that dissolution properties of TMP/beta-CD complex were superior compared to both pure TMP and the corresponding physical mixture of TMP and beta-CD.

Li N., Zhang Y. H., Xiong X. L., Li Z. G., Jin X. H., and Wu Y. N. (2005) Study of the physicochemical properties of trimethoprim with beta-cyclodextrin in solution. *J Pharm Biomed Anal* **38**, 370-374.

Abstract: The behavior of trimethoprim (TMP) in aqueous solutions containing different concentration of beta-cyclodextrin (beta-CD) was characterized by the solubility method, UV spectrophotometry and differential scanning calorimetry (DSC). The UV spectra enhancement of TMP as result of complex with beta-CD was investigated. Complexation with beta-CD increase the TMP aqueous solubility and the phase solubility diagram was A(L) type. Thermodynamic parameters of the complex process, K , ΔG , ΔH and ΔS , were determined from the phase solubility diagram at 298 and 318K, respectively. The experimental results indicated that the complex process was an enthalpy-driven process. Mechanism of the complex of beta-CD with TMP was further discussed using the molecular model program. Results showed that the 3,4,5-trimethoxybenzyl group of the TMP was partly embedded in the cavity of beta-CD.

Lim H. J., Cho E. C., Shim J., Kim D. H., An E. J. and Kim J. (2008) Polymer-associated liposomes as a novel delivery system for cyclodextrin-bound drugs. *J Colloid Interface Sci* **320**, 460-468.

Abstract: It is known that cyclodextrins (CDs) extract lipid components from bilayer of liposomes. This could undermine the potential benefits of liposomes as drug carriers. In this study, we demonstrated that PC-Chol liposomes with various CDs or rhapontin (Rh)-hydroxypropyl betaCD (HPbetaCD) complexes could be stabilized by association with the amphiphilic polyelectrolyte, poly(methacrylic acid-co-stearyl methacrylate). Based on the results of differential scanning calorimetry, photocalorimetry and transmission electron microscopy, the polymer-associated liposomes had the same vesicular form as liposome with clear boundaries and retained structural integrity for at least 1 month. In addition, the polymer-associated structure was unaffected by the type of CD, the composition and concentration of lipid components, and the concentration of the Rh-HPbetaCD complex. This contrasted with PC-Chol liposomes, whose structure was dependent on these factors. Using structurally different polymer-associated liposomes and PC-Chol liposomes containing the Rh-HPbetaCD complex, we also showed that the stability of vesicles could influence the skin permeability of CD-drug complexes

Liu J., Qiu L., Gao J., and Jin Y. (2006) Preparation, characterization and in vivo evaluation of formulation of baicalein with hydroxypropyl-beta-cyclodextrin. *Int J Pharm* **312**, 137-143.

Abstract: The interaction of 2-hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and a poorly water-soluble flavonoid, baicalein (Ba), chemically 5,6,7-trihydroxy flavone in solution and solid-state was studied. Ba/HP-beta-CD solid systems were prepared by freeze-drying method. The formation of Ba/HP-beta-CD complex in aqueous solution was demonstrated by UV spectroscopy, while Ba/HP-beta-CD co-lyophilized product was characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). Through complexation with HP-beta-CD, the solubility of Ba in neutral aqueous solution was improved significantly. The phase-solubility profile was AP-type, indicating the formation of higher-order complexes or complex aggregates. Ba/HP-beta-CD solid powders were amorphous and show a significantly improved dissolution rate in comparison with free Ba. Comparison of the pharmacokinetics between Ba/HP-beta-CD co-lyophilized product and free Ba was also performed in rats. The concentration of Ba and its mainly conjugated metabolite, 7-O-glucuronide of baicalein (BG) in rat plasma was determined by HPLC method.

The in vivo results show that Ba/HP-beta-CD co-lyophilized product exhibits the similar pharmacokinetics as that of free Ba after intravenous administration. Ba/HP-beta-CD co-lyophilized product displays earlier t_{max} and higher C_{max} of BG than free Ba after oral dosing. By comparing the AUC_{0-infinity} of BG between oral dosing, the relative bioavailability of Ba/HP-beta-CD co-lyophilized product to free Ba was 165.0%, which highlighted the evidence of significantly improved bioavailability of formulation of Ba with HP-beta-CD.

Liu L. and Zhu S. (2006) Preparation and characterization of inclusion complexes of prazosin hydrochloride with beta-cyclodextrin and hydroxypropyl-beta-cyclodextrin. *J Pharm Biomed Anal* **40**, 122-127.

Abstract: The slightly water-soluble drug prazosin hydrochloride (PRH) and its inclusion with either beta-cyclodextrin (betaCD) or hydroxypropyl-beta-cyclodextrin (HPbetaCD) were investigated. The phase solubility profiles of PRH with betaCD and HPbetaCD were classified as B(s)- and A(L)-types, respectively. Stability constants with 1:1 molar ratio were calculated from the phase solubility diagrams and the solubility of PRH could be enhanced by 27.6% for betaCD and 226.4% for HPbetaCD, respectively. Binary systems of PRH with betaCD or HPbetaCD prepared by various methods were characterized by differential scanning calorimetry and Fourier transformation-infrared spectroscopy. It could be concluded that PRH could form inclusion complex with either betaCD or HPbetaCD. The dissolution profiles of inclusion complexes were determined and compared with those of PRH alone and their physical mixtures. The dissolution rate of PRH was increased by betaCD and HPbetaCD inclusion complexation remarkably. Both the preparation technique and nature of the carriers played important roles in the dissolution performance of the systems. All the systems with HPbetaCD showed better performance than the corresponding ones with betaCD.

Liu X., Lin H. S., Thenmozhiyal J. C., Chan S. Y., and Ho P. C. (2003) Inclusion of acitretin into cyclodextrins: phase solubility, photostability, and physicochemical characterization. *J Pharm Sci* **92**, 2449-2457.

Abstract: Acitretin, a retinoid for the treatment of severe psoriasis, exhibits extremely low aqueous solubility and high photosensitivity. This study investigated the effects of the complexation of acitretin with the respective hydroxypropyl-beta-cyclodextrin (HPBCD) and randomly substituted methyl-beta-cyclodextrin (RMBCD) on the aqueous solubility and photostability of the drug. Phase-Solubility studies indicated that the solubility of acitretin was dramatically improved by formation of complexes and further increased by pH adjustment. Stability constants were much higher for acitretin complexed with RMBCD than with HPBCD. Both cyclodextrins acted to decrease degradation of acitretin in solution. The physicochemical properties of solid inclusion complexes were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffractometry. Molecular modeling with MMFF94s force field (SYBYL V6.6) was utilized to predict the preferred orientation of acitretin in the cyclodextrin cavity and the main structural features responsible for the enhancement of its solubility and photostability.

Liu Y., Chen G. S., Li L., Zhang H. Y., Cao D. X., and Yuan Y. J. (2003) Inclusion complexation and solubilization of paclitaxel by bridged bis(beta-cyclodextrin)s containing a tetraethylenepentaamino spacer. *J Med Chem* **46**, 4634-4637.

Abstract: A novel water-soluble paclitaxel complex has been prepared by inclusion complexation with bridged bis(beta-cyclodextrin)s and characterized by means of (1)H NMR, SEM, powder X-ray diffraction patterns, TG-DTA, DSC, FT-IR, and 2D NOESY. The cyclodextrins were able to solubilize paclitaxel to levels as high as 2 mg/mL. Furthermore, the cytotoxicity of the novel complexes was assessed using a K562 leukemia cell line which indicated that drug concentrations of 10 pg/mL elicited an inhibitory effect.

Liu Y., Chen G. S., Chen Y., and Lin J. (2005) Inclusion complexes of azadirachtin with native and methylated cyclodextrins: solubilization and binding ability. *Bioorg Med Chem* **13**, 4037-4042.

Abstract: The inclusion complexation behavior of azadirachtin with several cyclodextrins and their methylated derivatives has been investigated in both solution and the solid state by means of XRD, TG-DTA, DSC, NMR, and UV-vis spectroscopy. The results show that the water solubility of azadirachtin was obviously increased after resulting inclusion complex with cyclodextrins. Typically, beta-cyclodextrin (beta-CD), dimethyl-beta-cyclodextrin (DMbetaCD), permethyl-beta-cyclodextrin (TMbetaCD), and

hydroxypropyl-beta-cyclodextrin (HPbetaCD) are found to be able to solubilize azadirachtin to high levels up to 2.7, 1.3, 3.5, and 1.6 mg/mL (calculated as azadirachtin), respectively. This satisfactory water solubility and high thermal stability of the cyclodextrin-azadirachtin complexes, will be potentially useful for their application as herbal medicine or healthcare products.

Liu Y. Y. and Fan X. D. (2005) Synthesis, properties and controlled release behaviors of hydrogel networks using cyclodextrin as pendant groups. *Biomaterials* **26**, 6367-6374.

Abstract: Based on inclusion character of beta-cyclodextrin (beta-CD) with drug molecule and low glass transition temperature of poly(2-hydroxyethyl acrylate) (PHEA), a series of hydrogels with different compositions were synthesized by the copolymerization of a monovinyl cyclodextrin monomer with 2-hydroxyethyl acrylate (HEA). The structure and properties of the hydrogels were characterized by FTIR, DSC, TGA and swelling measurements. It is found that swelling ratios of these beta-CD hydrogels can keep a relative stability in the range of pH from 1.4 to 7.4, and are not sensitive to change in NaCl concentration. Using drug N-acety-5-methoxytryptamine (melatonin, MEL) as a model molecule, the controlled drug release behaviors of these hydrogels were investigated. The results indicate that the diffusion and permeation of MEL from the hydrogels may be a dominant factor for its release. Owing to the formation of MEL/beta-CD retarding diffusion rate of MEL, a sustained release of MEL from hydrogel with high content of beta-CD can be obtained compared with hydrogel PHEA without beta-CD.

