# EVALUATION OF SOLID FORM AND THERMODYNAMIC PROPERTIES FOR CARBAMAZEPINE-SACCHARIN (CBZ-SAC) CO-CRYSTAL

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## SUPERVISOR'S DECLARATION

I hereby declare that I have checked this thesis and in my opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Master of Science.

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## STUDENT'S DECLARATION

I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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## ABSTRAK

Pembentukan ko-penghabluran dipercayai boleh menambah baik sifat-sifat fizikokimia bahan aktif farmaseutikal (API). Carbamazepine (CBZ) ialah sejenis dadah yang digunakan sebagai ubat penenang untuk rawatan epilepsi dan mempunyai kebolehlarutan yang rendah yang menjejaskan pengambilan dos dalam merawat pesakit. Ianya telah digunakan sebagai model dadah dalam kajian ini bersama-sama sakarin (SAC) sebagai komponen hablur bersama. Ko-penghablur CBZ dan SAC telah dijalankan untuk mencari bentuk pejal dengan mempelbagaikan pelarut (etanol, acetonitril, ethyl acetate dan propanol), cara penghabluran dan SAC/CBZ nisbah molar ratio (0.50, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75 and 3.00). Kajian kebolehlarutan ko-hablur dan pembubaran sifat termodinamik pada suhu pelbagai (25-50 °C) telah ditentukan dalam rumusan etanol tulen dan lebihan nisbah SAC yang berbeza. Pengimbas kalorimetri (DSC), pembelauan X-ray hablur (PXRD), pengimbas sinar merah Fourier (FTIR) dan mikroskop optik telah digunakan untuk mencirikan ko-hablur yang terhasil, sementara kromatografi cecair berprestasi tinggi (HPLC) dan kaedah sintetik telah digunakan untuk menentukan kebolehlarutan ko-hablur. Daripada proses penghabluran, CBZ-SAC ko-hablur bentuk I telah dihasilkan. SAC/CBZ nisbah 2.25 telah dipilih sebagai nisbah terbaik memandangkan nisbah ini mempunyai 100 % penukaran ko-hablur. Kaedah penghabluran stirring dan pelarut etanol telah dipilih sebagai parameter terbaik berbanding yang lain disebabkan ko-hablur CBZ-SAC boleh terbentuk pada nisbah tertinggi dalam kaedah ini dan SAC tulen lebih larut dalam pelarut ini. Berdasarkan data yang dikumpul, kebolehlarutan ko-hablur telah didapati meningkat apabila suhu meningkat untuk semua keadaan yang digunakan. HPLC telah dipilih sebagai cara yang lebih baik berbanding sintetik memandangkan HPLC melaporkan nilai kebolehlarutan sampel yang diuji dengan tepat. Nilai kebolehlarutan ko-hablur adalah lebih tingi apabila dibandingkan dengan kebolehlarutan CBZ tulen, dengan itu menunjukkan kebolehlarutan bertambah baik dengan pembentukan ko-hablur CBZ-SAC pada semua suhu (25-50 °C). Kebolehlarutan ideal ko-hablur CBZ-SAC adalah sisihan positif dan kebolehlarutan ko-hablur eksperimen telah berkorelasi baik dengan model van't Hoff. Kesemua sifat termodinamik ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) didapati daripada analisis termodinamik yang ketara mempunyai nilai positif yang menunjukkan pembubaran endothermik dan entropi yang digerakkan ko-hablur dalam pelarut etanol. Data daripada kajian ini boleh memperkuatkan sifat-sifat fizikokimia ko-hablur CBZ-SAC dalam larutan akueus dan corak kebolehlarutan ko-hablur CBZ-SAC bertindak balas terhadap suhu juga dapat dilaporkan. Data kebolelarutan dan fisikokimia daripada kajian ini boleh digunakan dalam penyucian, hablur, pemisahan dan perkembangan rumusan CBZ dalam industry farmaseutikal dan kimia.

