

DSC XVIII: Drug Stability

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Abd-Elrahman M. I., Ahmed M. O., Ahmed S. M., aboul-Fadl T., and El Shorbagi A. (2002) Kinetics of solid state stability of glycine derivatives as a model for peptides using differential scanning calorimetry. *Biophys Chem* **97**, 113-120.

Abstract: Kinetics of solid state stability of seven derivatives of 3,5-disubstituted tetrahydro-2H-1,3,5-thiadiazine-2-thione (THTT) of glycine as a model for amino acids and peptide drugs were studied using differential scanning calorimetry (DSC). Each DSC curve for each derivative showed an endothermic peak followed by an exothermic one, which could be attributed to the melting and decomposition, respectively. The decomposition activation energy of each derivative was calculated using the Augis and Bennet, Kissinger equations and Mahadevan approximation. Also, the melting activation energies as well as the thermodynamic parameter (enthalpy) for the investigated derivatives were evaluated. The relative stability of the derivatives in the solid state according to the calculated values of the decomposition activation energy, frequency factors and half-life for each derivative could be determined.

Abdul-Fattah A. M. and Bhargava H. N. (2002) Preparation and in vitro evaluation of solid dispersions of halofantrine. *Int J Pharm* **235**, 17-33.

Abstract: The low aqueous solubility of halofantrine (HF) and its low bioavailability from commercially available tablets (Halfan) suggested the formulation of solid dispersions (SDs) of HF to reduce its particle size and improve its wettability and aqueous solubility. Preformulation studies involved the development of a high performance liquid chromatography (HPLC) method for the analysis of HF. In addition, solubility studies were conducted on HF in aqueous solutions containing different concentrations of various carriers. Formulation studies included the preparation of SDs and physical mixtures (PMs) of HF with different carriers and their physicochemical characterization using differential scanning calorimetry (DSC), Fourier-Transform infra-red (FT-IR) spectroscopy and dissolution studies. A 3-month stability study at elevated temperatures was conducted on representative SDs of HF with selected carriers.

Aberturas M. R., Molpeceres J., Guzman M., and Garcia F. (2002) Development of a new cyclosporine formulation based on poly(caprolactone) microspheres. *J Microencapsul* **19**, 61-72.

Abstract: The present study describes the development of a new cyclosporine formulation based on polycaprolactone (PCL) microspheres (MS) prepared by the solvent evaporation method. Ternary phase diagrams were used to identify the domains where MS were formed. The application of central composite designs established the influence of several technological (stirring speed) and formulation factors (polymer and surfactant amounts, and organic solvent volume) on the size of PCL MS. Cyclosporine-loaded MS of a size around 2.5 μm were prepared and characterized. The stability of the systems, either alone or loaded with cyclosporine, stored at 8 degrees C and room temperature (RT) was assessed as well. Freeze-drying was evaluated as an alternative method to achieve long-term stability. The experimental design showed that the stirring speed and the organic phase volume were the only parameters significantly affecting the MS size. Experimental conditions selected to obtain CyA-loaded MS of 2.5 μm resulted in a high entrapment percentage (98.4 +/- 0.66%) with the drug dissolved or molecularly dispersed within the dense polymeric matrix of MS. After 12 months of storage at 8 degrees C and RT, PCL MS remained physically stable, although the crystallinity of the polymer increased by 35% upon storage at both temperatures. Freeze-drying studies revealed that MS could be successfully lyophilized in the absence of cryoprotectants without significant changes of the drug entrapment; however, the presence of at least 5% cryoprotectant was essential to keep the initial particle size. Therefore, a stable MS-based CyA formulation was easily prepared and characterized. This formulation offer the possibility of CyA administration through different routes.

Albertini B., Cavallari C., Passerini N., Gonzalez-Rodriguez M. L., and Rodriguez L. (2003) Evaluation of beta-lactose, PVP K12 and PVP K90 as excipients to prepare piroxicam granules using two wet granulation techniques. *Eur J Pharm Biopharm* **56**, 479-487.

Abstract: The present investigation aimed at evaluating the use of different excipients, beta-lactose and polyvinylpyrrolidone of two molecular weights (PVP K12 and PVP K90), in the production of improved release piroxicam granules, by wet granulation using both water and steam as granulation liquid. The

formulations examined were: piroxicam (Px)/beta-lactose; Px/PVP K12 and Px/PVP K90, each one at a 1:9 weight ratio. The most significant difference between beta-lactose and PVP is that, using the first excipient, both steam and water granules were produced while, when PVP were employed, only steam granules were obtained. Image analysis revealed that beta-lactose steam granules had a larger surface area with respect to water granules, whereas lower values of this parameter were observed in PVP-s granules, confirming the Scanning Electron Microscopy micrographs and the fractal analysis results. As regards the enhancement of the dissolution profiles, the best result was obtained using beta-lactose steam granules followed by PVP K12 ones, even if the reactive dimension values indicated that during the dissolution process PVP K12 granules modified the surface more than beta-lactose granules. As regards PVP K90, this excipient was the one less influencing the granule morphology and the dissolution behaviour. Differential Scanning Calorimetry analysis suggested the partial amorphisation of the drug in the granules containing the three excipients. This result was then confirmed by X-ray powder diffraction analysis. Therefore, beta-lactose and PVP K12 could be proposed as useful excipients to enhance the dissolution rate of Px from granules prepared using the steam granulation technique.

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.

Araujo A. A., Storpirtis S., Mercuri L. P., Carvalho F. M., dos Santos F. M., and Matos J. R. (2003) Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. *Int J Pharm* **260**, 303-314.

Abstract: Modern thermal analysis techniques are frequently used because of their ability to provide detailed information about both the physical and the energetic properties of a substance. In the present work, the thermal decomposition of zidovudine (AZT) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Thermal analysis was supplemented using elemental analysis (C, H, and N), infrared (IR) spectroscopy, and X-ray powder diffraction to characterize the solid intermediates products. Volatile products of the thermal decomposition of AZT were studied by a system composed of the TG/DTA coupled gas chromatography/mass spectrometry (GC/MS). The physical-chemical properties and compatibilities of several commonly used pharmaceutical excipients with AZT were evaluated using thermal methods. The results showed that the product originated from the first thermal decomposition stage corresponds to the cleavage followed by elimination of the azide group and consequent formation of thymine. The second event corresponds to thermal decomposition of thymine. TG/DTA-GC/MS system identified thymine's decomposition products as furan and 2-furanmethanol like volatile species. Comparison of the thermoanalytical profiles of the mixtures with individual compounds did not give any evidence of interactions.

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.

Bodek K. H. (2002) Effect of microcrystalline chitosan on the solubility of ibuprofen. *Acta Pol Pharm* **59**, 105-108.

Abstract: It was found that MCCCh may be used for the enhancement of the solubility and dissolution rates of drugs. The solubility of IBA in water increased significantly (about 10-fold) when MCCCh was added. Differential scanning calorimetry (DSC), powder X-ray diffractometry, and IR spectroscopy were used to confirm that salt links between the drug and MCCCh occurred.

Bond L., Allen S., Davies M. C., Roberts C. J., Shivji A. P., Tendler S. J., Williams P. M., and Zhang J. (2002) Differential scanning calorimetry and scanning thermal microscopy analysis of pharmaceutical materials. *Int J Pharm* **243**, 71-82.

Abstract: Micro-thermal analysis (microTA) by scanning thermal microscopy is being used increasingly for the analysis of pharmaceutical dosage forms. However, there is currently little evidence to show that microTA data can compare directly with that from the established approach of differential scanning

calorimetry (DSC). This work compares DSC and microTA data from an active vitamin B6 analogue, pyridoxal hydrochloride, and two commonly used pharmaceutical excipients, Mannitol and Avicel which are used in its formulation. It is found that microTA provides precise and accurate micro-thermal analytical data with 0.1 K thermal sensitivity, which is comparable to that obtained by DSC measurements of bulk samples. It is also shown that microTA offers the opportunity to study single particles and the interfacial region between particles, data which is currently inaccessible through the DSC technique.