Liu Y. Y., Yu Y., Zhang G. B. and Tang M. F. (2007) Preparation, Characterization, and Controlled Release of Novel Nanoparticles Based on MMA/beta-CD Copolymers. *Macromol. Biosci.* **7**, 1250-1257.

Abstract: A series of random copolymers with different beta-cyclodextrin contents were synthesized by radical copolymerization of MMA with a monovinyl beta-CD monomer. The copolymers were characterized with IR spectroscopy, elemental analysis, DSC, and TGA. Based on these copolymers, their nanoparticles were prepared by using DMF, water, and acetone as solvents. Aqueous dispersions of the nanoparticles were further obtained by dialysis against water. Zetasizer Nano-ZS dynamic light scattering and transmission electron microscopy were employed to characterize the nanoparticles. Using camptothecin as a model drug molecule, the encapsulation efficiency and release behavior of the nanoparticles were investigated.

Lutka A. (2002) Investigation of interaction of promethazine with cyclodextrins. *Acta Pol Pharm* **59**, 45-51.

Abstract: The effect of beta-CD and its substituted derivatives (DM-beta-CD and HP-beta-CD) on the solubility and photostability of promethazine was investigated in solution and in the solid state. The soluble complexes of protonated (pH = 6.8) and basic (pH = 10.8) forms of promethazine with CDs were studied using the spectral method. The influence of pH and CD complexation on photostability of PM in solution was followed. It was found that the photochemical decomposition of promethazine (PM) alone and in the presence of CD proceeds according to the first order reaction. It was also established that as well the presence of CD as the acidic medium of reaction increased the photostability of PM in solution. Formation of solid inclusion complexes of PM with CDs was evaluated using FT IR, ¹³C NMR and DSC methods. The results obtained indicate that independently of the complexation method in the solid state (kneading or heating), the presence of CD decreases the solubility of PM; the reason may be that the phenothiazine ring of PM did not enter into the cavity of beta-CD and its derivatives.

Manca M. L., Zaru M., Ennas G., Valenti D., Sinico C., Loy G., and Fadda A. M. (2005) Diclofenac-beta-Cyclodextrin Binary Systems: Physicochemical Characterization and In Vitro Dissolution and Diffusion Studies. *AAPS PharmSciTech* **6**, E464-E472.

Abstract: The aim of this work was to study the influence of beta-cyclodextrin (beta-CD) on the biopharmaceutic properties of diclofenac (DCF). To this purpose the physicochemical characterization of diclofenac-beta-cyclodextrin binary systems was performed both in solution and solid state. Solid phase characterization was performed using differential scanning calorimetry (DSC), powder x-ray diffractometry (XRD), and Fourier transform infrared spectroscopy (FTIR). Phase solubility analyses, and in vitro permeation experiments through a synthetic membrane were performed in solution. Moreover, DCF/beta-CD interactions were studied in DMSO by ¹H nuclear magnetic resonance (NMR) spectroscopy. The effects of different preparation methods and drug-to-beta-CD molar ratios were also evaluated. Phase solubility studies revealed 1:1 M complexation of DCF when the freeze-drying method was used for the

preparation of the binary system. The true inclusion for the freeze-dried binary system was confirmed by (1)H NMR spectroscopy, DSC, powder XRD, and IR studies. The dissolution study revealed that the drug dissolution rate was improved by the presence of CDs and the highest and promptest release was obtained with the freeze-dried binary system. Diffusion experiments through a silicone membrane showed that DCF diffusion was higher from the saturated drug solution (control) than the freeze-dried inclusion complexes, prepared using different DCF-beta-CD molar ratios. However, the presence of the inclusion complex was able to stabilize the system giving rise to a more regular diffusion profile.

Masserini M., Pitto M., Raimondo F., Cazzaniga E., Sesana S., and Bellini T. (2005) Methyl-beta-cyclodextrin treatment affects the thermotropic behaviour of membranes and detergent-resistant membrane fractions of cultured A431 cells. *Biol Pharm Bull* **28**, 2185-2188.

Abstract: Membranes and detergent-resistant membrane fractions isolated from human epidermoid carcinoma A431 cells after treatment with methyl-beta-cyclodextrin, a compound commonly used in pharmaceutical applications and in manipulation of membrane cholesterol content, display thermotropic transitions at about 15 degrees C and above 37 degrees C, respectively, when analyzed by differential scanning calorimetry. The transitions, absent in untreated cells, were reversible upon cycling through heating and cooling scans, and attributable to lipid components of the membranes, possibly sphingolipids. These results suggest that, after treatment with methyl-beta-cyclodextrin, membranes may show thermotropic transitions, an unusual feature for cellular bilayers, which is likely to influence biological functions.

Memisoglu E., Bochot A., Sen M., Charon D., Duchene D., and Hincal A. A. (2002) Amphiphilic beta-cyclodextrins modified on the primary face: synthesis, characterization, and evaluation of their potential as novel excipients in the preparation of nanocapsules. *J Pharm Sci* **91**, 1214-1224.

Abstract: The purpose of this study was to synthesize and characterize amphiphilic beta-cyclodextrins modified on the primary face with substituents of varying chain lengths (C6 and C14) and bond types (ester or amide). We also aimed to evaluate the potentiality of the new amphiphilic beta-cyclodextrins as excipients for the preparation and optimization of nanocapsules without using surface-active agents. Amphiphilic beta-cyclodextrin derivatives were characterized by (1)H-nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy, mass spectroscopy, differential scanning calorimetry, and elemental analysis. Nanocapsules prepared by nanoprecipitation were characterized by particle size and zeta potential determination and freeze fracture followed by transmission electron microscopy. The appropriate amphiphilic beta-cyclodextrin and its optimum concentration to be used were determined. Formation and characteristics of the nanocapsules were highly dependent on the structural properties of the modified cyclodextrin, its behavior in the oil-water interface and the viscosity and miscibility of the organic solvent with water. Physical stability after 5-month storage was also evaluated. The results indicated that derivatives with 6C aliphatic chains on the primary face proved to be the most efficient among the amphiphilic beta-CDs in this study. They avoid the use of surfactants in parenteral formulations of nanocapsules.

Memisoglu E., Bochot A., Sen M., Duchene D., and Hincal A. A. (2003) Non-surfactant nanospheres of progesterone inclusion complexes with amphiphilic beta-cyclodextrins. *Int J Pharm* **251**, 143-153.

Abstract: Amphiphilic beta-cyclodextrins were formulated as nanospheres and characterised by particle size, zeta potential and TEM following freeze-fracture. The nanospheres were loaded with progesterone with different loading techniques involving the spontaneous formation of nanospheres from pre-formed inclusion complexes of amphiphilic beta-cyclodextrins modified on the primary or secondary face with progesterone. Inclusion complexes were characterised with various techniques including Differential Scanning Calorimetry (DSC), Fast Atom Bombardment Mass Spectrometry (FAB MS) and 1H NMR spectroscopy; and progesterone was believed to be partially included in the CD cavity. Loading properties of conventionally-loaded nanospheres were compared with those prepared directly from pre-formed inclusion complexes and loading technique was found to enhance associated drug percentage significantly ($P < 0.05$). Although both amphiphilic beta-cyclodextrins (6-N-CAPRO-beta-CD and beta-CDC6) were capable of high progesterone loading, beta-CDC6 displayed slightly higher entrapment efficiency due to the possible higher affinity of progesterone to the 14 alkyl chains surrounding this molecule resulting in higher drug adsorption to particle surface. Progesterone was released within a period of 1 h from all formulations. Progesterone-loaded amphiphilic beta-CD nanospheres were proved to be a promising non-

surfactant injectable delivery system providing high-quantity of water-insoluble progesterone rapidly within 1 h.

Mora P. C., Cirri M., Allolio B., Carli F., and Mura P. (2003) Enhancement of dehydroepiandrosterone solubility and bioavailability by ternary complexation with alpha-cyclodextrin and glycine. *J Pharm Sci* **92**, 2177-2184.

Abstract: In the present work we investigated the possibility of improving dehydroepiandrosterone (DHEA) solubility and bioavailability by high-energy cogrinding with alpha-cyclodextrin (alpha-Cd) in the presence or absence of different auxiliary substances (glycine, biomaltodextrin, poly(vinyl pyrrolidone), poly(ethylene glycol) 400). In all cases, ternary products exhibited higher drug solubilizing properties than the binary DHEA-alpha-Cd coground system. Glycine was the most effective component. The best combinations, corresponding to 1:1:2 and 1:2:3 drug-alpha-Cd-glycine molar ratios, were characterized by differential scanning calorimetry and X-ray powder diffractometry and evaluated for dissolution rate. The presence of glycine favored destruction of DHEA crystalline structure during cogrinding, as evidenced by the strong reduction in both time and vibration frequency of milling necessary to obtain total drug amorphization. Both ternary products showed better dissolution properties than the drug alone, affording, respectively, a 40 and 60% increase of dissolution efficiency. The 1:2:3 coground product was then selected for in vivo bioavailability studies in women suffering from adrenocortical insufficiency. DHEA and DHEA sulfate blood levels were significantly higher ($p < 0.001$) after oral administration of the coground product than after oral administration of untreated drug, with a 100% increase in the area under the curve (AUC) of concentration versus time. Moreover, the time to reach maximum concentration ($t(\max)$) decreased from 2.2 with the untreated drug to 0.5 h with the coground product, and the mean permanence time of DHEA within physiological levels was four times longer for the coground product compared with the untreated drug. These results indicate that the developed product is particularly suitable for oral DHEA formulations in hormone replacement therapies.

Mora P. C., Cirri M., and Mura P. (2006) Differential scanning calorimetry as a screening technique in compatibility studies of DHEA extended release formulations. *J Pharm Biomed Anal* **42**, 3-10.