## ABSTRACT

The formation of co-crystal is believed to improve the physicochemical properties of Active Pharmaceutical Ingredients (API). Carbamazepine (CBZ) is a drug that is used as anticonvulsant for treatment of epilepsy and known for having low solubility that can affect the dosage intake in treating patients. It was used as model drug in this study with saccharin (SAC) as co-crystal former. Co-crystallisation of CBZ and SAC was performed to find the co-crystal solid form by varying solvents (ethanol, acetonitrile, ethyl acetate and propanol), crystallisation methods (stirring crystallisation and slurry crystallisation) and SAC/CBZ mol ratio (0.50, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75 and 3.00). The solubility study and dissolution thermodynamic properties of the co-crystal at various temperatures (25-50 °C) were determined in pure ethanol solution and solution with excess of different SAC ratio. Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), Fourier Transform Infrared (FTIR) and optical microscopy were used to characterise the co-crystal solid form, while High Performance Liquid Chromatography (HPLC) and synthetic methods were used to determine the solubility of the co-crystal. From the co-crystallisation process, CBZ-SAC co-crystal Form I was successfully formed. SAC/CBZ ratio of 2.25 was chosen as the best ratio since it was the highest ratio that has 100 % conversion of co-crystal. Stirring crystallisation method and ethanol solvent were chosen as the best parameters among others due to CBZ-SAC co-crystal was able to form at higher ratio in this method and pure SAC more soluble in this solvent. Based on the data collected, the co-crystal solubility was found increases as temperature rises for all conditions used. HPLC was chosen as a better method compared to the synthetic as HPLC reported the exact solubility value of the sample tested. The solubility values of co-crystal were compared to be higher than pure CBZ solubility, thus show that the solubility improved with the formation of CBZ-SAC co-crystal at temperatures of 25-50 °C. CBZ-SAC co-crystal ideal solubilities have positive deviation and the experimental co-crystal solubility was correlated well with van't Hoff model. The thermodynamic properties ($\Delta_{sol}H^0$, $\Delta_{sol}G^0$ and $\Delta_{sol}S^0$) obtained from the apparent thermodynamic analysis have positive values which indicates an endothermic and entropy-driven dissolution of co-crystal in ethanol solvent. The data from this study could amplify the physicochemical properties of CBZ-SAC co-crystal in aqueous solution and the pattern of the CBZ-SAC co-crystal solubility reacting towards temperatures also could be reported. The solubility and physicochemical data from this research could be useful in purification, crystallisation, separation and formulation development of CBZ in pharmaceutical and chemical industries.

## TABLE OF CONTENT

## REFERENCES


Aakeröy, C. B., & Salmon, D. J. (2005). Building co-crystals with molecular sense and supramolecular sensibility. *Crystal Engineering Communication, 7*(72), 439. doi:10.1039/b505883j

Abbott, S. (2017). *Solubility Science: Principles and Practice*. United Kingdom: Creative Commons By-ND

Abd Rahim, S. (2012). *Understanding and predicting physicochemical properties and crystallisation behaviour of carbamazepine co-crystal.* (Ph.D), The University of Leads, UK.

Abd Rahim, S., Ab Rahman, F., Nasir, E. N. E. M., & Ramle, N. A. (2015). Carbamazepine Co-crystal Screening with Dicarboxylic Acids Co-Crystal Formers. *World Academy of Science, Engineering and Technology International Journal of Environmental, Chemical, Ecological, Geological and Geophysical Engineering, 9*(5), 433-436.

Abd Rahim, S., Hammond, R. B., Sheikh, A. Y., & Roberts, K. J. (2013). A comparative assessment of the influence of different crystallisation screening methodologies on the solid forms of carbamazepine co-crystals. *Crystal Engineering Communication, 15*(19), 3862-3873. doi:10.1039/c3ce26878k

Alhalaweh, A., Kaialy, W., Buckton, G., Gill, H., Nokhodchi, A., & Velaga, S. P. (2013). Theophylline Cocrystals Prepared by Spray Drying: Physicochemical Properties and Aerosolization Performance. *American Association of Pharmaceutical Scientists Pharmscitech, 14*(1), 265-276. doi:10.1208/s12249-012-9883-3

Almarri, F., Haq, N., Alanazi, F. K., Mohsin, K., Alsarra, I. A., Aleanizy, F. S., & Shakeel, F. (2017). Solubility and thermodynamic function of vitamin D3 in different mono solvents. *Journal of Molecular Liquids, 229*, 477-481. doi:10.1016/j.molliq.2016.12.105

Almarsson, O., Peterson, M. L., & Zaworotko, M. (2012). The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. *Pharmaceutical Patent Analyst, 1*(3), 313-327. doi:10.4155/ppa.12.29

Alshora, D. H., Haq, N., Alanazi, F. K., Ibrahim, M. A., & Shakeel, F. (2016). Solubility of rosuvastatin calcium in different neat solvents at different temperatures. *The Journal of Chemical Thermodynamics, 94*, 230-233. doi:10.1016/j.jct.2015.11.019

Aragón, D. M., Sosnik, A., & Martínez, F. (2009). Solution Thermodynamics of Triclocarban in Organic Solvents of Different Hydrogen Bonding Capability. *Journal of Solution Chemistry, 38*(12), 1493-1503. doi:10.1007/s10953-009-9464-6

Azizi, A., Ebrahimi, A., Habibi-Khorassani, M., Rezazadeh, S., & Behazin, R. (2014). The Effects of Interactions of Dicarboxylic Acids on the Stability of the Caffeine Molecule: A Theoretical Study. *Bulletin of the Chemical Society of Japan, 87*(10), 1116-1123. doi:10.1246/bcsj.20130287

Bag, P. P., Patni, M., & Reddy, C. M. (2011). A kinetically controlled crystallisation process for identifying new co-crystal forms: fast evaporation of solvent from solutions to dryness. *Crystal Engineering Communication, 13*(19), 5650-5652. doi:10.1039/c1ce05778b

Blagden, N., de Matas, M., Gavan, P. T., & York, P. (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews, 59*(7), 617-630. doi:10.1016/j.addr.2007.05.011

Bromfield, E. B., Cavazos, J. E., & Sirven, J. I. (2006). Clinical Epilepsy *An Introduction to Epilepsy*: West Hartford (CT): American Epilepsy Society.