Brodka-Pfeiffer K., Langguth P., Grass P., and Hausler H. (2003) Influence of mechanical activation on the physical stability of salbutamol sulphate. *Eur J Pharm Biopharm* **56**, 393-400.

Abstract: In order to obtain the optimal particle size distribution for pharmaceutical powders in dry powder inhalers the particles have to be micronised. In most cases the process of micronisation is connected with a high input of energy which induces disorder and defects on the surface of the drug particles and as a result changes in the crystallinity. Consequently, changes in the physical stability of the powders may occur. To investigate changes on the physical stability of the powder, different analytical methods are used in the present investigation: laser diffraction, Differential Scanning Calorimetry (DSC), isothermal microcalorimetry and DVS-method. Air-jet-milling is one of the most frequently used techniques in the pharmaceutical industry, in order to obtain particles of respirable size. In the treatise described here the influence of the critical parameters of the process, i.e. feed pressure, grind pressure and feed rate is assessed for salbutamol sulphate. The grind pressure is of utmost importance with respect to particle size distribution and the physical powder stability. For salbutamol sulphate, ground with a MC Jetmill 50, a grind pressure of 6 bar has been found optimal. Pressures below 6 bar are not sufficient to produce the required reduction in particle size. The feed pressure and rate have negligible influence on the powder quality. Furthermore, the micronisation process is optimised to achieve respirable particles while minimising the amorphous content. A correlation between mechanical activation and the amount of the amorphous regions is showed clearly. Air-jet-milling has been compared to ball milling in this investigation. In pilot tests ball milling was not suitable to achieve the needed particle size distribution, however, it generates a specific quantity of amorphous material. With the help of specific amorphous regions in the powder, the sensitivity of the used methods for salbutamol sulphate can be examined.

Burger A. and Lettenbichler A. (2000) Polymorphism and preformulation studies of lifibrol. *Eur J Pharm Biopharm* **49**, 65-72.

Abstract: Three polymorphic modifications of lifibrol, a novel cholesterol-lowering drug substance, were detected and thoroughly investigated and characterized by thermomicroscopy, DSC, IR-spectroscopy and X-ray powder diffractometry. Mod. I (m.p. 142 degrees C) and mod. II (m.p. 135 degrees C) are stable. Furthermore, true densities, solubilities as function of temperature and pH-value as well as the behavior of the crystal forms under the influence of humid air were determined. The three modifications show distinct differences by IR-spectroscopy, through which a distinction even is possible. The density of mod. I is lower than that of mod. II. The transition of mod. II into mod. I corresponds to an endothermic reaction; from this it follows, that between mod. I and mod. II enantiotropism exists. Mod. II is at 20 degrees C by about 44% less soluble as mod. I. Mod. III, which only can be produced by crystallizing the glassy solidified melt, has a negative heat of transition. That means that mod. III behaves monotropic with regard to both enantiotropic modifications I and II. Mod. I exists in form of small lamellae, mostly of irregular forms. Mod. II consists of rhombohedron grains. Because of this difference in habit, for mod. II one can predict the best properties in case of pressing tablets.

Bustamante P., Pena M. A., and Barra J. (1998) Partial-solubility parameters of naproxen and sodium diclofenac. *J Pharm Pharmacol* **50**, 975-982.

Abstract: The expanded Hansen method was tested for determination of the solubility parameters of two non-steroidal anti-inflammatory drugs, naproxen and sodium diclofenac. This work describes for the first time the application of the method to the sodium salt of a drug. The original dependent variable of the expanded Hansen method, involving the activity coefficient of the drug, was compared with the direct use of the logarithm of the mole fraction solubility $\ln X_2$ in the solubility models. The solubility of both drugs was measured in pure solvents of several chemical classes and the activity coefficient was obtained from the molar heat and the temperature of fusion. Differential scanning calorimetry was performed on the original powder and on the solid phase after equilibration with the pure solvents, enabling detection of possible changes of the thermal properties of the solid phase that might change the value of the activity

coefficient. The molar heat and temperature of fusion of sodium diclofenac could not be determined because this drug decomposed near the fusion temperature. The best results for both drugs were obtained with the dependent variable $\ln X_2$ in association with the four-parameter model which includes the acidic and basic partial-solubility parameters $\Delta(a)$ and $\Delta(b)$ instead of the Hansen hydrogen bonding parameter $\Delta(h)$. Because the dispersion parameter does not vary greatly from one drug to another, the variation of solubility among solvents is largely a result of the dipolar and hydrogen-bonding parameters, a fact that is being consistently found for other drugs of small molecular weight. These results support earlier findings with citric acid and paracetamol that the expanded Hansen approach is suitable for determining partial-solubility parameters. The modification introduced in the expanded Hansen method, i.e. the use of $\ln X_2$ as the dependent variable, provides better results than the activity coefficient used in the original method. This is advantageous for drugs such as sodium diclofenac for which the ideal solubility cannot be estimated. This paper shows for the first time that the method is suitable for determination of the partial-solubility parameters of a sodium salt of a drug, sodium diclofenac.

Bustamante P., Romero S., Pena A., Escalera B., and Reillo A. (1998) Enthalpy-entropy compensation for the solubility of drugs in solvent mixtures: paracetamol, acetanilide, and nalidixic acid in dioxane-water. *J Pharm Sci* **87**, 1590-1596.

Abstract: In earlier work, a nonlinear enthalpy-entropy compensation was observed for the solubility of phenacetin in dioxane-water mixtures. This effect had not been earlier reported for the solubility of drugs in solvent mixtures. To gain insight into the compensation effect, the behavior of the apparent thermodynamic magnitudes for the solubility of paracetamol, acetanilide, and nalidixic acid is studied in this work. The solubility of these drugs was measured at several temperatures in dioxane-water mixtures. DSC analysis was performed on the original powders and on the solid phases after equilibration with the solvent mixture. The thermal properties of the solid phases did not show significant changes. The three drugs display a solubility maximum against the cosolvent ratio. The solubility peaks of acetanilide and nalidixic acid shift to a more polar region at the higher temperatures. Nonlinear van't Hoff plots were observed for nalidixic acid whereas acetanilide and paracetamol show linear behavior at the temperature range studied. The apparent enthalpies of solution are endothermic going through a maximum at 50% dioxane. Two different mechanisms, entropy and enthalpy, are suggested to be the driving forces that increase the solubility of the three drugs. Solubility is entropy controlled at the water-rich region (0-50% dioxane) and enthalpy controlled at the dioxane-rich region (50-100% dioxane). The enthalpy-entropy compensation analysis also suggests that two different mechanisms, dependent on cosolvent ratio, are involved in the solubility enhancement of the three drugs. The plots of ΔH versus ΔG are nonlinear, and the slope changes from positive to negative above 50% dioxane. The compensation effect for the thermodynamic magnitudes of transfer from water to the aqueous mixtures can be described by a common empirical nonlinear relationship, with the exception of paracetamol, which follows a separate linear relationship at dioxane ratios above 50%. The results corroborate earlier findings with phenacetin. The similar pattern shown by the drugs studied suggests that the nonlinear enthalpy-entropy compensation effect may be characteristic of the solubility of semipolar drugs in dioxane-water mixtures.

Bustamante P., Navarro J., Romero S., and Escalera B. (2002) Thermodynamic origin of the solubility profile of drugs showing one or two maxima against the polarity of aqueous and nonaqueous mixtures: niflumic acid and caffeine. *J Pharm Sci* **91**, 874-883.