Abstract: Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of DHEA as ternary complex with alpha-cyclodextrin and glycine (c-DHEA) with some excipients suitable for preparation of sustained-release matrix tablets by direct compression. The effect of sample mechanical treatment due to the compression process was also evaluated. In order to investigate the possible interactions between the components, the DSC curves of c-DHEA and each selected excipient were compared with those of their 1:1 w/w physical mixtures, before and after compression, in order to evaluate any possible solid state modification. FT-IR spectroscopy and X-ray powder diffractometry were used as complementary techniques to adequately implement and assist in interpretation of the DSC results. On the basis of DSC results, c-DHEA was found to be compatible with xanthan gum, hydroxypropylmethylcellulose, sodium starch glycolate (Explotab(R)), polyvinylacetate-polyvinylpyrrolidone (Kollidon(R))SR and sodium chloride. Some drug-excipient interaction was observed with dextrate hydrate (Emdex(R)), mannitol and Magnesium stearate. Finally, the behaviour of the complete formulation, in the presence of all the excipients selected by means of the compatibility study, was investigated, in order to verify the absence of reciprocal interactions among the components.

Mourtzinis I., Makris D. P., Yannakopoulou K., Kalogeropoulos N., Michali I. and Karathanos V. T. (2008) Thermal stability of anthocyanin extract of Hibiscus sabdariffa L. in the presence of beta-cyclodextrin. *J Agric. Food Chem* **56**, 10303-10310.

Abstract: The thermal stability of anthocyanin extract isolated from the dry calyces of Hibiscus sabdariffa L. was studied over the temperature range 60-90 degrees C in aqueous solutions in the presence or absence of beta-cyclodextrin (beta-CD). The results indicated that the thermal degradation of anthocyanins followed first-order reaction kinetics. The temperature-dependent degradation was adequately modeled by the Arrhenius equation, and the activation energy for the degradation of H. sabdariffa L. anthocyanins during heating was found to be approximately 54 kJ/mol. In the presence of beta-CD, anthocyanins degraded at a decreased rate, evidently due to their complexation with beta-CD, having the same activation energy. The formation of complexes in solution was confirmed by nuclear magnetic resonance studies of beta-CD solutions in the presence of the extract. Moreover, differential scanning calorimetry revealed that the inclusion complex of H. sabdariffa L. extract with beta-CD in the solid state was more stable against

oxidation as compared to the free extract, as the complex remained intact at temperatures 100-250 degrees C where the free extract was oxidized. The results obtained clearly indicated that the presence of beta-CD improved the thermal stability of nutraceutical antioxidants present in *H. sabdariffa* L. extract, both in solution and in solid state

Mourtzinis I., Kalogeropoulos N., Papadakis S. E., Konstantinou K. and Karathanos V. T. (2008) Encapsulation of nutraceutical monoterpenes in beta-cyclodextrin and modified starch. *J Food Sci* **73**, S89-S94.

Abstract: The encapsulation of thymol and geraniol in beta-cyclodextrin (beta-CD) and modified starch (MS) by spray- and freeze-drying was studied. The formation of thymol/beta-CD and geraniol/beta-CD inclusion complexes was confirmed by differential scanning calorimetry (DSC). Oxidative DSC revealed that the monoterpenes enclosed in the beta-CD cavity were protected against oxidation, remaining intact in temperatures at which free monoterpenes were oxidized. Phase solubility studies showed that the inclusion complexes of thymol and geraniol with beta-CD are more soluble in water than the free molecules themselves. Furthermore, in order to evaluate the fraction of monoterpenes that can be released from their complexes with MS in aqueous media, a series of release experiments were conducted

Mura P., Furlanetto S., Cirri M., Maestrelli F., Corti G., and Pinzauti S. (2005) Interaction of naproxen with ionic cyclodextrins in aqueous solution and in the solid state. *J Pharm Biomed Anal* **37**, 987-994.

Abstract: The possible role of the cyclodextrin charge in the interaction with an acidic drug such as naproxen (pKa 4.8) has been evaluated. Sulfobutylether-beta-cyclodextrin (SBE-betaCyd) and trimethylammonium-beta-cyclodextrin (TMA-betaCyd) were selected as, respectively, anionically and cationically charged carriers and their performance was compared with that of the parent beta-cyclodextrin (betaCyd) and of its methyl-derivative (Me betaCyd) previously found as the best partner for the drug. Interactions in solution were investigated by phase-solubility, fluorescence and circular dichroism analyses. Equimolar drug-carrier products prepared by different techniques (blending, cogrinding, sealed-heating, colyophilization) were characterized by differential scanning calorimetry and X-ray powder diffractometry and tested for drug dissolution properties. Anionic charges of SBE-betaCyd did not negatively influence interactions in unbuffered aqueous solutions (pH approximately 5) with the acidic drug. In fact, it was a very effective carrier, exhibiting solubilizing and complexing properties considerably better than the parent betaCyd and comparable to those of Me betaCyd. On the contrary, the positive charges of TMA-betaCyd did not favour interactions with the counter-ionic drug (despite the presence of about 60% ionised drug) and it was less efficacious also than native betaCyd. Therefore, the role of the Cyd charge on the complexing and solubilizing properties towards naproxen was not important whereas other factors, such as steric hindrance effects and favourable hydrophobic interactions were significant in determining the drug affinity for the Cyd inclusion. Solid state studies evidenced similar amorphizing properties of both charged Cyds towards naproxen. On the other hand, dissolution tests, in agreement with solution studies, showed that all products with SBE-betaCyd exhibited significantly better dissolution properties than the corresponding ones with TMA-betaCyd. A clear influence of the preparation method of drug-Cyd solid systems on the performance of the end product was also observed. Colyophilization was the most effective technique, followed by the cogrinding one. Colyophilized product with SBE-betaCyd allowed a 10-times increase in drug dissolution efficiency (D.E.) (with respect to the five-times increase obtained with the corresponding coground product) and a reduction of t(50%) from about 60 min (for the coground product) to less than 2 min.

Mura P., Faucci M. T., Manderioli A., and Bramanti G. (1999) Influence of the preparation method on the physicochemical properties of binary systems of econazole with cyclodextrins. *Int J Pharm* **193**, 85-95.

Abstract: Equimolar combinations of econazole, a very poorly water soluble antifungal agent, with beta-cyclodextrin and statistically substituted methyl-beta-cyclodextrin were investigated for both solid state characterization (differential scanning calorimetry, hot-stage microscopy, infrared spectroscopy, scanning electron microscopy) and dissolution properties (dispersed amount method). The influence of the preparation method (physical mixing, ball-milling, kneading, sealed-heating) on the physicochemical properties of the products was evaluated. Kneading and sealed-heating techniques led to amorphous products in the case of systems with methyl-beta-cyclodextrin, whereas crystalline drug was still clearly detectable in all products with beta-cyclodextrin. Independently of the preparation technique, all combinations with methyl-beta-cyclodextrin yielded better performance than the corresponding ones with

beta-cyclodextrin. However, the influence of the preparation method was clearly more marked for products with methyl-beta-cyclodextrin and made to be possible to better display the different performance of the examined carriers. In fact, the sealed-heated with the beta-derivative showed an increase of drug dissolution efficiency of 130% with respect to the corresponding physical mixture, in comparison to the 70% increase obtained from that with beta-cyclodextrin. Moreover, whereas the difference in dissolution efficiency values between coground products was only about 8% in favor of the beta-derivative, it reached 80 and 90% between sealed-heated and kneaded products, respectively.

Mura P., Faucci M. T., and Parrini P. L. (2001) Effects of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties. *Drug Dev Ind Pharm* **27**, 119-128.

Abstract: Ground mixtures of ketoprofen (KETO) with native crystalline beta-cyclodextrin, amorphous statistically substituted methyl-beta-cyclodextrin, and microcrystalline cellulose were investigated for both solid phase characterization (differential scanning calorimetry (DSC) powder X-ray diffractometry, and infrared (IR) spectrometry) and dissolution properties (dispersed amount and rotating disk methods) to evaluate the role of the carrier on the performance of the final product. The effects of different grinding conditions, partial sample dehydration, and 1 year storage at room temperature were also investigated. The results pointed out the importance of the carrier nature on the efficiency of the cogrinding process. Both cyclodextrins were much more effective than was microcrystalline cellulose, even though no true inclusion complex formation occurred by mechanochemical activation. The best results were obtained from ground mixtures with methyl-beta-cyclodextrin, which showed the best amorphizing and solubilizing power toward the drug and permitted an increase of approximately 100 times its intrinsic dissolution rate constant, in comparison with the approximate 10 times increase obtained from ground mixtures with beta-cyclodextrin.

Mura P., Faucci M. T., and Bettinetti G. P. (2001) The influence of polyvinylpyrrolidone on naproxen complexation with hydroxypropyl-beta-cyclodextrin. *Eur J Pharm Sci* **13**, 187-194.

Abstract: The combined effect of hydroxypropyl-beta-cyclodextrin (HPbetaCD) and polyvinylpyrrolidone (PVP) on the solubility of naproxen (NAP) was studied. Phase-solubility analysis at different temperatures was used to investigate interactions in aqueous solution between NAP and the carriers, either alone or in combination. Equimolar NAP-HPbetaCD solid systems, in the presence or the absence of 15% (w/w) PVP, were prepared by cogrinding, kneading, coevaporation or freeze-drying, and characterized by differential scanning calorimetry, X-ray powder diffraction analysis, infrared spectroscopy and dissolution rates. The combined use of PVP and HPbetaCD resulted in a synergistic increasing effect of the aqueous solubility of NAP (120 times that of the pure drug). The phenomenon was interpreted in terms of the strongest complexation capacity of HPbetaCD towards NAP, which was reflected by an about 65% increase in the apparent stability constant of the NAP-HPbetaCD complex in the presence of only 0.1% (w/v) PVP. Variations in thermodynamic parameters accounted for a PVP role in the formation of a NAP-HPbetaCD-PVP ternary complex. The positive effect of PVP also reflected on NAP dissolution rates from solid preparations, because all ternary systems, with the exception of physical mixtures, dissolved faster than the corresponding NAP-HPbetaCD binary systems. The results of solid state studies accounted for the occurrence of mechanically- and/or thermally-induced stronger interactions in ternary than in binary systems, that in some cases led to a complete loss of NAP crystallinity.