Cakar, M., & Popovic, G. (2006). Determination of saccharin in pharmaceuticals by high performance thin layer chromatography. *Journal of the Serbian Chemical Society, 71*(6), 669-676. doi:10.2298/Jsc0606669c

Cao, X.-X., Tong, R.-J., Zhao, Y., Lv, T.-T., Song, Y., & Yao, J.-C. (2012). Determination and Correlation of Pyridazin-3-amine Solubility in Eight Organic Solvents at Temperatures Ranging from (288.05 to 333.35) K. *Journal of Chemical & Engineering Data, 57*(8), 2360-2366. doi:10.1021/je300517q

Chattopadhyay, S., Raychaudhuri, U., & Chakraborty, R. (2014). Artificial sweeteners - a review. *Journal of Food Science and Technology-Mysore, 51*(4), 611-621. doi:10.1007/s13197-011-0571-1

Cheney, M. L., Shan, N., Healey, E. R., Hanna, M., Wojtas, L., Zaworotko, M. J., Sava, V., Song, S., & Sanchez-Ramos, J. R. (2010). Effects of Crystal Form on Solubility and Pharmacokinetics: A Crystal Engineering Case Study of Lamotrigine. *Crystal Growth & Design, 10*(1), 394-405. doi:10.1021/cg901010v

Childs, S. L., Rodriguez-Hornedo, N., Reddy, L. S., Jayasankar, A., Maheshwari, C., McCausland, L., Shipplett, R., & Stahly, B. C. (2008). Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *Crystal Engineering Communication, 10*(7), 856-864. doi:10.1039/b715396a

Childs, S. L., & Zaworotko, M. J. (2009). The Reemergence of Cocrystals: The Crystal Clear Writing Is on the Wall Introduction to Virtual Special Issue on Pharmaceutical Cocrystals. *Crystal Growth & Design, 9*(10), 4208-4211. doi:10.1021/cg901002y

Chun, N.-H., Lee, M.-J., Song, G.-H., Chang, K.-Y., Kim, C.-S., & Choi, G. J. (2014). Combined anti-solvent and cooling method of manufacturing indomethacin–saccharin (IMC–SAC) co-crystal powders. *Journal of Crystal Growth, 408*, 112-118. doi:10.1016/j.jcrysgro.2014.07.057

Cue, B. W., & Zhang, J. (2009). Green process chemistry in the pharmaceutical industry. *Green Chemistry Letters and Reviews, 2*(4), 193-211. doi:10.1080/17518250903258150

Czernicki, W., & Baranska, M. (2013). Carbamazepine polymorphs: Theoretical and experimental vibrational spectroscopy studies. *Vibrational Spectroscopy, 65*, 12-23. doi:10.1016/j.vibspec.2012.11.011

Di, L., Fish, P. V., & Mano, T. (2012). Bridging solubility between drug discovery and development. *Drug Discovery Today, 17*(9-10), 486-495. doi:10.1016/j.drudis.2011.11.007

Du, Y., Fang, H. X., Zhang, Q., Zhang, H. L., & Hong, Z. (2016). Spectroscopic investigation on cocrystal formation between adenine and fumaric acid based on infrared and Raman techniques. *Spectrochim Acta A Molecular and Biomolecular Spectroscopy, 153*, 580-585. doi:10.1016/j.saa.2015.09.020

Eddleston, M. D., Patel, B., Day, G. M., & Jones, W. (2013). Cocrystallisation by Freeze-Drying: Preparation of Novel Multicomponent Crystal Forms. *Crystal Growth & Design, 13*(10), 4599-4606. doi:10.1021/cg401179s

Fleischman, S. G., Kuduva, S. S., McMahon, J. A., Moulton, B., Walsh, R. D. B., Rodriguez-Hornedo, N., & Zaworotko, M. J. (2003). Crystal engineering of the composition of pharmaceutical phases: Multiple-component crystalline solids involving carbamazepine. *Crystal Growth & Design, 3*(6), 909-919. doi:10.1021/cg034035x

Fuliaş, A., Vlase, G., Vlase, T., Şuta, L.-M., Şoica, C., & Ledeţi, I. (2015). Screening and characterisation of cocrystal formation between carbamazepine and succinic acid. *Journal of Thermal Analysis and Calorimetry, 121*(3), 1081-1086. doi:10.1007/s10973-015-4473-8