Abstract: The purpose of this work was to investigate the origin of the different solubility profiles of drugs against the polarity of solvent mixtures with a common cosolvent. Niflumic acid and caffeine were chosen as model drugs. The solubilities were measured at five or six temperatures in aqueous (ethanol-water) and nonaqueous (ethyl acetate-ethanol) mixtures. The enthalpies of solution were obtained at the harmonic mean of the experimental temperature. Solid phase changes were analyzed using differential scanning calorimetry and thermomicroscopy. A single solubility maximum was obtained for niflumic acid against the solubility parameter of both mixtures that is not related to solid phase changes. In contrast, caffeine displays two maxima and anhydrous-hydrate transition occurs at the solubility peak in the amphiprotic mixture. The apparent enthalpies of solution of both drugs show endothermic maxima against solvent composition that are related to hydrophobic hydration. A general explanation for the cosolvent action in aqueous mixtures is proposed. The dominant mechanism shifts from entropy to enthalpy at a certain cosolvent ratio dependent on the hydrophobicity and the solubility parameter of the drug. Niflumic acid and caffeine show enthalpy-entropy compensation in ethanol-water, and this relationship is demonstrated for

the first time in nonaqueous mixtures. The results support that enthalpy-entropy compensation is a general effect for the solubility of drugs in solvent mixtures. The shape of the solubility curves is correlated with the compensation plots. The solubility peaks separate different enthalpy-entropy relationships that also differentiate the solubility behavior of the hydrate and the anhydrous forms of caffeine.

Caira M. R., Bettinetti G., and Sorrenti M. (2002) Structural relationships, thermal properties, and physicochemical characterization of anhydrous and solvated crystalline forms of tetroxoprim. *J Pharm Sci* **91**, 467-481.

Abstract: Six distinct phases of the antibacterial tetroxoprim (TXP) have been isolated by recrystallization from various solvents. These comprise two polymorphs, forms I and II, and four solvates with the following solvents and TXP solvent stoichiometric ratios: chloroform (3:2), water (3:2), methanol (2:1), and ethanol (2:1). Thermal and infrared spectral data showed that forms I and II are enantiotropically related with form II being stable below the transition temperature of 118 degrees C and form I melting at 159 degrees C. The crystal structure of form I contains three crystallographically independent TXP molecules arranged in layers formed by extensive base pairing between the 2,4-diaminopyrimidine rings. This species invariably results upon heating the solvates of TXP. Thermogravimetry and differential scanning calorimetry respectively showed one-step mass losses and progressively increasing desolvation temperatures for the solvates with chloroform, water, ethanol, and methanol. X-ray diffraction studies revealed that the latter three solvates are isostructural, belonging to the class of "isolated site" solvates. Extensive base pairing maintains the common TXP crystalline framework. Thermal data for the desolvation of these phases are reconciled with the observed crystal packing features. Experimental and computed powder X-ray patterns for form I and the solvates with water, methanol, and ethanol are presented.

Caira M. R., Bettinetti G., Sorrenti M., and Catenacci L. (2003) Order-disorder enantiotropy, monotropy, and isostructurality in a tetroxoprim-sulfametrole 1:1 molecular complex: Crystallographic and thermal studies. *J Pharm Sci* **92**, 2164-2176.

Abstract: Two enantiotropic polymorphs of a tetroxoprim (TXP)-sulfametrole (SMTR) 1:1 molecular complex monohydrate and two isostructural TXP-SMTR 1:1 molecular complex solvates with methanol and ethanol were grown and studied by X-ray diffraction and thermal methods (thermogravimetric analysis and differential scanning calorimetry). Interconversion of the polymorphic hydrates is essentially an order/disorder transition involving a substituent on the TXP molecule. These hydrated phases may be described as "nearly isostructural" with the methanol and ethanol solvates. Thermal data for decomposition of the solvates were rationalized on the basis of the location and topologies of solvent crystallographic sites. Solid-state properties of two monotropic polymorphs of the unsolvated TXP-SMTR 1:1 molecular complex were also investigated and the theoretical and experimental phase diagrams of the individual components were assessed. The existence of polymorphic and pseudopolymorphic forms is determined by conformational flexibility of the TXP-SMTR bimolecular complex components, a tendency for molecular disorder in TXP, the ability of the drug complex to form intricate, highly stabilized hydrogen-bonded frameworks, and the competition between nonspecific van der Waals and specific hydrogen bond interactions.

Cavallari C., Albertini B., Gonzalez-Rodriguez M. L., Rodriguez L., and Abertini B. (2002) Improved dissolution behaviour of steam-granulated piroxicam. *Eur J Pharm Biopharm* **54**, 65-73.

Abstract: In this paper we prepared and characterized improved release granulates containing Piroxicam and beta-cyclodextrins (1:2.5 molar ratio), obtained by steam-aided granulation, using a one-step rotogranulator, Rotolab. These granulates were compared to those prepared by traditional wet granulation, to the physical mixture, and to the kneaded and dry granulates. The experimental data showed a significant reduction of the water amount required (50%) and of the working time, with respect to traditional wet granulation. The samples examined by scanning electron microscopy and fractal analysis revealed morphological differences related to the method of preparation: the steam-granulated material showed a diffuse porosity, as confirmed by the porosity test. Differential scanning calorimetry, infrared and X-ray analysis revealed the absence of polymorphs in the solid state of the drug. The results of the dissolution tests suggest that the steam-aided granulation may be considered a useful method to improve the in vitro dissolution rate of Piroxicam, enabling also a considerable reduction in the processing time.

Ceschel G. C., Badiello R., Ronchi C., and Maffei P. (2003) Degradation of components in drug formulations: a comparison between HPLC and DSC methods. *J Pharm Biomed Anal* **32**, 1067-1072.

Abstract: Information about the stability of drug components and drug formulations is needed to predict the shelf-life of the final products. The studies on the interaction between the drug and the excipients may be carried out by means of accelerated stability tests followed by analytical determination of the active principle (HPLC and other methods) and by means of the differential scanning calorimetry (DSC). This research has been focused to the acetyl salicylic acid (ASA) physical-chemical characterisation by using DSC method in order to evaluate its compatibility with some of the most used excipients. It was possible to show, with the DSC method, the incompatibility of magnesium stearate with ASA; the HPLC data confirm the reduction of ASA concentration in the presence of magnesium stearate. With the other excipients the characteristic endotherms of the drug were always present and no or little degradation was observed with the accelerated stability tests. Therefore, the results with the DSC method are comparable and in good agreement with the results obtained with other methods.

Chadha R., Kashid N., and Jain D. V. (2003) Microcalorimetric studies to determine the enthalpy of solution of diclofenac sodium, paracetamol and their binary mixtures at 310.15 K. *J Pharm Biomed Anal* **30**, 1515-1522.

Abstract: A sensitive and selective microcalorimetric technique has been used to determine the enthalpy of solution of diclofenac sodium (DS), paracetamol (PC) and their binary mixtures over a wide range of composition in the pH range 4-12. The systems showed endothermic behavior. The molar enthalpies of solutions of DS vary between 42.26 \pm 0.16 and 50.48 \pm 0.03 kJ mol⁻¹ at pH 4-9 and for PC from 24.28 \pm 0.05 to 36.03 \pm 0.01 kJ mol⁻¹ at pH 5-12. The excess molar enthalpy of their mixtures has also been determined. The values of excess molar enthalpy of solutions are negative and very low in magnitude indicating no specific interaction between DS and PC in solution.

Chadha R., Kashid N., and Jain D. V. (2003) Kinetics of degradation of diclofenac sodium in aqueous solution determined by a calorimetric method. *Pharmazie* **58**, 631-635.

Abstract: An isothermal heat conduction microcalorimeter has been used to study the stability of diclofenac sodium both alone and its inclusion complex with beta-cyclodextrin in aqueous solution. The rates of heat evolved during degradation of diclofenac sodium have been measured by a highly sensitive microcalorimetric technique as function of concentration, pH and temperature. The calorimetric accessible data have been incorporated in the equations for determination of rate constants, change in enthalpy and order of reaction. The decomposition of diclofenac sodium both alone and its inclusion complex with beta-cyclodextrin in solution corresponds to a pseudo-first order reaction. The values of rate constants, k's at 338.15 K, (calculated from the variation of heat evolution with the time) for the degradation of diclofenac sodium at pH 5, 6, 7, 8 and its inclusion complex with beta-cyclodextrin at pH 7 are found to be 4.71 x 10⁻⁴, 5.69 x 10⁻⁴, 6.12 x 10⁻⁴, 6.57 x 10⁻⁴ and 4.26 x 10⁻⁴ h⁻¹ respectively. There is good agreement between calorimetric determined t(0.5) and literature values. It has been found that beta-cyclodextrin retards the degradation of diclofenac sodium. The kinetic parameters have been calculated for the reaction. The negative entropy of activation suggests the formation of an ordered transition state.