Mura P., Zerrouk N., Faucci M., Maestrelli F., and Chemtob C. (2002) Comparative study of ibuprofen complexation with amorphous beta-cyclodextrin derivatives in solution and in the solid state. *Eur J Pharm Biopharm* **54**, 181-191.

Abstract: The complexing, solubilizing and amorphizing abilities toward ibuprofen (a poorly water-soluble anti-inflammatory agent) of some randomly substituted amorphous beta-cyclodextrin derivatives (i.e. methyl- (MebetaCd), hydroxyethyl- (HEbetaCd), and hydroxypropyl- (HPbetaCd) beta-cyclodextrins) were investigated and compared with those of the parent beta-cyclodextrin. Equimolar drug-cyclodextrin solid systems were prepared by blending, cogrinding, coevaporation, and colyophilization. Drug-carrier interactions were studied in both the liquid and solid state by phase solubility analysis, supported by molecular modelling, differential scanning calorimetry, X-ray powder diffractometry, Fourier transform infrared spectroscopy and scanning electron microscopy. All the betaCd derivatives showed greater solubilizing efficacies toward ibuprofen than the parent one, due to their higher water solubility. On the contrary, a clear reduction of complexing ability was observed, indicative of some steric interferences to

drug inclusion due to the presence of substituents, as confirmed by molecular modelling studies. However, this negative effect was not reflected in the dissolution behaviour (evaluated according to the dispersed amount method) of their solid binary systems, probably thanks to the greater amorphizing properties shown (DSC and X-ray analyses) by betaCd derivatives. In fact their dissolution efficiencies were not significantly different (MebetaCd) or only slightly lower (HEbetaCd and HPbetaCd) than those of the corresponding products with beta-cyclodextrin. Colyophilized products were in all cases the most effective, followed by coground and coevaporated systems, whose dissolution efficiencies were over four times higher than the corresponding physical mixtures and about 15 times higher than the pure drug.

Mura P., Faucci M. T., Maestrelli F., Furlanetto S., and Pinzauti S. (2002) Characterization of physicochemical properties of naproxen systems with amorphous beta-cyclodextrin-epichlorohydrin polymers. *J Pharm Biomed Anal* **29**, 1015-1024.

Abstract: Ground mixtures of naproxen with amorphous beta-cyclodextrin-epichlorohydrin soluble (betaCd-EPS) or insoluble cross-linked (betaCd-EPI) polymers were investigated for both solid phase characterization (Differential Scanning Calorimetry, powder X-ray Diffractometry) and dissolution properties (dispersed amount method). The effect of different grinding conditions and of drug-to-carrier ratio was also evaluated. Co-grinding induced a decrease in drug crystallinity to an extent which depended on the grinding time, and was most pronounced for the cross-linked insoluble polymer, particularly in combinations at the lowest drug content. Both cyclodextrin polymers were more effective in improving the naproxen dissolution properties, not only than the parent betaCd but also than hydroxyalkyl-derivatives, and their performance was almost comparable to that of methyl-derivatives, previously found as the best carriers for naproxen. Dissolution efficiencies of naproxen from physical mixtures with betaCd-EPS, thanks to the high water solubility of this Cd-derivative, were up to three times higher than those from the corresponding products with betaCd-EPI. However this difference in their performance became much less evident in co-ground products and tended to progressively diminish with increasing the polymer content in the mixture, according to the better amorphizing power shown by betaCd-EPI during the co-grinding process. The 10/90 (w/w) drug-carrier co-ground products exhibited the best dissolution properties, giving dissolution efficiencies about 30 times higher than that of naproxen alone.

Mura P., Maestrelli F., and Cirri M. (2003) Ternary systems of naproxen with hydroxypropyl-beta-cyclodextrin and aminoacids. *Int J Pharm* **260**, 293-302.

Abstract: The purpose of the present study was to investigate the combined effect of hydroxypropyl-beta-cyclodextrin and different aminoacids (L-lysine, LYS; L-valine, VAL; L-iso-leucine, LEU; and L-arginine, ARG) on the solubility of naproxen, a poorly water-soluble anti-inflammatory drug. Aqueous solubilities of naproxen in binary and ternary systems with hydroxypropyl-beta-cyclodextrin and each aminoacid were determined. The pH was measured in all solubility studies and its role on drug solubility variation was evaluated. Arginine was the most effective aminoacid in improving drug solubility and the only one which showed a synergistic effect when used in combination with hydroxypropyl-beta-cyclodextrin. In contrast, some reduction with respect to the theoretical drug solubility (i.e. the sum of the solubilities in the presence of cyclodextrin and aminoacid separately) was observed in ternary combinations with the other aminoacids. This occurred also in the case of lysine, despite the higher solubility of its ternary system in comparison with the binary cyclodextrin complex at pH 7. Phase-solubility experiments showed that the ternary system with arginine (pH approximately 7) exhibited a stability constant 3.6 times higher and was about 5.5 times more effective in improving drug solubility than the binary complex in buffered (pH approximately 7) aqueous solutions. These results demonstrated that the high increase in the drug solubility shown by ternary systems with arginine was not simply due to a favorable pH change but to multicomponent complex formation. Solid products of naproxen with hydroxypropyl-beta-cyclodextrin, and/or arginine, prepared by different methods, were characterized by Differential Scanning Calorimetry (DSC), Hot Stage Microscopy (HSM) and Scanning Electron Microscopy (SEM).

Nalluri B. N., Chowdary K. P., Murthy K. V., Hayman A. R., and Becket G. (2003) Physicochemical characterization and dissolution properties of nimesulide-cyclodextrin binary systems. *AAPS PharmSciTech* **4**, E2.

Abstract: The objective of this work is physicochemical characterization of nimesulide-cyclodextrin binary systems both in solution and solid state and to improve the dissolution properties of nimesulide (N) via complexation with alpha-, beta-, and gamma-cyclodextrins (CDs). Detection of inclusion complexation

was done in solution by means of phase solubility analysis, mass spectrometry, and ¹H nuclear magnetic resonance (¹H-NMR) spectroscopic studies, and in solid state using differential scanning calorimetry (DSC), powder x-ray diffractometry (X-RD), scanning electron microscopy (SEM), and in vitro dissolution studies. Phase solubility, mass spectrometry and ¹H-NMR studies in solution revealed 1:1 M complexation of N with all CDs. A true inclusion of N with beta-CD at 1:2 M in solid state was confirmed by DSC, powder X-RD and SEM studies. Dissolution properties of N-CD binary systems were superior when compared to pure N.

Nishijo J. and Mizuno H. (1998) Interactions of cyclodextrins with DPPC liposomes. Differential scanning calorimetry studies. *Chem Pharm Bull (Tokyo)* **46**, 120-124.

Abstract: The interaction of cyclodextrins (CDs) with dipalmitoylphosphatidylcholine (DPPC) liposomes has been studied using differential scanning calorimetry (DSC). The phase transition temperature and the enthalpy change due to the gel-to-liquid crystalline phase transition of the liposomes were measured in the presence of alpha-CD, beta-CD, gamma-CD, heptakis (2,6-di-O-methyl)-beta-CD (DOM-beta-CD), heptakis (2,3,6-tri-O-methyl)-beta-CD (TOM-beta-CD) and 2-hydroxypropyl beta-CD, respectively. The effects on the change of enthalpy of the transition temperature were remarkable in the order of DOM-beta-CD > alpha-CD > TOM-beta-CD. The residual CDs caused scarcely detectable changes in the enthalpy changes and the transition temperatures. In order to clarify the DSC curves in the presence of the CDs mentioned above, the type of interactions which occurred between CDs and DPPC liposomes were studied. Consequently, it was found that DOM-beta-CD forms a soluble complex and alpha-CD forms an insoluble complex with DPPC liposomes, whereas only a slight amount of TOM-beta-CD was suggested to penetrate the matrix of the liposomes.

Nishijo J., Shiota S., Mazima K., Inoue Y., Mizuno H., and Yoshida J. (2000) Interactions of cyclodextrins with dipalmitoyl, distearoyl, and dimyristoyl phosphatidyl choline liposomes. A study by leakage of carboxyfluorescein in inner aqueous phase of unilamellar liposomes. *Chem Pharm Bull (Tokyo)* **48**, 48-52.

Abstract: The interaction of cyclodextrins (CDs) with L-alpha-dipalmitoyl phosphatidyl choline (DPPC), L-alpha-distearoyl phosphatidyl choline (DSPC), and L-alpha-dimyristoyl phosphatidyl choline (DMPC) unilamellar liposomes was investigated by the leakage of carboxyfluorescein (CF) entrapped in the inner aqueous phase of liposomes, at 25 degrees C (DPPC and DSPC liposomes) and at 5 degrees C (DMPC liposomes). The efficiency of CDs for CF leakage was remarkable in the order of heptakis (2,6-di-O-methyl)-beta-CD (DOM-beta-CD) > alpha-CD > heptakis (2,3,6-tri-O-methyl)-beta-CD (TOM-beta-CD) from DPPC liposomes, in the order of DOM-beta-CD > TOM-beta-CD > alpha-CD from DSPC liposomes and in the order of alpha-CD > DOM-beta-CD > TOM-beta-CD from DMPC liposomes. The other CDs used in the present studies, beta-CD, 2-hydroxypropyl beta-CD, and gamma-CD scarcely induced the CF leakage from above the three liposomes. From the profiles of % CF leakage, together with measurements of differential scanning calorimetry, it was found that hydrophobic DOM-beta-CD penetrates the matrix of the liposomes to interact with them as well as TOM-beta-CD, and that less hydrophobic alpha-CD exists at the surface of the membrane to interact with the liposomes. Further, it was found that the interaction of CDs with liposomes changes depending not only on the length of fatty acid chain of phospholipid (condensation force and hydrophobicity) but also the hydrophobicity and the cavity size of CD.