Gadade, D. D., & Pekamwar, S. S. (2016). Pharmaceutical Cocrystals: Regulatory and Strategic Aspects, Design and Development. *Advanced Pharmaceutical Bulletin, 6*(4), 479-494. doi:10.15171/apb.2016.062

Getsoian, A., Lodaya, R. M., & Blackburn, A. C. (2008). One-solvent polymorph screen of carbamazepine. *International Journal of Pharmaceutics, 348*(1-2), 3-9. doi:10.1016/j.ijpharm.2007.06.053

Good, D. J., & Rodriguez-Hornedo, N. (2009). Solubility Advantage of Pharmaceutical Cocrystals. *Crystal Growth & Design, 9*(5), 2252-2264. doi:10.1021/cg801039j

Grodowska, K., & Parczewski, A. (2010). Organic solvents in the pharmaceutical industry. *Acta Poloniae Pharmaceutica, 67*(1), 3-12.

Grzesiak, A. L., Lang, M. D., Kim, K., & Matzger, A. J. (2003). Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *Journal of Pharmaceutical Sciences, 92*(11), 2260-2271. doi:10.1002/jps.10455

Hickey, M. B., Peterson, M. L., Scoppettuolo, L. A., Morrisette, S. L., Vetter, A., Guzman, H., Remenar, J. F., Zhang, Z., Tawa, M. D., Haley, S., Zaworotko, M. J., & Almarsson, O. (2007). Performance comparison of a co-crystal of carbamazepine with marketed product. *European Journal of Pharmaceutics and Biopharmaceutics, 67*(1), 112-119. doi:10.1016/j.ejpb.2006.12.016

Holguín, A. R., Rodríguez, G. A., Cristancho, D. M., Delgado, D. R., & Martínez, F. (2012). Solution thermodynamics of indomethacin in propylene glycol+water mixtures. *Fluid Phase Equilibria, 314*, 134-139. doi:10.1016/j.fluid.2011.11.001

Huber, J. S., Hanrahan, S. M., Moses, W. W., Derenzo, S. E., Reutter, B. W., O'Neil, J. P., & Gullberg, G. T. (2009). Development of a High-Sensitivity Radiation Detector for Chromatography. *2009 Ieee Nuclear Science Symposium Conference Record, Vols 1-5*, 2620-2624. doi: 10.1109/Nssmic.2009.5402006

Inoue, M., & Hirasawa, I. (2013). The relationship between crystal morphology and XRD peak intensity on CaSO4.2H2O. *Journal of Crystal Growth, 380*, 169-175. doi:10.1016/j.jcrysgro.2013.06.017

Issa, N., Barnett, S. A., Mohamed, S., Braun, D. E., Copley, R. C. B., Tocher, D. A., & Price, S. L. (2012). Screening for cocrystals of succinic acid and 4-aminobenzoic acid. *Crystal Engineering Communication, 14*(7), 2454. doi:10.1039/c2ce06325e

Issa, N., Karamertzanis, P. G., Welch, G. W. A., & Price, S. L. (2009). Can the Formation of Pharmaceutical Cocrystals Be Computationally Predicted? I. Comparison of Lattice Energies. *Crystal Growth & Design, 9*(1), 442-453. doi:10.1021/cg800685z

Jasud, S., Warad, S., Rahul, S., Jagdale, G., & Zinjad, S. (2013). Co-crystal: A Novel Approach for Bioavailability Enhancement. *World Journal of Pharmacy and Pharmaceutical Sciences, 2*, 4682-4697.

Javadzadeh, Y., Jafari-Navimipour, B., & Nokhodchi, A. (2007). Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). *International Journal of Pharmaceutics, 341*(1-2), 26-34. doi:10.1016/j.ijpharm.2007.03.034

Jayasankar, A., Reddy, L. S., Bethune, S. J., & Rodrı´guez-Hornedo, N. r. (2009). Role of Cocrystal and Solution Chemistry on the Formation and Stability of Cocrystals with Different Stoichiometry. *Crystal Growth & Design, 9*(2), 889-897.