Damian F., Blaton N., Kinget R., and Van den M. G. (2002) Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire 44/14 and PVP K30. *Int J Pharm* **244**, 87-98.

Abstract: This paper describes the physical stability of solid dispersions of UC-781 with PEG 6000, Gelucire 44/14 and PVP K30 prepared by the solvent and melting methods. The concentration of the drug in the solid dispersions ranged from 5 to 80% w/w. The solid dispersions were stored at 4-8 and 25 degrees C (25% RH), then their physicochemical properties were analysed by differential scanning calorimetry (DSC), X-ray powder diffraction and dissolution studies as a function of storage time. The DSC curves of solid dispersions of UC-781 with PVP K30 did not show any melting peaks corresponding to UC-781 after storage, indicating no recrystallization of the drug. The DSC data obtained from PEG 6000 and Gelucire 44/14 showed some variations in melting peak temperatures and enthalpy of fusion of the carriers. It was shown that the enthalpy of fusion of PEG 6000 in the dispersions increased after storage; it was more pronounced for samples stored at 25 degrees C compared to those at 4-8 degrees C indicating the reorganization of the crystalline domains of the polymer. Similarly, the enthalpy of fusion of Gelucire 44/14 in the solid dispersions increased as a function of time. Dissolution of UC-781 from all solid dispersions decreased as a function of storage time. While these observations concurred with the DSC data

for all solid dispersions, they were not reflected by X-ray powder diffraction data. It was concluded that it is the change of the physical state of the carriers and not that of the drug, which is responsible for the decreased dissolution properties of the solid dispersions investigated.

Eriksson J. H., Hinrichs W. L., de Jong G. J., Somsen G. W., and Frijlink H. W. (2003) Investigations into the stabilization of drugs by sugar glasses: III. The influence of various high-pH buffers. *Pharm Res* **20**, 1437-1443.

Abstract: PURPOSE: To study the effect of the high-pH buffers ammediol, borax, CHES, TRIS, and Tricine on the glass transition temperature of the freeze concentrated fraction (Tg') of trehalose/buffer and inulin/buffer solutions at pH 6.0 and pH 9.8. Also, the glass transition temperature (Tg) of sugar glasses obtained after freeze drying of these solutions was elucidated. Additionally, the effect occurring during the freezing process on the pH of the various buffers was investigated. Furthermore, the stability of alkaline phosphatase (AP) incorporated in these sugar glasses prepared from solutions at pH 9.8 was evaluated. METHODS: The Tg' and Tg were measured using differential scanning calorimetry (DSC), and the change of pH during freezing was estimated by using an indicator solution added to the respective solutions. The enzymatic activity of AP after freeze drying and storage at 60 degrees C was evaluated by an enzymatic activity assay. RESULTS: It was found that the Tg' and Tg of the samples investigated are strongly influenced by the presence of the buffer. On freezing, only minor changes of the pH were observed. The samples with the lowest Tg and the samples containing buffers that formed complexes with the sugars showed the poorest stability of the AP. CONCLUSIONS: The stabilizing capacities of sugars that are currently recognized as excellent stabilizers for proteins during drying and storage can be completely lost if certain high-pH buffers such as ammediol, borax, and TRIS are used at high concentrations. Loss of stabilizing capacities can be ascribed to strong depression of the Tg' and Tg or to complex formation.

Fathy M., Hassan M. A., and Mohamed F. A. (2002) Differential scanning calorimetry to investigate the compatibility of ciprofloxacin hydrochloride with excipients. *Pharmazie* **57**, 825-828.

Abstract: The compatibility between ciprofloxacin hydrochloride (CFX) and some excipients was evaluated using differential scanning calorimetry (DSC). Physical mixture, coground mixture, compressed mixture and kneaded mixture were prepared to study the effect of sample manipulation. In addition, the samples of physical mixture were also accelerated at 55 degrees C for three weeks to obtain more reliable conclusions. Different types of excipients currently used in tablet or capsule formulations namely, calcium phosphate dibasic dihydrate (Emcompress), magnesium stearate lactose, sorbitol, mannitol, croscarmellose sodium (Ac-Di-Sol), sodium carboxymethyl starch (Primojel), microcrystalline cellulose (Avicel PH 101, Emcocil) were examined. The DSC scan of CFX displayed two endothermic peaks probably as a result of a fusion process followed by a decomposition process. CFX appeared to interact with sorbitol, mannitol, Ac-Di-Sol, Primojel, Avicel PH 101 and Emcocil.

Filipovic-Grcic J., Perissutti B., Moneghini M., Voinovich D., Martinac A., and Jalsenjak I. (2003) Spray-dried carbamazepine-loaded chitosan and HPMC microspheres: preparation and characterisation. *J Pharm Pharmacol* **55**, 921-931.

Abstract: In this study, the potential of the spray-drying technique for preparing microspheres able to modify the release profile of carbamazepine was investigated. Low-, medium- and high-molecular-weight chitosan and hydroxypropyl methylcellulose (HPMC) in different drug-polymer ratios were used for the preparation of microspheres. The microspheres, characterized by X-ray powder diffractometry (XRD) and differential scanning calorimetry (DSC), were also studied with respect to particle size distribution, drug content and drug release. The results indicated that the entrapment efficiency (EE), as well as carbamazepine release profile, depended on polymeric composition and drug-polymer ratios of the microspheres prepared. The best entrapment efficiencies were obtained when chitosan of low-molecular-weight (CL) or HPMC were used for the microencapsulation. For all types of polymer used, the microspheres with low carbamazepine loading (6.3% w/w) showed better control of drug release than the microspheres with higher drug loadings. The HPMC microspheres showed the slowest carbamazepine release profile with no initial burst effect. Carbamazepine release profiles from ternary systems, carbamazepine-CL-HPMC microspheres, depended mostly on HPMC content and showed similar carbamazepine release profile as CL microspheres when HPMC content was low (9:1 CL-HPMC ratio, w/w). Otherwise, the carbamazepine release from CL-HPMC microspheres was remarkably faster than

from either chitosan or HPMC microspheres. The release profile of carbamazepine from the microspheres was highly correlated with the crystalline changes occurring in the matrix.

Ganguly S., Jayappa S., and Dash A. K. (2003) Evaluation of the stability of creatine in solution prepared from effervescent creatine formulations. *AAPS PharmSciTech* **4**, E25.

Abstract: The objectives of this study were to determine the cause of the crystallization in a large volume creatine supplement solution made from effervescent powders containing di-creatine citrate, and to characterize these crystals using thermal analyses and x-ray diffractometry. Creatine effervescent powders were dissolved in deionized water (pH 6.2) and stored both at room temperature (RT) (25 degrees C) and refrigerated condition (4 degrees C) over a period of 45 days. Creatine concentration was determined using high-performance liquid chromatography (HPLC). Intrinsic dissolution and saturated solubility of creatine, creatine monohydrate, and di-creatine citrate in water were determined and compared. Crystal growth was detected only in the refrigerated samples on the seventh day of storage. Differential Scanning Calorimetry (DSC) and x-ray diffraction (XRD) studies revealed that the crystals formed were of creatine monohydrate. Ninety percent creatine degradation was observed within 45 days for RT samples. However, at refrigerated condition this degradation was 80% within the same time period. The pH of the RT samples also increased from 3.6 to 4.5 during storage. No such increase was observed in the case of refrigerated samples. The intrinsic dissolution rate constants of the compounds decreased in the following order: di-creatine citrate > creatine > creatine monohydrate. In conclusion, di-creatine citrate used in effervescent formulation dissociates to creatine in aqueous solution and eventually crystallizes out as creatine monohydrate. Significant decrease in solubility and effect of pH contribute to this crystallization process.

Gloger O., Witthohn K., and Muller B. W. (2003) Lyoprotection of aviscumine with low molecular weight dextrans. *Int J Pharm* **260**, 59-68.