Palmieri G. F., Wehrle P., and Martelli S. (1998) Interactions between lonidamine and beta- or hydroxypropyl-beta-cyclodextrin. *Drug Dev Ind Pharm* **24**, 653-660.

Abstract: The possibility of obtaining inclusion complexes between lonidamine and beta- or hydroxypropyl-beta-cyclodextrin have been evaluated by phase solubility diagram, differential scanning calorimetry (DSC), and x-ray diffractometry. The applied complexation methods were spray-drying, kneading, and solid dispersion. DSC and x-ray analyses of the powders revealed an external interaction between lonidamine and cyclodextrins. Dissolution profiles of the obtained powders were also studied to define the most appropriate preparation method and molar ratio to use in attempts to increase lonidamine water solubility.

Perdomo-Lopez I., Rodriguez-Perez A. I., Yzquierdo-Peiro J. M., White A., Estrada E. G., Villa T. G., and Torres-Labandeira J. J. (2002) Effect of cyclodextrins on the solubility and antimycotic activity of sertaconazole: experimental and computational studies. *J Pharm Sci* **91**, 2408-2415.

Abstract: This study investigated the effects of the complexation of sertaconazole nitrate with different

cyclodextrin (CD) derivatives (alpha-CD, beta-CD, gamma-CD, hydroxypropyl-beta-CD, and hydroxypropyl-gamma-CD) on the aqueous solubility and antimycotic activity of the drug. Phase solubility studies indicated that the solubility of sertaconazole in enzyme-free simulated gastric- and enzyme-free simulated enteric fluids was significantly increased in the presence of cyclodextrins. The observed order of solubility increasing effect was: gamma-CD > HPgamma-CD > HPbeta-CD > beta-CD > alpha-CD. Solid-state sertaconazole-cyclodextrin complexes were prepared by freeze drying, and characterized by X-ray powder diffractometry, differential scanning calorimetry (DSC), and infrared spectroscopy (FTIR). Freeze-dried complexes showed markedly higher solubility than both physical mixtures and sertaconazole alone. The antimycotic activities of sertaconazole-cyclodextrin complexes in solution were evaluated by inhibition zone assays with *Candida albicans*. The activity ranking agrees with the solubility ranking observed for these complexes, with the gamma-CD-sertaconazole complex showing the strongest antimycotic activity. Finally, molecular modeling studies were carried out using the MM2 force field method, for complexes in vacuum and in water. This enable identification of the preferred orientation of sertaconazole in the gamma-CD cavity and of the main structural features responsible for the enhancement of its solubility and antimycotic activity.

Perlovich G. L., Skar M., and Bauer-Brandl A. (2003) Driving forces and the influence of the buffer composition on the complexation reaction between ibuprofen and HPCD. *Eur J Pharm Sci* **20**, 197-200. **Abstract:** Cyclodextrins are often used in order to increase the aqueous solubility of drug substances by complexation. In order to investigate the complexation reaction of ibuprofen and hydroxypropyl-beta-cyclodextrin, titration calorimetry was used as a direct method. The thermodynamic parameters of the complexation process (stability constant, $K(11)$; complexation enthalpy, $\Delta H(c)$ degrees) were obtained in two different buffer systems (citric acid/sodium-phosphate and phosphoric acid) at various pH values. Based on these data the relative contributions of the enthalpic and entropic terms of the Gibbs energy to the complexation process have been analyzed. In both buffers the enthalpic and entropic terms are of different sign and this case corresponds to a 'nonclassical' model of hydrophobic interaction. In citric buffer, the main driving force of complexation is the entropy, which increases from 60 to 67% while the pH of the solution increases from 3.2 to 8.0. However, for the phosphoric buffer the entropic term decreases from 60 to 45%, while the pH-value of the solution increases from 5.0 to 8.2, and the driving force of the complexation process changes from entropy to enthalpy. The experimental data of the present study are compared to results of other authors and discrepancies discussed in detail.

Pinto L. M., Fraceto L. F., Santana M. H., Pertinhez T. A., Junior S. O., and de Paula E. (2005) Physico-chemical characterization of benzocaine-beta-cyclodextrin inclusion complexes. *J Pharm Biomed Anal* **39**, 956-963.

Abstract: Local anesthetics are able to induce pain relief by binding to the sodium channel of excitable membranes, blocking the influx of sodium ions and the propagation of the nervous impulse. Benzocaine (BZC) is a local anesthetic whose low water-solubility limits its application to topical formulations. The present work focuses on the characterization of inclusion complexes of BZC in beta-cyclodextrin (beta-CD). Differential scanning calorimetry and electron microscopy gave evidences of the formation and the morphology of the complex. Fluorescence spectroscopy showed a BZC/beta-CD 1:1 stoichiometry. Phase-solubility diagrams allowed the determination of the association constants between BZC and beta-CD (549 M(-1)) and revealed that a three-fold increase in BZC solubility can be reached upon complexation with beta-CD. The details of BZC/beta-CD molecular interaction were analyzed by ¹H ²D NMR allowing the proposition of an inclusion model for BZC into beta-CD where the aromatic ring of the anesthetic is located near the head of the beta-CD cavity. Moreover, in preliminary toxicity studies, the complex seems to be less toxic than BZC alone, since it induced a decrease in the in vitro oxidation of human hemoglobin. These results suggest that the BZC/beta-CD complex represents an effective novel formulation to enhance BZC solubility in water, turning it promising for use outside its traditional application, i.e., in infiltrative anesthesia.

Pose-Vilarnovo B., Perdomo-Lopez I., Echezarreta-Lopez M., Schroth-Pardo P., Estrada E., and Torres-Labandeira J. J. (2001) Improvement of water solubility of sulfamethizole through its complexation with beta- and hydroxypropyl-beta-cyclodextrin. Characterization of the interaction in solution and in solid state. *Eur J Pharm Sci* **13**, 325-331.

Abstract: The aim of this study was to increase the solubility of sulfamethizole in water by complexing it

with beta-cyclodextrin (BCD) and hydroxypropyl-beta-cyclodextrin (HPBCD). The interaction of sulfamethizole with the cyclodextrins was evaluated by the solubility, ¹H NMR spectrometry and molecular modelling. The stability constants calculated from the phase solubility method increase in order HPBCD < BCD. From the NMR studies could be concluded that the sulfamethizole:cyclodextrin mole ratio was 1:1 (mol/mol) in the BCD complex and 2:3 (mol/mol) in the HPBCD complex. In both cases the sulfamethizole moiety included in the cyclodextrin was the thiadiazole group. MM2 calculations, either in vacuum or in the presence of a solvent, support this structure. Solid inclusion complexes of sulfamethizole with BCD and HPBCD were obtained by freeze drying 1:1 (mol/mol) solutions in aqueous ammonium hydroxide. Host-guest interactions were studied in the solid state by powder X-ray diffractometry and differential scanning calorimetry. The dissolution rates of sulfamethizole increased by the complexation with BCD or HPBCD.

Proniuk S. and Blanchard J. (2001) Influence of degree of substitution of cyclodextrins on their colligative properties in solution. *J Pharm Sci* **90**, 1086-1090.

Abstract: The purpose of this study was to investigate the effect of the total degree of substitution (TDS) on the colligative properties of substituted cyclodextrins (CDs; i.e., beta- and gamma-cyclodextrins substituted with sulfobutylether or hydroxypropyl groups) in solution. The osmotic pressure (OP) of aqueous CD solutions was determined over the concentration range 100-350 mmol/kg using vapor pressure osmometry. A chloride ion-selective electrode was used to help determine the possible mechanism for any CD-water interactions that might occur by measuring the chloride-ion activity of a sodium chloride solution containing various CDs. Titration microcalorimetry was used to verify that sodium chloride did not interact with the CDs, thereby permitting the chloride ion activity to be utilized as an indicator of any possible CD-water interaction. The results indicate that CDs with different total degrees of substitution (TDS) exhibit different colligative properties in solution. It was observed that increases in the degree of substitution of the CD produced an increased OP. All substituted CDs exhibited an OP above their theoretical values, whereas the OP of the unsubstituted gamma-CD was below its expected value, likely due to self-association. The results obtained with the chloride-ion selective electrode did not exhibit a consistent trend; however, it was observed that changes in the TDS caused significant changes in the activity of chloride ions in solution. These findings are of interest in using CDs to formulate parenteral and ophthalmic solutions where the OP of the solutions must be considered.

Rawat S. and Jain S. K. (2003) Rofecoxib-beta-cyclodextrin inclusion complex for solubility enhancement. *Pharmazie* **58**, 639-641.

Abstract: Complex formation of rofecoxib and beta-cyclodextrin in aqueous solution and in solid state and the possibility of improving the solubility and dissolution rate of rofecoxib via complexation with cyclodextrin were investigated. Phase solubility studies indicated the formation of an 1:1 complex in solution and the value of apparent stability constant was 769 M⁻¹. Solid inclusion complexes of rofecoxib and cyclodextrin were prepared by the kneading method in different molar ratios. Differential scanning calorimetry studies indicated the formation of solid inclusion complexes of rofecoxib and cyclodextrin at different molar ratios and the solid complexes exhibited a higher rate of dissolution than the physical mixture and the pure drug.

Ribeiro L., Loftsson T., Ferreira D., and Veiga F. (2003) Investigation and physicochemical characterization of vinpocetine-sulfobutyl ether beta-cyclodextrin binary and ternary complexes. *Chem Pharm Bull (Tokyo)* **51**, 914-922.