Jayasankar, A., Somwangthanaroj, A., Shao, Z. J., & Rodriguez-Hornedo, N. (2006). Cocrystal formation during cogrinding and storage is mediated by amorphous phase. *Pharmaceutical Research, 23*(10), 2381-2392. doi:10.1007/s11095-006-9110-6

Kasim, N. A., Whitehouse, M., Ramachandran, C., Bermejo, M., Lennernas, H., Hussain, A. S., Junginger, H. E., Stavchansky, S. A., Midha, K. K., Shah, V. P., & Amidon, G. L. (2004). Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Molecular Pharmaceutics, 1*(1), 85-96. doi:10.1021/mp034006h

Keraliya, R. A., Soni, T. G., Thakkar, V. T., & Gandhi, T. R. (2010). Effect of Solvent on Crystal Habit and Dissolution Behavior of Tolbutamide by Initial Solvent Screening. *Dissolution Technologies, 17*(1), 16-21. doi:10.14227/dt170110p16

Kitamura, M., Hayashi, Y., & Hara, T. (2008). Effect of solvent and molecular structure on the crystallisation of polymorphs of BPT esters. *Journal of Crystal Growth, 310*(12), 3067-3071. doi:10.1016/j.jcrysgro.2008.03.014

Kobayashi, Y., Ito, S., Itai, S., & Yamamoto, K. (2000). Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. *International Journal of Pharmaceutics, 193*(2), 137-146. doi: 10.1016/S0378-5173(99)00315-4

Kroger, M., Meister, K., & Kava, R. (2006). Low-calorie sweeteners and other sugar substitutes: A review of the safety issues. *Comprehensive Reviews in Food Science and Food Safety, 5*(2), 35-47. doi: 10.1111/j.1541-4337.2006.tb00081.x

Krug, R. R., Hunterlib, W. G., & Grlegerl, R. A. (1976). Enthalpy-Entropy Compensation. 2. Separation of the Chemical from the Statistical Effect. *The Journal of Physical Chemistry, 80*(21), 2341-2351.

Kudo, S., & Takiyama, H. (2014). Production method of carbamazepine/saccharin cocrystal particles by using two solution mixing based on the ternary phase diagram. *Journal of Crystal Growth, 392*, 87-91. doi:10.1016/j.jcrysgro.2014.02.003

Lee, M.-J., Wang, I.-C., Kim, M.-J., Kim, P., Song, K.-H., Chun, N.-H., Park, H.-G., & Choi, G. J. (2015). Controlling the polymorphism of carbamazepine-saccharin cocrystals formed during antisolvent cocrystallisation using kinetic parameters. *Korean Journal of Chemical Engineering, 32*(9), 1910-1917. doi:10.1007/s11814-014-0384-9

Li, M., Qiao, N., & Wang, K. (2013). Influence of sodium lauryl sulfate and tween 80 on carbamazepine-nicotinamide cocrystal solubility and dissolution behaviour. *Pharmaceutics, 5*(4), 508-524. doi:10.3390/pharmaceutics5040508

Li, Y. J., Wu, K., Li, Y., Zhang, Y., Liu, J. J., & Wang, X. Z. (2017). Solubility in Different Solvents, Crystal Polymorph and Morphology, and Optimization of Crystallization Process of AIBN. *Journal of Chemical & Engineering Data, 63*(1), 27-38. doi:10.1021/acs.jced.7b00538

Lide, D. R. (2005). *CRC Handbook of Chemistry and Physics* Retrieved from http://www.hbcpnetbase.com

Lin, H. L., Huang, Y. T., & Lin, S. Y. (2016). Spectroscopic and thermal approaches to investigate the formation mechanism of piroxicam-saccharin co-crystal induced by liquid-assisted grinding or thermal stress. *Journal of Thermal Analysis and Calorimetry, 123*(3), 2345-2356. doi:10.1007/s10973-015-5058-2

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2012). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews, 64*, 4-17. doi:10.1016/j.addr.2012.09.019

Liu, W., Dang, L., & Wei, H. (2013). Thermal, phase transition, and thermal kinetics studies of carbamazepine. *Journal of Thermal Analysis and Calorimetry, 111*(3), 1999-2004. doi:10.1007/s10973-012-2214-9

Liu, W. J., Dang, L. P., Black, S., & Wei, H. Y. (2008). Solubility of carbamazepine (form III) in different solvents from (275 to 343) K. *Journal of Chemical and Engineering Data, 53*(9), 2204-2206. doi:10.1021/je8002157

Loftsson, T., & Brewster, M. E. (2010). Pharmaceutical applications of cyclodextrins: basic science and product development. *Journal of Pharmacy and Pharmacology, 62*(11), 1607-1621. doi:10.1111/j.2042-7158.2010.01030.x

Lu, M. Y., Guo, F., Fan, B. J., Ren, Z. Q., & Li, Q. S. (2017). Solubility and solution thermodynamics of Raspberry Ketone in pure organic solvents and binary solvent mixtures from T = (293.15 to 333.15) K. *Journal of Molecular Liquids, 246*, 332-341. doi:10.1016/j.molliq.2017.09.084

Manrique, Y. J., Pacheco, D. P., & Martínez, F. (2007). Thermodynamics of Mixing and Solvation of Ibuprofen and Naproxen in Propylene Glycol + Water Cosolvent Mixtures. *Journal of Solution Chemistry, 37*(2), 165-181. doi:10.1007/s10953-007-9228-0

McConvey, I. F., Woods, D., Lewis, M., Gan, Q., & Nancarrow, P. (2012). The Importance of Acetonitrile in the Pharmaceutical Industry and Opportunities for its Recovery from Waste. *Organic Process Research & Development, 16*(4), 612-624. doi:10.1021/op2003503

McPolin, O. (2009). *An Introduction to HPLC for Pharmaceutical Analysis*. United Kingdom: Mourne Training Services.