Abstract: The aim of this research was to ascertain whether dextrans with low molecular weight will stabilize aviscumine. During freeze-drying increasing concentrations of dextran T1 (MW 1000) stabilized aviscumine. Eight percent of dextran resulted in a nearly 100% recovery of the activity and in addition a complete amorphous structure of the solid phase was obtained. By decreasing the molecular weight of the dextran from 75 to 1 kDa, the protein activity was increased by 20% in the lyophilisate. Combinations of dextran with either trehalose or mannitol showed no additional effects on stability. The improved stabilization of aviscumine using low molecular weight dextrans is explained by an increased interaction between the protein and the dextran molecules (like hydrogen bonds), whereas they are sterically hindered if larger dextran molecules are used. When the protein concentration was increased from 10 to 100 µg/ml (in formulas with 8% dextran T1), no influence on the protein activity could be found. With regard to the carbohydrate-binding activity of the protein, it was shown that the optimal content of residual water in the lyophilisate should be about 2%. Above and below this percentage a destabilization of the protein was observed. The often discussed failure of dextran as a stabilizing excipient in the freeze-drying of proteins seems to be a question of the selection of the correct molecular weight.

Hirasawa N., Ishise S., Miyata H., and Danjo K. (2003) An attempt to stabilize nilvadipine solid dispersion by the use of ternary systems. *Drug Dev Ind Pharm* **29**, 997-1004.

Abstract: Firstly, we investigated the physical stability of nilvadipine (NIL)/crospovidone (cl-PVP) solid dispersion during storage (40 degrees C, 75% relative humidity) with powder x-ray diffraction, differential scanning calorimetry (DSC) and dissolution test. These studies indicated that recrystallization occurred during storage and that the dissolution of NIL greatly decreased, compared with that of the initial finding. Secondly, to improve the amorphous form physical stability of NIL, methylcellulose (MC) was added to NIL/cl-PVP solid dispersions as a dispersion carrier and NIL/cl-PVP/MC ternary solid dispersion systems were obtained by the solvent method. Powder x-ray diffraction and DSC studies indicated that the amorphous form physical stability of NIL clearly improved in the NIL/cl-PVP/MC solid dispersion systems during storage. Moreover, the dissolution properties of NIL/cl-PVP/MC solid dispersion systems were characterized by cl-PVP markedly enhancing the dissolution of NIL and MC inhibiting the change of the dissolution of NIL during storage. Finally, we obtained an ideal solid dispersion that was accompanied by a consistently higher rate of dissolution.

Juppo A. M., Boissier C., and Khoo C. (2003) Evaluation of solid dispersion particles prepared with SEDS. *Int J Pharm* **250**, 385-401.

Abstract: Formation of solid solution particles in the Solution Enhanced Dispersion by Supercritical fluids (SEDS) process from a model drug and two different types of carriers, mannitol and Eudragit E100 was evaluated. The crystal properties of samples and molecular interactions were investigated with DSC and FTIR, respectively. The effect of co-crystallisation of drug and mannitol on dissolution rate was studied. Even if a true one-phase solid dispersion was not obtained, the crystal structure of both drug and mannitol was mutually affected by the presence of the other. The drug was not in highly crystalline form in the co-precipitates. The interactions between the drug and mannitol could also be identified as hydrogen bonding between the amine or hydroxyl groups of the drug and the hydroxyl groups of mannitol. These interactions and changes in the crystal structure are probably directly related to the increase in the dissolution rate observed. A true solid solution was obtained when the drug was co-processed with Eudragit E100. A clear interaction between the acid hydroxyl group of the drug and the basic carbonyl group on the Eudragit E100 was observed. SEDS was shown to be an effective process for forming intimate blends and solid solutions for the drug and two different types of carriers.

Kawakami K., Numa T., and Ida Y. (2002) Assessment of amorphous content by microcalorimetry. *J Pharm Sci* **91**, 417-423.

Abstract: The amorphous content of model drugs was evaluated by isotherm microcalorimetry. Two model drugs were employed; lactose as a hydrophilic one and erythromycin as a hydrophobic one. When amorphous lactose was loaded in a sample cell with a water vial, a sharp exothermic peak due to the crystallization was observed. When a mixture of the amorphous and the crystalline forms was loaded, the peak area of the exothermic heat flow was proportional to the amorphous content. Quantification could be done with much higher accuracy than by the X-ray powder diffraction method reported in earlier literature. When erythromycin was used as a model drug, the crystallization was not completed by water but by organic solvents, which can dissolve erythromycin. The most adequate solvent for erythromycin was acetonitrile, of which the suitability was elucidated in terms of solubility and vapor pressure. This is the first report in which the role of the vapor pressure on crystallization behavior is discussed. The time needed to obtain the crystallization peak was controlled by mixing acetonitrile with water. The strategy to obtain the crystallization peak by microcalorimetry, which enables quantification of the amorphous content with high accuracy, is discussed.

Kawakami K. and Ida Y. (2003) Direct observation of the enthalpy relaxation and the recovery processes of maltose-based amorphous formulation by isothermal microcalorimetry. *Pharm Res* **20**, 1430-1436.

Abstract: PURPOSE: The applicability of isothermal microcalorimetry (IMC) for evaluating enthalpy relaxation and recovery processes of amorphous material was assessed. METHODS: A maltose-based formulation was prepared by freeze-dry method. Differential scanning calorimetry (DSC) was used to investigate its glass transition and relaxation behaviors. IMC was applied to quantitatively analyze the relaxation and the recovery processes. The IMC data were analyzed using a derivative of the Kohlrausch-Williams-Watts equation. RESULTS: The glass transition temperature of the formulation and its fictive temperature stored at 15 degrees C for 1 year were 62 and 32 degrees C, respectively. DSC study showed that annealing below the fictive temperature increased the enthalpy recovery, but it was decreased by annealing at higher temperatures. IMC enabled direct observation of the heat flow during both the relaxation and the recovery processes. The decay constant for the recovery process (recovery time) was much smaller and less sensitive to the temperature than that for the relaxation process (relaxation time). CONCLUSIONS: IMC was successfully used to obtain quantitative information on both relaxation and recovery processes of amorphous material. The relaxation parameters obtained by this method could explain the thermodynamic behavior of the formulation.

Kinoshita M., Baba K., Nagayasu A., Yamabe K., Shimooka T., Takeichi Y., Azuma M., Houchi H., and Minakuchi K. (2002) Improvement of solubility and oral bioavailability of a poorly water-soluble drug, TAS-301, by its melt-adsorption on a porous calcium silicate. *J Pharm Sci* **91**, 362-370.

Abstract: The aim of the present study was to improve the solubility and oral bioavailability of a poorly water-soluble drug, 3-bis(4-methoxyphenyl) methylene-2-indolinone (TAS-301), by its melt-adsorption on a porous calcium silicate, Florite RE (FLR), without any solvents. The melt-adsorbed products were prepared by two methods: the small-scale batch method and the twin screw extruder method. The drug was melted and adsorbed on FLR (i.e., "melt-adsorption"), above its melting point. Crystallinity of the drug in the melt-adsorbed product was estimated by differential scanning calorimetry (DSC) and powder X-ray

diffraction analysis. The dissolution test was conducted by the JP XIII paddle method. Oral absorption of the melt-adsorbed product was studied in fasted and fed dogs. The melt-adsorbed products prepared by the two methods were in powder forms. The drug existed in an amorphous state in the product and hardly recrystallized even after storing at a stressed condition (60 degrees C/80% RH for 3 days). The TAS-301 dissolution rate from the melt-adsorbed product was markedly enhanced compared with drug crystals. The area under the plasma concentration-time curve (AUC) and peak concentration (C(max)) values of the drug after dosing the melt-adsorbed product were significantly greater than those after dosing the drug crystals. The solubility and bioavailability of TAS-301 were improved by its melt-adsorption on FLR. The present findings suggest melt-adsorption is a useful technique for improving solubility and bioavailability of poorly water-soluble drugs.

Lechuga-Ballesteros D., Abdul-Fattah A., Stevenson C. L., and Bennett D. B. (2003) Properties and stability of a liquid crystal form of cyclosporine—the first reported naturally occurring peptide that exists as a thermotropic liquid crystal. *J Pharm Sci* **92**, 1821-1831.