Abstract: The purpose of this study was to investigate the interactions between vinpocetine (VP), sulfobutyl ether beta-cyclodextrin (SBEbetaCD) and the water-soluble polymers polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC). The water-soluble polymers were shown to improve the complexation efficiency of SBEbetaCD, and thus less SBEbetaCD was needed to prepare solid VP-SBEbetaCD complexes in the presence of the polymers. The interactions between VP and SBEbetaCD, with or without PVP or HPMC, were thoroughly investigated in aqueous solutions using the phase-solubility method as well as in the solid state. The amount of VP solubilized in water or aqueous polymer solution increased linearly with increasing SBEbetaCD concentration, demonstrating A(L)-type plots. We estimated the apparent stability constant (K(c)) at room temperature of VP-SBEbetaCD binary complex to be 340 M⁻¹ and this value increased to 490 M⁻¹ or 390 M⁻¹, respectively, with the addition of PVP and HPMC, assuming a 1 : 1 VP-SBEbetaCD molar ratio. Improvement in the K(c) values for ternary

complexes clearly confirmed the benefit of the addition of water-soluble polymers to promote higher complexation efficiency. Solid VP-SBEbetaCD binary and ternary systems were prepared by physical mixing, kneading, coevaporation, and lyophilization methods and fully characterized by scanning electron microscopy, differential scanning calorimetry, and X-ray diffractometry. The results obtained suggest that coevaporation and lyophilization methods yield a higher degree of amorphous entities and indicated formation of VP-SBEbetaCD binary and ternary complexes.

Ribeiro L. S., Ferreira D. C., and Veiga F. J. (2003) Physicochemical investigation of the effects of water-soluble polymers on vinpocetine complexation with beta-cyclodextrin and its sulfobutyl ether derivative in solution and solid state. *Eur J Pharm Sci* **20**, 253-266.

Abstract: The studies reported in this work aimed to elucidate the inclusion complex formation of vinpocetine (VP), a poorly water-soluble base type drug, with beta-cyclodextrin (betaCD) and its sulfobutyl ether derivative (sulfobutyl ether beta-cyclodextrin (SBEbetaCD)), with or without water-soluble polymers (PVP and HPMC), by thoroughly investigating their interactions in solution and solid state. Phase solubility studies were carried out to evaluate the solubilizing power of both cyclodextrins (CDs), in association with water-soluble polymers, towards VP and to determine the apparent stability constants (K(c)) of the complexes. SBEbetaCD showed higher solubilizing efficacy toward VP than the parent betaCD due to its greater solubility and complexing abilities, what was reflected in higher K(c) values. Improvement in K(c) values for ternary complexes clearly proves the benefit on the addition of water-soluble polymers to promote higher complexation efficiency. VP-CDs (1:1) binary and ternary systems were prepared by physical mixing, kneading, co-evaporation, and lyophilization methods. In the solid state, drug-carrier interactions were studied by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and Fourier-transform infrared spectroscopy. The results of these analysis suggested the formation of new solid phases, some of them in amorphous state, allowing to the conclusion of strong evidences of binary and ternary inclusion complex formation between VP, CD and water-soluble polymers, particularly for co-evaporated and lyophilized binary and ternary products.

Rode T., Frauen M., Muller B. W., Dusing H. J., Schonrock U., Mundt C., and Wenck H. (2003) Complex formation of sericoside with hydrophilic cyclodextrins: improvement of solubility and skin penetration in topical emulsion based formulations. *Eur J Pharm Biopharm* **55**, 191-198.

Abstract: The main objective of this study was to devise novel methods for improving the solubility of the anti-inflammatory triterpenoid sericoside, the main component of *Terminalia sericea* extract, thus enabling its incorporation into topical formulations. Sericoside was stabilized by complex formation with hydrophilic derivatives of beta- and gamma-cyclodextrins in a molar ratio of 1.0:1.1. The complex of extract and cyclodextrin was equilibrated in water at 25 degrees C for approximately 24 h. The dehydrated complexes of *T. sericea* extract and cyclodextrin were characterized by differential scanning calorimetry, thermogravimetry analysis and X-ray diffraction. Complex formation with beta-cyclodextrin as well as gamma-cyclodextrin derivatives was detectable using these three analytical tools; however, only complexes with gamma-cyclodextrin derivatives showed stability upon storage after incorporation into topical o/w or w/o formulations. Furthermore, a *T. sericea* extract/gamma-cyclodextrin complex incorporated in an o/w formulation resulted in a 2.6-fold higher percutaneous penetration of sericoside in *in vitro* excised pig skin as compared to pure *T. sericea* extract. For the first time, the virtually insoluble anti-inflammatory active sericoside was incorporated into a topical emulsion based formulation in a stable manner, resulting in efficient skin penetration.

Rodriguez-Perez A. I., Rodriguez-Tenreiro C., Alvarez-Lorenzo C., Taboada P., Concheiro A., and Torres-Labandeira J. J. (2006) Sertaconazole/hydroxypropyl-beta-cyclodextrin complexation: isothermal titration calorimetry and solubility approaches. *J Pharm Sci* **95**, 1751-1762.

Abstract: Complexation of sertaconazole (SN) with hydroxypropyl-beta-cyclodextrin (HP-beta-CD) was characterized by phase-solubility diagram measurements and isothermal calorimetry (ITC) in aqueous medium, and by differential scanning calorimetry (DSC), Raman spectroscopy and X-ray diffractometry in solid state. The strongest interaction was observed at pH 1.2, at which two different 1:1 complexes can be formed depending on the hydrophobic ring of the drug involved in the process. At pH 5.8 and 7.4 the likelihood of 1:2 stoichiometry increases as a consequence of the simultaneous complexation of the nonprotonized imidazolyl and the dichlorophenyl groups. In the presence of 20% HP-beta-CD, SN solubility is enhanced by a factor of 116, 107, and 5 at pH 1.2, 5.8, and 7.4, respectively. Complexation

enthalpy recorded by ITC showed the same tendency which confirms the practical interest of this technique for fast screening of the potential of CDs as drug solubilizers. Solubility and dissolution rate of the drug from compacts prepared with freeze-dried complexes were significantly greater than those obtained with SN powder or compacts made with physical blends.

Scalia S., Tursilli R., Sala N., and Iannuccelli V. (2006) Encapsulation in lipospheres of the complex between butyl methoxydibenzoylmethane and hydroxypropyl-beta-cyclodextrin. *Int J Pharm* **320**, 79-85.
Abstract: The aim of this study was to investigate the incorporation into lipospheres of the complex between hydroxypropyl-beta-cyclodextrin (HP-beta-CD) and the sunscreen agent, butyl methoxydibenzoylmethane (BMDBM) and to examine the influence of this system on the sunscreen photostability. The formation of the inclusion complex was confirmed by thermal analysis and powder X-ray diffraction. Lipid microparticles loaded with free BMDBM or its complex with HP-beta-CD were prepared using tristearin as the lipid material and hydrogenated phosphatidylcholine as the emulsifier. The obtained lipospheres were characterized by scanning electron microscopy and differential scanning calorimetry. The microparticle size (15-40µm) was not affected by the presence of the complex. Release of BMDBM from the lipospheres was lower when it was incorporated as inclusion complex rather than as free molecule. Unencapsulated BMDBM, its complex with HP-beta-CD, the sunscreen-loaded lipospheres or the lipoparticles containing the BMDBM/HP-beta-CD complex, were introduced into a model cream (oil-in-water emulsion) and irradiated with a solar simulator. The photodegradation studies showed that all the examined systems achieved a significant reduction of the light-induced decomposition of the free sunscreen agent (the BMDBM loss decreased from 28.9 to 17.3-15.2%). However, photolysis experiments performed during 3 months storage of the formulations, demonstrated that the photoprotective properties of the HP-beta-CD complex and of BMDBM alone-loaded lipospheres decreased over time, whereas the microencapsulated HP-beta-CD/BMDBM complex retained its photostabilization efficacy. Therefore, incorporation in lipid microparticles of BMDBM in the cyclodextrin complex form is more effective in enhancing the sunscreen photostability than the complex alone or the liposphere-entrapped free BMDBM.

Sri K. V., Kondaiah A., Ratna J. V. and Annapurna A. (2007) Preparation and characterization of quercetin and rutin cyclodextrin inclusion complexes. *Drug Dev. Ind. Pharm.* **33**, 245-253.

Abstract: The objective of the present study is to prepare and characterize cyclodextrin inclusion complexes of quercetin and rutin to improve their aqueous solubility and dissolution properties. Inclusion complexes of quercetin and rutin with beta-cyclodextrin (beta-CD) and hydroxyl propyl-beta-cyclodextrin (HP-beta-CD) were prepared by kneading and coevaporation methods. Characterization of inclusion complexes was done by phase solubility analysis and was supported by X-ray powder diffractometry (XRD), differential scanning calorimetry (DSC), and Fourier-transform infra red spectroscopy (FT-IR) analysis. Inclusion complexes exhibited higher rates of dissolution than the corresponding physical mixtures and pure drug. Higher dissolution rates were observed with HP-beta-CD kneaded complexes in comparison to the products with beta-CD.

Sridevi S., Chauhan A. S., Chalasani K. B., Jain A. K., and Diwan P. V. (2003) Enhancement of dissolution and oral bioavailability of gliquidone with hydroxy propyl-beta-cyclodextrin. *Pharmazie* **58**, 807-810.

Abstract: The virtual insolubility of gliquidone in water results in poor wettability and dissolution characteristics, which may lead to a variation in bioavailability. To improve these characteristics of gliquidone, binary systems with hydroxypropyl-beta-cyclodextrin (HP-beta-CD) were prepared by classical methods such as physical mixing, kneading, co-evaporation and co-lyophilization. The solid state interaction between the drug and HP-beta-CD was assessed by evaluating the binary systems with X-ray diffraction, differential scanning calorimetry and IR- spectroscopy. The results establish the molecular encapsulation and amorphization of gliquidone. The phase solubility profile of gliquidone in aqueous HP-beta-CD vehicle resulted in an A(L) type curve with a stability constant of 1625 M^{-1} . The dissolution rate of binary systems was greater than that of pure drug and was significantly higher in the case of co-lyophilized and co-evaporated systems. Upon oral administration, [AUC]-alpha was significantly higher in case of co-lyophilized (2 times) and co-evaporated systems (1.5 times) compared to pure drug suspension while other binary systems showed only a marginal improvement. The study ascertained the utility of HP-beta-CD in enhancing the oral bioavailability of gliquidone, and points towards a strong influence of the preparation method on the physicochemical properties.