Miroshnyk, I., & Mirza, S. (2010). Capturing the advantage of co-crystal. *Pharmaceutical Technology Europe, 22*(7), 31-35.

Miroshnyk, I., Mirza, S., & Sandlert, N. (2009). Pharmaceutical co-crystals-an opportunity for drug product enhancement. *Expert Opinion on Drug Delivery, 6*(4), 333-341. doi:10.1517/17425240902828304

Morissette, S. L., Almarsson, O., Peterson, M. L., Remenar, J. F., Read, M. J., Lemmo, A. V., Ellis, S., Cima, M. J., & Gardner, C. R. (2004). High-throughput crystallisation: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. *Advanced Drug Delivery Reviews, 56*(3), 275-300. doi:10.1016/j.addr.2003.10.020

Mota, F. L., Carneiro, A. P., Queimada, A. J., Pinho, S. P., & Macedo, E. A. (2009). Temperature and solvent effects in the solubility of some pharmaceutical compounds: Measurements and modeling. *European Journal of Pharmaceutical Sciences, 37*(3-4), 499-507. doi:10.1016/j.ejps.2009.04.009

Najib, F. M., & Mustafa, M. S. (2014). Four Spectrophotometric Methods For Simultaneous Determination Of Carbamazepine And Lamotrigine In Binary Mixtures And Urine Samples. *The Malaysian Journal of Analytical Sciences, 18*(3), 491-506.

Nanjwade, V. K., Manvi, F. V., Shamrez Ali. M, Nanjwade, B. K., & Maste, M. M. (2011). New Trends in the Co-crystallisation of Active Pharmaceutical Ingredients. *Journal of Applied Pharmaceutical Science, 1*(8), 1-5.

Nehm, S. J., Rodriguez-Spong, B., & Rodriguez-Hornedo, N. (2006). Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. *Crystal Growth & Design, 6*(2), 592-600. doi:10.1021/cg0503346

O'Mahony, M. A., Maher, A., Croker, D. M., Rasmuson, Å. C., & Hodnett, B. K. (2012). Examining Solution and Solid State Composition for the Solution-Mediated Polymorphic Transformation of Carbamazepine and Piracetam. *Crystal Growth & Design, 12*(4), 1925-1932. doi:10.1021/cg201665z

Pagire, S. K., Jadav, N., Vangala, V. R., Whiteside, B., & Paradkar, A. (2017). Thermodynamic Investigation of Carbamazepine-Saccharin Co-Crystal Polymorphs. *Journal of Pharmaceutical Sciences, 106*(8), 2009-2014. doi:10.1016/j.xphs.2017.04.017

Pagire, S. K., Korde, S. A., Whiteside, B. R., Kendrick, J., & Paradkar, A. (2013). Spherical Crystallisation of Carbamazepine/Saccharin Co-Crystals: Selective Agglomeration and Purification through Surface Interactions. *Crystal Growth & Design, 13*(10), 4162-4167. doi:10.1021/cg400804x

Panahi-Azar, V., Shayanfar, A., Martinez, F., Acree, W. E., & Jouyban, A. (2011). Thermodynamic studies of fluphenazine decanoate solubility in propylene glycol plus water mixtures and correlation with the Jouyban-Acree model. *Fluid Phase Equilibria, 308*(1-2), 72-77. doi:10.1016/j.fluid.2011.06.008

Patil, S. P., Modi, S. R., & Bansal, A. K. (2014). Generation of 1:1 Carbamazepine:Nicotinamide cocrystals by spray drying. *European Journal of Pharmaceutical Sciences, 62,* 251-257. doi:10.1016/j.ejps.2014.06.001

Pinto, M. A. L., Ambrozini, B., Ferreira, A. P. G., & Cavalheiro, É. T. G. (2014). Thermoanalytical studies of carbamazepine: hydration/dehydration, thermal decomposition, and solid phase transitions. *Brazilian Journal of Pharmaceutical Sciences, 50*(4), 877-884. doi:10.1590/s1984-82502014000400023

Porter III, W. W., Elie, S. C., & Matzger, A. J. (2008). Polymorphism in carbamazepine cocrystals. *Crystal Growth & Design, 8*(1), 14-16. doi:10.1021/cg701022e

Prasad, R. V., Rakesh, M. G., Jyotsna, R. M., Mangesh, S. T., Anita, P. S., & Mayur, P. K. (2012). Pharmaceutical Cocrystallisation : A Review. *INTERNATIONAL JOURNAL OF PHARMACEUTICAL AND CHEMICAL SCIENCES, 1*(3), 1074-1085.