Abstract: A new solid-state form of cyclosporine produced by spray-drying exhibited characteristics consistent with a liquid crystal. No sharp diffraction peaks were observed by powder X-ray diffraction; however, analysis by both small-angle X-ray diffraction (SAXR) and microscopic under polarized light (PLM) confirmed the existence of two-dimensional ordered liquid crystal. Hot stage microscopy revealed a solid-to-liquid transition, in the range of 118 to 125 degrees C. Moreover, the solid-to-liquid transition showed frequency dependence by dielectric analysis (DEA), and was coincidental with a stepwise heat capacity change measured by differential scanning Calorimetry (DSC). The two-dimensional order was maintained above the solid-to-liquid transition temperature indicated by low-angle diffraction by SAXR and birefringence by PLM. However, birefringence was lost at temperatures above 170 degrees C, indicating the conversion of the liquid crystal into an isotropic liquid. In situ annealing experiments, by DSC, revealed the presence of an endotherm, unexplained by either a phase transition or solvent loss, and it is believed to be the result of a structural rearrangement that has no impact on the macroscopic properties of the material. Spray-dried cyclosporine at room temperature is therefore a frozen thermotropic liquid crystal due to the presence of two-dimensional order and the lack of substantial residual solvent. This is, to our knowledge, the first report of the existence of a thermotropic liquid crystal of a naturally occurring peptide.

Li J., Masso J., and Guertin J. (2002) Prediction of drug solubility in an acrylate adhesive based on the drug-polymer interaction parameter and drug solubility in acetonitrile. *J Control Release* **83**, 211-221.

Abstract: This paper describes the correlation of drug solubility in isoocetyl acrylate/acrylamide/vinyl acetate (IOA/ACM/VOAc, 75:5:20) adhesive with a relative drug-polymer interaction parameter. This parameter, defined previously as the amount of molecules (L_n) sorbed onto the adhesive when swollen by acetonitrile (ACN) [J. Controlled Release 82 (2002) 1], represents the differential interaction of drug with the adhesive relative to ACN. When the drug solubility in the adhesive (L_n) and ACN (L_n) are used to describe drug-polymer and drug-ACN interactions, the following linear relationship is expected: $L_n = L_n(0) + pL_n + qL_n$ (p and q are coefficients). This model is evaluated by the drug solubility in the adhesive measured by differential scanning calorimetry (DSC), and drug solubility in ACN. It is concluded that there is an excellent linear relationship for the parameters involved. As a result, the model can be used to compute the solubility in the polymer for new drug candidates. Moreover, the amount of sorbed molecules and solubility in ACN can be either easily measured or computed based on their molecular properties.

Li J., Guo Y., and Zografi G. (2002) Effects of a citrate buffer system on the solid-state chemical stability of lyophilized quinapril preparations. *Pharm Res* **19**, 20-26.

Abstract: PURPOSE: The objective of this study was to examine the effect of a citric acid-citrate buffer system on the chemical instability of lyophilized amorphous samples of quinapril hydrochloride (QHCl). METHODS: Molecular dispersions of QHCl and citric acid were prepared by colyophilization from their corresponding aqueous solutions with a molar ratio of QHCl to citric acid from 1:1 to 6:1 and solution pH from 2.49 to 3.05. Solid samples were subjected to a temperature of 80 degrees C and were analyzed for degradation using high-performance liquid chromatography. The glass transition temperature, T_g , of all samples was measured by differential scanning calorimetry. RESULTS: Samples were first examined by varying the T_g and maintaining the initial solution pH constant. At pH 2.49 the rate of reaction was found

to be less dependent on the sample Tg, whereas at $\text{pH} \geq 2.75$ the rate decreased with an increase in Tg. In a second set of experiments at a constant Tg of approximately 70 degrees C, the reaction rate increased as the pH increased. CONCLUSION: The overall solid-state chemical reactivity of amorphous quinapril depends on the relative amount of QHCl and Q⁺-, the zwitterionic form of quinapril. At high proportions of Q⁺- (higher pH values) the reaction rate seems to be strongly influenced by the Tg of the mixture, and hence the molecular mobility, whereas at higher proportions of QHCl (lower pH) the reaction rate is less sensitive to Tg, presumably because of different mechanistic rate determining steps for the two sets of conditions.

Longer M., Shetty B., Zamansky I., and Tyle P. (1995) Preformulation studies of a novel HIV protease inhibitor, AG1343. *J Pharm Sci* **84**, 1090-1093.

Abstract: AG1343 is a novel human immunodeficiency virus (HIV) protease inhibitor designed using protein structure-based techniques and intended for chronic oral administration in the treatment of AIDS-related conditions. The compound is the mesylate salt of a basic amine with a molecular weight of 663.90, pKa of 6.0, and partition coefficient (log P) of 4.1. Examination of the physicochemical properties of a bench-scale lot of the bulk drug was undertaken in order to establish a preformulation database and to begin development of an oral formulation suitable for phase I clinical trials. A stability-indicating gradient HPLC method was developed, and initial stability studies indicated that the compound is relatively stable under accelerated conditions. Water solubility and intrinsic dissolution rate studies, however, revealed the potential for dissolution rate-limited absorption. Alternative salts were prepared and evaluated for water solubility relative to the mesylate. A pH-solubility profile for AG1343 was generated and its solubility in various pharmaceutical solvents was determined. Formulation into several prototypical oral dosage forms for in-vitro evaluation in animal models prior to phase I clinical trials resulted in a several-fold difference in bioavailability between these formulations.

Marin M. T., Margarit M. V., and Salcedo G. E. (2002) Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone. *Farmaco* **57**, 723-727.

Abstract: Flunarizine is a selective calcium entry blocker poorly water-soluble. In this report, the interactions of this drug with polyvinylpyrrolidone in solid dispersions, prepared according to the dissolution method using methanol as the solvent, have been investigated. For purposes of comparison physical mixtures were prepared by simple mixture and homogeneization of the two pulverized components. Combinations of flunarizine/polyvinylpyrrolidone of the following percentage proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40 and 80/20 (mean particle size of 0.175 mm). The physicochemical properties of solid dispersions were investigated with X-ray diffraction, infrared spectroscopy, differential scanning calorimetry and solubility in equilibrium. X-ray patterns and differential scanning calorimetry have shown that polyvinylpyrrolidone inhibits the crystallization of flunarizine when percentages drug/polymer are 10/90, 20/80 and 30/70. The infrared spectra suggest that there was no chemical interaction between flunarizine and polyvinylpyrrolidone. Equilibrium solubility studies showed that drug solubility was enhanced as the polymer content increased. In general, the solubility increase was greater in solid dispersions than in physical mixtures and the solubility in equilibrium for solid dispersions and physical mixtures at the same drug/polymer proportion showed significant differences ($P < 0.05$).

McDaid F. M., Barker S. A., Fitzpatrick S., Petts C. R., and Craig D. Q. (2003) Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug-excipient interactions. *Int J Pharm* **252**, 235-240.

Abstract: The early prediction of drug-excipient incompatibility is vital in the pharmaceutical industry to avoid costly material wastage and time delays. We report here on the use of high sensitivity differential scanning calorimetry (HSDSC) to examine the compatibility between an experimental drug (Drug A) and common pharmaceutical excipients. Short-term HSDSC experiments (up to 25h) indicated that Drug A was stable in the presence of moisture and was compatible with both lactose monohydrate and magnesium stearate in the dry state, but showed degradation in the presence of magnesium stearate and water in combination. These results agreed with conventional stability studies, in which extensive degradation was observed in the Drug A-magnesium stearate system after storage at 40 degrees C/75% RH for 4 weeks but not under other conditions. These results indicate that HSDSC may be used to examine the compatibility of experimental drugs with conventional excipients and, in particular, illustrate the importance of

incorporating humidity as an experimental variable in order to fully establish the stability profile of the material under test.

Michnik A., Michalik K., and Marcoin W. (2004) Influence of magnesium glutamate on stability of penicillin G aqueous solution. *Int J Pharm* **273**, 149-158.