Trapani G., Lopedota A., Boghetich G., Latrofa A., Franco M., Sanna E., and Liso G. (2003) Encapsulation and release of the hypnotic agent zolpidem from biodegradable polymer microparticles containing hydroxypropyl-beta-cyclodextrin. *Int J Pharm* **268**, 47-57.

Abstract: The goal of this study was to design a prolonged release system of the hypnotic agent zolpidem (ZP) useful for the treatment of insomnia. In this work, ZP alone or in the presence of HP-beta-CD was encapsulated in microparticles constituted by poly(DL-lactide) (PDLLA) and poly(DL-lactide-co-glycolide) (PLGA) and the drug release from these systems was evaluated. ZP alone-loaded microparticles were prepared by the classical O/W emulsion-solvent evaporation method. Conversely, ZP/HP-beta-CD containing microparticles were prepared by the W/O/W emulsion-solvent evaporation method following two different procedures (i.e. A and B). Following procedure A, the previously produced ZP/HP-beta-CD solid complex was added to the water phase of primary emulsion. In the procedure B, HP-beta-CD was added to the aqueous phase and ZP to the organic phase. The resulting microparticles were characterized about morphology, size, encapsulation efficiency and release rates. FT-IR, X-ray, and DSC results suggest the drug is in an essentially amorphous state within the microparticles. The release profiles of ZP from microparticles were in general biphasic, being characterized by an initial burst effect and a subsequent slow ZP release. It resulted that co-encapsulating ZP with or without HP-beta-CD in PDLLA and PLGA the drug release from the corresponding microparticles was protracted. Moreover, in a preliminary pharmacological screening, the ataxic activity in rats was investigated and it was found that intragastric administration of the ZP/HP-beta-CD/PLGA microparticles prepared according to procedure B produced the same ataxic induction time as the one induced by the currently used formulation Stilnox((R)). Interestingly moreover, there was a longer ataxic lasting and a lower intensity of ataxia produced by the ZP/HP-beta-CD/PLGA-B-formulation already after 60min following the administration. However, a need for further pharmacokinetic and pharmacodynamic studies resulted to fully evaluate the utility of this last formulation for the sustained delivery of ZP.

Van Hees T., Piel G., de Hassonville S. H., Evrard B., and Delattre L. (2002) Determination of the free/included piroxicam ratio in cyclodextrin complexes: comparison between UV spectrophotometry and differential scanning calorimetry. *Eur J Pharm Sci* **15**, 347-353.

Abstract: Few analytical techniques allow to evaluate the inclusion yield of cyclodextrin-drug complexes, because most manufacturing processes give amorphous products. In this study, we have developed an alternative method to differential scanning calorimetry, to accurately determine the free/complexed piroxicam ratio by UV spectroscopy. This method is based on the differential solubility of the piroxicam-beta-cyclodextrin 1:2.5 mol/mol complex in water-acetonitrile (1:1, v/v) (Solvent A) or in anhydrous acetonitrile (Solvent B), both containing 0.05 M HCl. In anhydrous acetonitrile, beta-cyclodextrin is insoluble and the included drug remains entrapped, allowing the free piroxicam determination, while with 50% of water, the complex is totally dissolved, allowing the determination of the total guest content. This method was validated for linearity, precision and accuracy. The presence of cyclodextrin does not influence the assays, but more than 0.5% of water in Solvent B significantly affects the determination of the free piroxicam content. In comparison with differential scanning calorimetry, both detectability and precision were improved. It is now possible to analyse complexes with an inclusion purity greater than 99%.

Veiga M. D. and Merino M. (2002) Interactions of oxyphenbutazone with different cyclodextrins in aqueous medium and in the solid state. *J Pharm Biomed Anal* **28**, 973-982.

Abstract: The interactions between a nonsteroidal anti-inflammatory drugs, oxyphenbutazone (OPB), with two cyclodextrins, beta-cyclodextrin (beta-CD) and gamma-cyclodextrin (gamma-CD), have been studied in an aqueous medium and in the solid state. Differential scanning calorimetry, hot stage microscopy, thermogravimetric analysis and X-ray diffraction (XRD) powder have been the techniques used to characterize the interactions in the solid state. Although OPB forms inclusion compounds with beta- and gamma-CD in the aqueous medium, only the OPB/gamma-CD inclusion compound was obtained in the solid state by the kneading method. The XRD powder used at different temperatures has proven be a useful tool in characterizing the behaviour of these binary systems.

Ventura C. A., Fresta M., Paolino D., Pedotti S., Corsaro A., and Puglisi G. (2001) Biomembrane model interaction and percutaneous absorption of papaverine through rat skin: effects of cyclodextrins as penetration enhancers. *J Drug Target* **9**, 379-393.

Abstract: The effects of different concentrations of beta-cyclodextrin (beta-CyD), hydroxypropyl-beta-

cyclodextrin (HP-beta-CyD) and 2,6-di-O-methyl-beta-cyclodextrin (DM-beta-CyD) on percutaneous absorption of papaverine hydrochloride (PAP) were investigated. Abdominal rat skin mounted in Franz cells was used for in vitro experiments. To evaluate CyD interaction with a bilayer structure model, dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and DPPC-Chol (8:2 mole ratio) vesicles were used. CyD vesicle interaction was evaluated by differential scanning calorimetry. Permeation through rat skin and calorimetric experiments demonstrated that at low concentrations DM-beta-CyD shows higher enhancer activity as a possible result of a perturbing action on the skin by a complexation of its lipid components, but at higher concentrations HP-beta-CyD is the most effective. By considering that HP-beta-CyD presents a very moderate destabilizing action on the skin, we conclude that a 10% aqueous solution of this macrocycle appears to be the most suitable transdermal absorption enhancer for PAP.

Ventura C. A., Tommasini S., Falcone A., Giannone I., Paolino D., Sdrafkakis V., Mondello M. R., and Puglisi G. (2006) Influence of modified cyclodextrins on solubility and percutaneous absorption of celecoxib through human skin. *Int J Pharm* **314**, 37-45.

Abstract: We evaluated the ability of two modified cyclodextrins, hydroxypropyl-beta-cyclodextrin (HP-beta-CyD) and 2,6-di-O-methyl-beta-cyclodextrin (DM-beta-CyD), to influence the percutaneous absorption through isolated human stratum corneum and epidermis (SCE) of celecoxib (CCB). Previous studies demonstrated that DM-beta-CyD includes the drug, producing a significant increase of water solubility (0.5 mg/ml at 25 degrees C) and dissolution rate of CCB. In this work chemical-physical characterization studies were performed to evaluate the ability of HP-beta-CyD to include CCB. We showed that only an external interaction could exist between CCB and HP-beta-CyD that positively influences the water solubility of the drug (0.12 mg/ml at 25 degrees C for CCB-HP-beta-CyD system and 4.12×10^{-3} mg/ml at 25 degrees C for free CCB). In vitro percutaneous experiments were performed using samples in solution and in suspension containing different Cyd concentrations. Both HP-beta-CyD and DM-beta-CyD enhanced drug flux through SCE by means of an increase of dissolution rate of the drug as well as a direct action on the stratum corneum (SC). Histological analysis of treated SCE showed a protective effect of the two Cyds towards an invasive action shown by CCB on SC.

Ventura C. A., Giannone I., Musumeci T., Pignatello R., Ragni L., Landolfi C., Milanese C., Paolino D., and Puglisi G. (2006) Physico-chemical characterization of disoxaril-dimethyl-beta-cyclodextrin inclusion complex and in vitro permeation studies. *Eur J Med Chem* **41**, 233-240.

Abstract: In this work we evaluated the ability of 2,6-di-O-methyl-beta-cyclodextrin (DM-beta-CyD) to include the anti-rhinovirus drug Disoxaril (WIN 51711), increasing its water solubility and stability. The complex, prepared by kneading method, was characterized in the solid state by differential scanning calorimetry and in aqueous solution using circular dichroism and NMR spectroscopy. The formation of 1:1 and 1:2 drug-CyD complexes was hypothesized. Stability constants for both complexes were determined on the basis of an Ap-type phase solubility diagrams and evidenced a very high stability for the 1:1 complex. Thermodynamic parameters of the binding process showed the existence of classical hydrophobic interactions in the 1:1 complex with the formation of a less ordered system after complexation. An enthalpic contribution rather than an entropic one accompanied the association of the second Cyd molecule. DM-beta-CyD was able to significantly increase water solubility of WIN 51711, from 0.000123 to 0.47142 mg/ml. Free drug shows a very low water stability, it is completely hydrolyzed after 36 h in PBS (pH 7.0), at 4 degrees C. In the presence of DM-beta-CyD only a 10% of WIN 51711 was degraded, to the same conditions, after 12 days. DM-beta-CyD increases the permeation of WIN 51711 across excised bovine nasal mucosa mounted on Franz cells, with respect to the free drug. Nevertheless, the permeation process had a lag time of 2 h so that the drug might assure its pharmacological activity on the outer surface of the mucosa. In vivo studies on rabbits evidenced that WIN 51711 is well tolerated, having no observable effect on the nasal mucosa following repeated administration.

Williams R. O., III and Liu J. (1999) Influence of formulation technique for hydroxypropyl-beta-cyclodextrin on the stability of aspirin in HFA 134a. *Eur J Pharm Biopharm* **47**, 145-152.