Privalov, P. L., & Potekhin, S. A. (1986). Scanning microcalorimetry in studying temperature-induced changes in proteins. *Methods in Enzymology, 131,* 4-51. doi: 10.1016/0076-6879(86)31033-4

Rahman, Z., Agarabi, C., Zidan, A. S., Khan, S. R., & Khan, M. A. (2011). Physico-mechanical and Stability Evaluation of Carbamazepine Cocrystal with Nicotinamide. *American Association of Pharmaceutical Scientists Pharmscitech, 12*(2), 693-704. doi:10.1208/s12249-011-9603-4

Ramle, N. A., Abd Rahim, S., Anuar, N., & El-Hadad, O. (2017). Solubility of Carbamazepine Co-Crystals in Ethanolic Solution. *3rd International Conference on Chemical Materials and Process (Iccmp 2017), 1879*. doi:Unsp 04000110.1063/1.5000468

Ramle, N. A., Abd Rahim, S., El-Hadad, O., & Anuar, N. (2015). Solubility of Carbamazepine-Succinic Co-crystal in Ethanolic Solvent System. *Advanced Materials Research, 1113*, 434-439. doi:10.4028/www.scientific.net/AMR.1113.434

Rask, M. B., Knopp, M. M., Olesen, N. E., Holm, R., & Rades, T. (2018). Comparison of two DSC-based methods to predict drug-polymer solubility. *International Journal of Pharmaceutics, 540*(1-2), 98-105. doi:10.1016/j.ijpharm.2018.02.002

Ruidiaz, M. A., Delgado, D. R., Martinez, F., & Marcus, Y. (2010). Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures. *Fluid Phase Equilibria, 299*(2), 259-265. doi:10.1016/j.fluid.2010.09.027

Savjani, J. K., & Pathak, C. (2016). Improvement of physicochemical parameters of acyclovir using cocrystallisation approach. *Brazilian Journal of Pharmaceutical Sciences, 52*(4), 727-734. doi:10.1590/s1984-82502016000400017

Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug solubility: importance and enhancement techniques. *International Scholarly Research Notices Pharmaceutics, 2012*, 195727. doi:10.5402/2012/195727

Schultheiss, N., & Newman, A. (2009). Pharmaceutical Cocrystals and Their Physicochemical Properties. *Crystal Growth & Design, 9*(6), 2950-2967. doi:10.1021/cg900129f

Shakeel, F., Haq, N., Alanazi, F. K., & Alsarra, I. A. (2015). Solubility of anti-inflammatory drug lornoxicam in ten different green solvents at different temperatures. *Journal of Molecular Liquids, 209,* 280-283. doi:10.1016/j.molliq.2015.05.035

Shakeel, F., Haq, N., Alanazi, F. K., & Alsarra, I. A. (2017). Solubility and thermodynamics of apremilast in different mono solvents: Determination, correlation and molecular interactions. *International Journal of Pharmaceutics, 523*(1), 410-417. doi:10.1016/j.ijpharm.2017.03.067

Shan, N., & Zaworotko, M. J. (2008). The role of cocrystals in pharmaceutical science. *Drug Discovery Today, 13*(9-10), 440-446. doi:10.1016/j.drudis.2008.03.004

Shayanfar, A., Asadpour-Zeynali, K., & Jouyban, A. (2013). Solubility and dissolution rate of a carbamazepine-cinnamic acid cocrystal. *Journal of Molecular Liquids, 187*, 171-176. doi:10.1016/j.molliq.2013.06.015

Shayanfar, A., Velaga, S., & Jouyban, A. (2014). Solubility of carbamazepine, nicotinamide and carbamazepine-nicotinamide cocrystal in ethanol-water mixtures. *Fluid Phase Equilibria, 363*, 97-105. doi:10.1016/j.fluid.2013.11.024

Skieneh, J., Khalili Najafabadi, B., Horne, S., & Rohani, S. (2016). Crystallisation of Esomeprazole Magnesium Water/Butanol Solvate. *Molecules, 21*(4), 544. doi:10.3390/molecules21040544

Soares, F. L., & Carneiro, R. L. (2017). In-line monitoring of cocrystallization process and quantification of carbamazepine-nicotinamide cocrystal using Raman spectroscopy and chemometric tools. *Spectrochim Acta A Mol Biomol Spectrosc, 180*, 1-8. doi:10.1016/j.saa.2017.02.045

Stahly, G. P. (2007). Diversity in single- and multiple-component crystals. The search for and prevalence of polymorphs and cocrystals. *Crystal Growth & Design, 7*(6), 1007-1026. doi:10.1021/cg060838j