Abstract: Differential scanning microcalorimetry (DSC) has been used to determine the influence of magnesium glutamate on the stability of penicillin G in aqueous solution. The degradation of penicillin is accompanied by an evolution of heat and has been observed as an irreversible, scan rate dependent, broad exothermic transition. The increase of the transition temperature T_m and enthalpy change ΔH with increasing magnesium glutamate concentration indicates the increase of penicillin G stability. The kinetic parameters describing the penicillin decomposition process, obtained for a reaction following a first-order course, suggest maximum penicillin G stability if about two molecules of salt per one penicillin molecule are present in solution.

Mosharraf M. and Nystrom C. (2003) Apparent solubility of drugs in partially crystalline systems. *Drug Dev Ind Pharm* **29**, 603-622.

Abstract: Using several griseofulvin samples, representing different solid-state structures, the solubility behavior of drugs in both one-state (totally ordered, semioordered or disordered) and two-state systems was studied. Special attention was directed towards the surface structure of the particles. The partially crystalline samples were obtained by milling the raw material (crystalline standard) or storing the quenched sample (amorphous standard). The solid-state structure of the materials was studied using x-ray diffraction (XRD), differential scanning calorimetry (DSC), isothermal microcalorimetry (IMC), and scanning electron microscopy (SEM). The saturation concentration of the materials was studied in suspensions containing different dispersion concentrations of drug after centrifugation and filtration, using spectrophotometry. In all cases these dispersion concentrations exceeded the solubility of the drug. The solubilities were plotted vs. dispersion concentrations for each sample. Several solubility plateaus were found. The lowest and highest solubility plateaus corresponded to the solubilities of crystalline and amorphous standards. These plateaus were reached at 8 and 44 $\mu\text{g/mL}$ for crystalline and amorphous griseofulvin standards, respectively. An intermediate plateau served as an indication of the existence of a totally semioordered structure. This was reached at 19 $\mu\text{g/mL}$ for griseofulvin. Any deviation from these plateaus was suggested to be indicative of the existence of heterogeneity on the surface structure, which in most cases could be described as a two state system. In such cases, the apparent solubility was a function of dispersion concentration, until at very high dispersion concentrations (4000-20,000 $\mu\text{g/mL}$) the saturation concentration of the totally disordered (44 $\mu\text{g/mL}$) or semioordered (19 $\mu\text{g/mL}$) one-state phase was reached. No reduction in these values was observed during storage for 50 days. It is thus concluded that, in partially crystalline systems, the saturation concentration is an interfacial phenomenon, which depends on the amount, reactivity, and solid-state structure of the exposed solid surfaces in equilibrium with the solution. A simplified solubility model is proposed to qualitatively describe the relationship between established apparent solubilities (saturation concentrations) and different combinations of solid-state structures.

Otsuka M., Ishii M., and Matsuda Y. (2003) Effect of surface modification on hydration kinetics of carbamazepine anhydrate using isothermal microcalorimetry. *AAPS PharmSciTech* **4**, E5.

Abstract: The purpose of this research was to improve the stability of carbamazepine (CBZ) bulk powder under high humidity by surface modification. The surface-modified anhydrates of CBZ were obtained in a specially designed surface modification apparatus at 60 degrees C via the adsorption of n-butanol, and powder x-ray diffraction, Fourier-Transformed Infrared spectra, and differential scanning calorimetry were used to determine the crystalline characteristics of the samples. The hydration process of intact and surface-modified CBZ anhydrate at 97% relative humidity (RH) and 40 +/-C 1 degrees C was automatically monitored by using isothermal microcalorimetry (IMC). The dissolution test for surface-modified samples (20 mg) was performed in 900 mL of distilled water at 37 +/-C 0.5 degrees C with stirring by a paddle at 100 rpm as in the Japanese Pharmacopoeia XIII. The heat flow profiles of hydration of intact and surface-modified CBZ anhydrates at 97% RH by using IMC profiles showed a maximum peak at around 10 hours and 45 hours after 0 and 10 hours of induction, respectively. The result indicated that hydration of CBZ anhydrate was completely inhibited at the initial stage by surface modification of n-butanol and thereafter transformed into dihydrate. The hydration of surface-modified samples followed a 2-dimensional phase boundary process with an induction period (IP). The IP of intact and surface-modified samples decreased

with increase of the reaction temperature, and the hydration rate constant (k) increased with increase of the temperature. The crystal growth rate constants of nuclei of the intact sample were significantly larger than the surface-modified sample's at each temperature. The activation energy (E) of nuclei formation and crystal growth process for hydration of surface-modified CBZ anhydrate were evaluated to be 20.1 and 32.5 kJ/mol, respectively, from Arrhenius plots, but the Es of intact anhydrate were 56.3 and 26.8 kJ/mol, respectively. The dissolution profiles showed that the surface-modified sample dissolved faster than the intact sample at the initial stage. The dissolution kinetics were analyzed based on the Hixon-Crowell equation, and the dissolution rate constants for intact and surface-modified anhydrates were found to be $0.0102 \pm 0.008 \text{ mg}^{1/3} \times \text{min}^{-1}$ and $0.1442 \pm 0.0482 \text{ mg}^{1/3} \times \text{min}^{-1}$. The surface-modified anhydrate powders were more stable than the nonmodified samples under high humidity and showed resistance against moisture. However, surface modification induced rapid dissolution in water compared to the control.

Perissutti B., Rubessa F., Moneghini M., and Voinovich D. (2003) Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. *Int J Pharm* **256**, 53-63.

Abstract: This work describes a new approach to prepare a fast-release dosage form for carbamazepine (CBZ), involving the use of melt granulation process in high shear mixer for the production of tablets. In particular, the granules containing CBZ were prepared using polyethylene glycol (PEG) 4000 as a melting binder and lactose monohydrate as a hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated. After the analysis of their solid state performed by means of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC), the granules were characterised from the technological and dissolution point of view. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of crospovidone. Besides the remarkable enhancement of drug dissolution rate of the granulates in comparison to physical mixtures and pure drug, no significant differences were found between the dissolution profiles of the granulates containing lactose or crospovidone. However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular crospovidone highlight the necessity of this disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of crospovidone gave rise to a further amelioration of the disintegration and dissolution performances.

Rodante F., Vecchio S., Catalani G., and Tomassetti M. (2002) Compatibility between active components of a commercial drug. *Farmaco* **57**, 833-843.

Abstract: A thermal and a kinetic analysis on the decomposition processes of a commercial drug named diampicil (AD), obtained by an antibiotic combination of ampicillin (A) and dicloxacillin (D), have been carried out to find their thermal stability. The DSC/TG curves of this commercial drug were compared with those of its active components and an excipient, the magnesium stearate (M). Kinetic study was carried out using both isothermal and dynamic TG curves. Decomposition mechanisms for both active components and commercial drug tested were not found. The kinetic data obtained by the non-isothermal isoconversional method showed that D component causes a decrease of the kinetic stability of the active A component. Additive magnesium stearate does not decrease the stability of the two components. Moreover, storage time values at room temperature were calculated.

Rollinger J. M., Gstrein E. M., and Burger A. (2002) Crystal forms of torasemide: new insights. *Eur J Pharm Biopharm* **53**, 75-86.

Abstract: Crystallization from various organic solvents results in three crystal forms of torasemide: monotropically related mod. I (melting point, 158-161 degrees C) and mod. II (melting point, 155-158 degrees C), as well as a pseudopolymorphic crystal form (form A, channel inclusion compound with 1.9-4.2% water and alcohol). Physicochemical properties were determined by thermoanalysis (hot-stage microscopy, differential scanning calorimetry, thermogravimetry), Fourier transform infra-red and Raman spectroscopy, and X-ray powder diffractometry. The hygroscopicity, relative stability, true density, and heat of solutions were determined, respectively. The dissolution behaviour of mod. I and II was investigated as a function of pH, temperature, and in addition to surfactants. Mod. II is nearly three times more soluble than mod. I (mod. I, 0.34 mmol l^{-1} ; mod. II, 0.93 mmol l^{-1} at 20 degrees C, pH 4.90) and proved to be highly kinetically stable. By crystallization from 1-butanol, a new compound was synthesized, which was identified as [[4-[(3-Methylphenyl)amino]-3-pyridinyl]sulfonyl]-carbamic acid, butyl ester

(TOBC). The most important properties of this torasemide derivative are given. The present results give a thorough physicochemical characterization of the crystal forms of torasemide. They clearly indicate a mistaken identity of mod. II with crystal form A in formerly published articles.