Abstract: The objective of this study was to determine the influence of the formulation technique for 2-hydroxypropyl-beta-cyclodextrin (HP beta CD) on the stability of aspirin in a suspension-based pressurized metered-dose inhaler (pMDI) formulation containing a hydrofluoroalkane (HFA) propellant. HP beta CD was formulated in a pMDI as a lyophilized inclusion complex or a physical mixture with aspirin. A pMDI formulation containing aspirin alone was used as the control. The chemical stability of aspirin in each

pMDI formulation was determined over 6-months storage at 5, 25 and 40 degrees C. The quantity of water taken up into the pMDI canister was determined by Karl Fisher titration after storage for 6 months. Differential scanning calorimetry (DSC) was used to confirm the formation of a complex between HP beta CD and aspirin. Aspirin in the lyophilized inclusion complex exhibited the most significant degree of degradation during the 6-months storage, while aspirin alone in the pMDI demonstrated a moderate degree of degradation. Aspirin formulated in the physical mixture displayed the least degree of degradation. The water uptake study showed that water ingress occurred to the greatest extent for formulations containing aspirin and HP beta CD physical mixture, and to the least extent for formulations containing aspirin alone. Finally, the DSC study indicated that an inclusion complex was formed in situ in the pMDI formulations containing the HP beta CD and aspirin physical mixture. In conclusion, HP beta CD may be used to enhance the stability of a chemically labile drug, but the drug stability may be affected by the method of preparation of the formulation.

Wong J. W. and Yuen K. H. (2003) Inclusion complexation of artemisinin with alpha-, beta-, and gamma-cyclodextrins. *Drug Dev Ind Pharm* **29**, 1035-1044.

Abstract: The present study was conducted to investigate the inclusion complexation of artemisinin (ART) with natural cyclodextrins (CyD), namely alpha-, beta-, and gamma-CyDs with the aim of improving its solubility and dissolution rate. Complex formation in aqueous solution and solid state was studied by solubility analysis, dissolution, and thermal analysis. Solubility diagrams indicated that the complexation of ART and the three CyDs occurred at a molar ratio of 1:1, and showed a remarkable increase in ART solubility. Moreover, the thermodynamic parameters calculated by using the van't Hoff equation revealed that the complexation process was associated with negative enthalpy of formation and occurred spontaneously. The complexation capability of CyDs with ART increased in the order of alpha- < gamma- < beta-CyDs and could be ascribed to the structural compatibility between the molecular size of ART and the diameter of the CyD cavities. Dissolution profiles of the three complexes demonstrated an increased rate and extent of dissolution compared with those of their respective physical mixtures and a commercial preparation. In solid-state analysis, using differential scanning calorimetry, the gamma-CyD was capable of complexing the highest percentage of ART, followed by beta- and alpha-CyDs. The respective estimated percentage of ART complexed by the CyDs were 85%, 40%, and 12%.

Xia Y., Qiu L. Y., and Jin Y. (2005) [Preparation and characterization of indomethacin/poly(N-isopropylacrylamide)-beta-cyclodextrin complex with temperature-sensitivity]. *Yao Xue Xue Bao* **40**, 187-192.

Abstract: AIM: To synthesize poly(N-isopropylacrylamide)/cyclodextrin conjugate (PNIPA-beta-CD) as thermosensitive drug carrier, incorporate indomethacin into the conjugate and evaluate the drug release from the carrier in vitro. METHODS: PNIPA-beta-CD was synthesized by introducing carboxyl terminated PNIPA into the primary hydroxy group of beta-CD. The obtained conjugate was characterized by FTIR, ¹H NMR and DSC. The indomethacin/PNIPA-beta-CD complex was prepared by lyophilization. In vitro drug release from the complex was carried out at 25 degrees C and 37 degrees C respectively. RESULTS: Thermosensitive PNIPA-beta-CD was synthesized successfully. The LCST is 35 degrees C, as measured by turbidity method. The drug release from indomethacin/PNIPA-beta-CD complex was slower at 37 degrees C than that at 25 degrees C. CONCLUSION: Thermosensitive PNIPA-beta-CD with molecular inclusion capacity is a potential carrier for drug sustained release.

Yap K. L., Liu X., Thenmozhiyal J. C., and Ho P. C. (2005) Characterization of the 13-cis-retinoic acid/cyclodextrin inclusion complexes by phase solubility, photostability, physicochemical and computational analysis. *Eur J Pharm Sci* **25**, 49-56.

Abstract: 13-cis-Retinoic acid (13-cis-RA) is a synthetic retinoid commonly used in the treatment of severe acne. It has also been found to possess potential chemopreventive activity. It has extremely low aqueous solubility and high photo-sensitivity. This study investigated the effects of the complexation of 13-cis-RA with alpha-cyclodextrin (alpha-CD) and hydroxypropyl-beta-cyclodextrin (HP-beta-CD) on its phase solubility. HP-beta-CD was found to be more effective in increasing the aqueous solubility of 13-cis-RA compared to alpha-CD. Phase solubility studies indicated that the solubility of 13-cis-RA was increased dramatically by the formation of inclusion complex with HP-beta-CD. The solubility was further enhanced by pH adjustment. The photostability of the selected inclusion complex of 13-cis-RA:HP-beta-CD was then evaluated. Complexation with HP-beta-CD was found to delay the photo-degradation of 13-cis-RA in

aqueous solution. The physicochemical properties of the solid inclusion complex were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffractometry (XRD). Molecular modeling with MMFF94s force field (SYBYL V6.6) was utilized to predict the preferred orientation of 13-cis-RA in the CD cavity and the main structural features responsible for the enhancement of its solubility and photostability. The energy scores estimated from the computational analysis were found capable of reflecting the stability constants of the cyclodextrin complexes obtained in the phase solubility studies. The results showed that HP-beta-CD was a proper excipient for increasing solubility and stability of 13-cis-RA.

Zannou E. A., Streng W. H., and Stella V. J. (2001) Osmotic properties of sulfobutylether and hydroxypropyl cyclodextrins. *Pharm Res* **18**, 1226-1231.

Abstract: PURPOSE: The purpose of this study was to determine the osmolality of sulfobutylether (SBE) and hydroxypropyl (HP) derivatives of cyclodextrins (CDs) via vapor pressure osmometry (VPO) and freezing point depression (FPD). (SBE) and HP-CDs are efficient excipients capable of solubilizing and stabilizing poorly water-soluble drugs in parenteral formulations. (SBE)-CDs have also been used as solubility enhancers and osmotic agents for the sustained release of poorly water-soluble drugs from osmotic pump tablets. The knowledge of the CD's osmolality in solution or inside such tablets would allow one to further characterize the release mechanisms. METHODS: Experiments were conducted at 37 degrees C with eight types of HP and (SBE)-CDs. The aqueous solutions ranged from 0.005-0.350 mol⁻¹. Methods were developed to allow the measurement of high osmolalities using a vapor pressure osmometer or a differential scanning calorimeter. RESULTS: The osmolality calculations from the VPO and FPD measurements correlated well. The osmolality of (SBE)-CDs was significantly higher than the osmolality of HP-CDs and increased with the total degree of substitution (TDS). All CDs showed deviations from ideality at high concentrations. CONCLUSIONS: Empirical correlations of osmolality with concentration and TDS allowed the prediction of osmolality over a wide concentration range. This study also gave some useful insights into the behavior of CD derivatives in solution.

Zhang A., Liu W., Wang L., and Wen Y. (2005) Characterization of inclusion complexation between fenoxaprop-p-ethyl and cyclodextrin. *J Agric Food Chem* **53**, 7193-7197.

Abstract: Cyclodextrins (CDs) derived from natural starches are capable of forming inclusion complexes with a variety of organic compounds. This work evaluated the complexation role of CDs toward fenoxaprop-p-ethyl (FE) in an attempt to assess their potential as new formulation additives for more efficient FE delivery and better environmental approaches. beta-CD and its two derivatives, randomly methylated beta-CD (RAMEB) and 2-hydroxypropyl beta-CD (HP-beta-CD), were tested. The solubility of FE was enhanced in the presence of the CDs due to the formation of inclusion complexes, with RAMEB being >6 times more effective than the other two. The complexation was confirmed by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD), where the FE melting peaks in DSC, the FTIR bands, and the XRD peaks were generally weakened. Within the tested time up to 60 min, the dissolution of the FE-CD complexes resulted in higher FE concentrations than did that of FE by itself. The dissolution of the FE-RAMEB complex was much faster than other complexes and FE alone. These results indicate that RAMEB was a better inclusion complexation agent for FE in terms of both solubility enhancement and dissolution rate. RAMEB may thus be used to improve FE delivery and to mobilize FE in soil for bioremediation.

Zingone G. and Rubessa F. (2005) Preformulation study of the inclusion complex warfarin-beta-cyclodextrin. *Int J Pharm* **291**, 3-10.

Abstract: Inclusion complex between warfarin and beta-cyclodextrin was obtained to improve the in vitro bioavailability of the drug in acidic media. Inclusion complexation in solution was studied by phase solubility technique. The apparent stability constant was influenced by the pH of the medium ranging from 633.26 M⁽⁻¹⁾ (at pH 1.2, where the drug was in unionised form) to 99.81 M⁽⁻¹⁾ (at pH 7.4, where the drug was in ionised form). Phase solubility study showed an AL-type diagram indicating the formation of an inclusion complex in 1:1 molar ratio. Solid binary mixtures of the drug with beta-cyclodextrin were prepared by several methods (physical mixing, kneading, co-evaporation, freeze-drying). Physicochemical characterizations were performed using differential scanning calorimetry, powder X-ray diffractometry and dissolution studies. Preparation method influenced the physicochemical properties of the binary mixtures. An inclusion complex was obtained by freeze-drying, and it showed a high solubility and drug dissolution

rate. The physical stability of the complex was also studied. After one year storage in glass container at room temperature no significant changes were detected in the diffractogram, thermogram and dissolution profile of the freeze-dried product.