Sun, C. C., & Hou, H. (2008). Improving mechanical properties of caffeine and methyl gallate crystals by cocrystallisation. *Crystal Growth & Design, 8*(5), 1575-1579. doi:10.1021/cg700843s

Swartz, M. (2010). Hplc Detectors: A Brief Review. *Journal of Liquid Chromatography & Related Technologies, 33*(9-12), 1130-1150. doi:Pii 92437123210.1080/10826076.2010.484356

Sypek, K., Burns, I. S., Florence, A. J., & Sefcik, J. (2012). In Situ Monitoring of Stirring Effects on Polymorphic Transformations during Cooling Crystallisation of Carbamazepine. *Crystal Growth & Design, 12*(10), 4821-4828. doi:10.1021/cg3005689

Thakuria, R., Delori, A., Jones, W., Lipert, M. P., Roy, L., & Rodriguez-Hornedo, N. (2013). Pharmaceutical cocrystals and poorly soluble drugs. *International Journal of Pharmaceutics, 453*(1), 101-125. doi:10.1016/j.ijpharm.2012.10.043

Tomaszewska, I., Karki, S., Shur, J., Price, R., & Fotaki, N. (2013). Pharmaceutical characterisation and evaluation of cocrystals: Importance of in vitro dissolution conditions and type of coformer. *International Journal of Pharmaceutics, 453*(2), 380-388. doi:10.1016/j.ijpharm.2013.05.048

Trask, A. V. (2007). An overview of pharmaceutical cocrystals as intellectual property. *Molecular Pharmaceutics, 4*(3), 301-309. doi:10.1021/mp070001z

Trask, A. V., Motherwell, W. D., & Jones, W. (2004). Solvent-drop grinding: green polymorph control of cocrystallisation. *Chemical Communications (Camb)*(7), 890-891. doi:10.1039/b400978a

Valeria Soares de Araujo Pinho, F., Felipe da Silva, G., Echeverria Macedo, G., Raquel Muller, K., Kemmerich Martins, I., Lausmann Ternes, A. P., Martins da Costa, J. G., Athayde, M. L., Boligon, A. A., Kamdem, J. P., Franco, J. L., Rose Alencar de Menezes, I., & Posser, T. (2014). Phytochemical Constituents and Toxicity of Duguetia furfuracea Hydroalcoholic Extract in Drosophila melanogaster. *Evidence Based Complementary and Alternative Medicine, 2014*, 838101. doi:10.1155/2014/838101

Varma, M. M., & Begum, S. K. R. (2012). Formulation, Physicochemical Evaluation, and Dissolution Studies of Carbamazepine Solid Dispersions. *International Journal of Pharmaceutical Sciences and Nanotechnology, 5*(3), 1790-1807.

Vitthalrao, M. A., Kumar, F. N., & Radheshyam, B. K. (2013). Cocrystallisation: An Alternative Approach for Solid Modification. *Journal of Drug Delivery & Therapeutics, 3*(4), 166-172.

Wang, H., Lin, Q., Dou, X., Yang, T., & Han, Y. (2017). A Different View of Solvent Effects in Crystallization. *Crystals, 7*(12), 357. doi:10.3390/cryst7120357

Wang, I. C., Lee, M. J., Sim, S. J., Kim, W. S., Chun, N. H., & Choi, G. J. (2013). Anti-solvent co-crystallisation of carbamazepine and saccharin. *International Journal of Pharmaceutics, 450*(1-2), 311-322. doi:10.1016/.j.ijpharm.2013.04.012

Wang, L., & Lv, T.-T. (2013). Determination and modeling of the solubility and prediction of the dissolution properties of 2, 4-dichlorophenoxyacetic acid in toluene, tetrachloromethane and the binary solvent mixtures of (cyclohexane+ethyl acetate). *Journal of Molecular Liquids, 181*, 29-33. doi:10.1016/j.molliq.2013.02.005

Weyna, D. R., Cheney, M. L., Shan, N., Hanna, M., Zaworotko, M. J., Sava, V., Song, S., & Sanchez-Ramos, J. R. (2012). Improving solubility and pharmacokinetics of meloxicam via multiple-component crystal formation. *Molecular Pharmaceutics, 9*(7), 2094-2102. doi:10.1021/mp300169c

Xu, C. H., Zou, M. J., Liu, Y., Ren, J. G., Tian, Y., Yan, J., Wang, Y. P., & Cheng, G. (2011). Pharmacokinetics of Carbamazepine Polymorphs and Dihydrate in Rats, Related to Dogs and Humans. *Archives of Pharmacal Research, 34*(11), 1973-1982. doi:10.1007/s12272-011-1118-8

Yadav, A. V., Shete, A. S., Dabke, A. P., Kulkarni, P. V., & Sakhare, S. S. (2009). Co-Crystals: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients. *Indian Journal of Pharmaceutical Sciences, 71*(4), 359-370. doi: 10.4103/0250-474x.57283