Sertsou G., Butler J., Hempenstall J., and Rades T. (2003) Physical stability and enthalpy relaxation of drug-hydroxypropyl methylcellulose phthalate solvent change co-precipitates. *J Pharm Pharmacol* **55**, 35-41.

Abstract: The poorly water-soluble drug GWX was co-precipitated with hydroxypropyl methylcellulose phthalate (HPMCP) using a solvent change method. The two co-precipitate formulations made, with drug-HPMCP ratios of 2:8 and 5:5, were analysed using modulated temperature differential scanning calorimetry. They were found to consist of completely amorphous solid solution and a mixture of amorphous solid solution, crystalline drug and amorphous drug, respectively. Stability with respect to crystallization of the two co-precipitates and pure amorphous drug made by quench cooling was compared by storing preparations at 25 degrees C and 40 degrees C, under vacuum over P(2)O(5), and at 75% relative humidity (r.h.). Humidity (75% r.h. compared with dry) had a larger influence on crystallization of the amorphous drug than temperature (25 degrees C compared with 40 degrees C). The solid solution phase in co-precipitates had a relatively higher stability than amorphous drug alone, with respect to crystallization, in presence of the plasticizer water, and crystalline drug. These findings were partly explained by evidence of decreased molecular mobility in the amorphous solid solution with respect to amorphous drug alone, using enthalpy relaxation measurements. At an ageing temperature of 65 degrees C, the calculated half-life for enthalpy relaxation of the 2:8 drug-HPMCP ratio coprecipitate was about 6 orders of magnitude greater than that of amorphous drug alone, indicating a large difference in relative molecular mobility.

Sohn Y. T. and Park B. Y. (2003) Characterization of the physicochemical properties of KR-31378. *Arch Pharm Res* **26**, 526-531.

Abstract: KR-31378 is a new drug candidate intended for the use in the prevention of ischemia-reperfusion damage. The objective of this preformulation study was to determine the physicochemical properties of KR-31378. The n-octanol to water partition coefficients of KR-31378 were 0.0504 at pH 3 and 0.8874 at pH 10. Accelerated stability of KR-31378 in solution and solid state was studied at 5, 40, 60 degrees C. The stability testing indicated that the t90 for the drug in solid was estimated to be 2 years and 128.6 days at 25 degrees C, while that in aqueous solution was 68.6 days at 25 degrees C. The KR-31378 was also found to be unstable under the relative humidity of 76%, probably because of the hygroscopic nature of the drug. In order to study compatibility of KR-31378 with typical excipients, potential change in differential scanning calorimetry spectrum was studied in 1:1 binary mixtures of KR-31378 and Aerosil, Avicel, Eudragit, lactose, PEG, talc, CMC, PVP, starch. As a result, CMC, PVP, and starch were found to be incompatible with KR-31378, indicating the addition of these excipients may complicate the manufacturing of the formulation for the drug. Particle size distribution of KR-31378 powder was in the size range of 9-93 µm with the mean particle size of 37.9 µm. The flowability of KR-31378 was apparently inadequate, indicating the granulation may be necessary for the processing of the drug to solid dosage forms. Crystallization of the drug with a number of organic solvents did not lead a crystalline polymorphism. In addition, dissolution of the drug from the powder was adequately rapid at 37 degrees C in water.

Tarawneh R. T., Hamdan I. I., Bani-Jaber A., and Darwish R. M. (2005) Physicochemical studies on Ciclopirox olamine complexes with divalent metal ions. *Int J Pharm* **289**, 179-187.

Abstract: Ciclopirox olamine (CPO) metal complexes have been prepared and characterized using elemental analysis, infra red (IR), melting point and differential scanning calorimetry (DSC). Spectroscopic titration using molar ratio method indicated the occurrence of 1:1 complexes for CPO with almost all the examined metals. Physicochemical properties were also studied including aqueous solubility and apparent partition coefficient. Results showed that generally complex formation dramatically decreased the solubility and increased apparent partition coefficient. However, some metal complexes exhibited opposite effect. It could be concluded that complex formation can modify the solubility and apparent partition coefficient, which may suggest the use of complexes to manipulate the physicochemical properties of the drug.

van Tonder E. C., Mahlatji M. D., Malan S. F., Liebenberg W., Caira M. R., Song M., and de Villiers M. M. (2004) Preparation and physicochemical characterization of 5 niclosamide solvates and 1 hemisolvate.

AAPS PharmSciTech **5**, E12.

Abstract: The purpose of the study was to characterize the physicochemical, structural, and spectral properties of the 1:1 niclosamide and methanol, diethyl ether, dimethyl sulfoxide, N,N' dimethylformamide, and tetrahydrofuran solvates and the 2:1 niclosamide and tetraethylene glycol hemisolvate prepared by recrystallization from these organic solvents. Structural, spectral, and thermal analysis results confirmed the presence of the solvents and differences in the structural properties of these solvates. In addition, differences in the activation energy of desolvation, batch solution calorimetry, and the aqueous solubility at 25 degrees C, 24 hours, showed the stability of the solvates to be in the order: anhydrate > diethyl ether solvate > tetraethylene glycol hemisolvate > methanol solvate > dimethyl sulfoxide solvate > N,N' dimethylformamide solvate. The intrinsic and powder dissolution rates of the solvates were in the order: anhydrate > diethyl ether solvate > tetraethylene glycol hemisolvate > N,N' dimethylformamide solvate > methanol solvate > dimethyl sulfoxide solvate. Although these nonaqueous solvates had higher solubility and dissolution rates than the monohydrous forms, they were unstable in aqueous media and rapidly transformed to one of the monohydrous forms.

Zhou D., Zhang G. G., Law D., Grant D. J., and Schmitt E. A. (2002) Physical stability of amorphous pharmaceuticals: Importance of configurational thermodynamic quantities and molecular mobility. *J Pharm Sci* **91**, 1863-1872.

Abstract: This work relates the thermodynamic quantities (G_c , H_c , and S_c) and the molecular mobility values ($1/\tau$) of five structurally diverse amorphous compounds to their crystallization behavior. The model compounds included: ritonavir, ABT-229, fenofibrate, sucrose, and acetaminophen. Modulated temperature DSC was used to measure the heat capacities as a function of temperature for the amorphous and crystalline phases of each compound. Knowledge of the heat capacities and fusion data allowed calculation of the configurational thermodynamic quantities and the Kauzmann temperatures ($T(K)$) using established relationships. The molecular relaxation time constants (τ) were then calculated from the Vogel-Tammann-Fulcher representation of the Adam-Gibbs model. Amorphous samples were heated at 1 K/min and a reduced crystallization temperature, defined as $(T_c - T_g)/(T_m - T_g)$, was used to compare crystallization tendencies. Crystallization was observed for all compounds except ritonavir. The configurational free energy values (G_c) show that thermodynamic driving forces for crystallization follow the order: ritonavir > acetaminophen approximately fenofibrate > sucrose > ABT-229. The entropic barrier to crystallization, which is inversely related to the probability that the molecules are in the proper orientation, followed the order: ritonavir > fenofibrate > ABT-229 > acetaminophen approximately sucrose. Molecular mobility values, which are proportional to molecular collision rates, followed the order: acetaminophen > fenofibrate > sucrose > ABT-229 approximately ritonavir. Crystallization studies under nonisothermal conditions revealed that compounds with the highest entropic barriers and lowest mobilities were most difficult to crystallize, regardless of the thermodynamic driving forces. This investigation demonstrates the importance of both configurational entropy and molecular mobility to understanding the physical stability of amorphous pharmaceuticals.