References

1. Tuca A, Guell E, Losada EM, Codorniu N. Malignant bowel obstruction in advanced cancer patients: Epidemiology, management, and factors influencing spontaneous resolution. Cancer Manag Res. 2012; 4: 159-169.
2. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36.
3. Baines MJ. Management of intestinal obstruction in patients with advanced cancer. Gynecol Oncol 2002;84:176–9.
4. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002.Cancer incidence, mortality and prevalence worldwide. IARC CancerBase 2004, 5, version 2.0. IARC Press, Lyon.
5. Kingsley C Ekwueme, Malcolm A West, Paul S Rooney. Emergency first presentation of colorectal cancer following air travel: a case series J R Soc Med Sh Rep May 2011 2:36; doi:10.1258/shorts.2011.011002
6. Kronborg O., Backer O., Sprechler M. Acute obstruction in cancer of the colon and rectum. Dis colon Rectum 1975; 18: 22-27.
7. Ansaloni L, Andersson RE, Bazzoli F, Catena F, Cennamo V, Di Saverio S, Fuccio L, Jeekel H, Leppäniemi A, Moore E, Pinna AD, Pisano M, Repici A, Sugarbaker PH, Tuech JJ. Guidelenines in the management of obstructing cancer of the left colon: consensus conference of the world society of emergency surgery (WSES) and peritoneum and surgery (PnS) society. World J Emerg Surg. 2010 Dec 28;5:29.
8. Johnson PM, Porter GA, Ricciardi R, Baxter NN. Increasing negative lymph node count is independently associated with improved long-term survival in stage III B and III C colon cancer. J Clin Oncol 2006; 24: 3570-5.
9. Burton S, Norman AR, Brown G, Abulafi AM, Swift RI. Predictive poor prognostic factors in colonic carcinoma. Surg Oncol 2006; 5: 71-78. Burton S, Norman AR, Brown G, Abulafi AM, Swift RI. Predictive poor prognostic factors in colonic carcinoma. Surg Oncol 2006; 5: 71-78.
10. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003; 10: 65-71.
11. Claudio Coco, Alessandro Verbo, Alberto Manno, Claudio Mattana, Marcello Covino, Giorgio Pedretti, Luigi Petito, Gianluca Rizzo and Aurelio Picciocchi. Impact of Emergency Surgery in the Outcome of Rectal and Left Colon Carcinoma. World J Surg (2005) 29: 1458–1464.
12. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, Ganiats T, Levin T, Woolf S, Johnson
13. D, Kirk L, Litin S, Simmang C; Gastrointestinal Consortium Panel. Colorectal cancer screening and surveillance: clinical guidelines and rationale: update based on new evidence. Gastroenterology 2003; 124: 544-560.
14. Masaichi Ogawa, Michiaki Watanabe, Ken Eto, Takahiro Omachi, Makoto Kosuge, Ken Hanyu, Lohta Noaki, Tetsuji Fujita, Katsuhiko Yanaga. Clinicopathological features of perforated colorectal cancer. Anticancer Research (2009) Volume: 29, Issue: 5, Pages: 1681-1684.
15. Zielinski MD, Merchea A, Heller SF, You YN. Emergency Management of Perforated Colon Cancers: How Aggressive Should We Be? Journal of Gastrointestinal Surgery (Sep 2011).
16. Ripamonti CI, Easson AM, Gerdes H. Management of malignant bowel obstruction. Eur J Cancer. 2008; 44: 1105-1115.
17. Compton CC. Pathology report in colon cancer: what is prognostically important? Dig Dis 1999;17:67-79
18. Hernanz F, García-Somacarrera E, Fernández F. The assessment of lymph nodes missed in mesenteric tissue after standard dissection of colorectal cancer specimens. Colorectal Dis 2010;12:e57-e60
19. Fan L, Levy M, Aguilar CE, et al. Lymph node retrieval from colorectal resection specimens for adenocarcinoma: is it worth the extra effort to find at least 12 nodes? Colorectal Dis 2011;13:1377-83.
20. Fleming M, Ravula S, Tatishchev SF, Wang HL. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol 2012;3(3):153-173. DOI: 10.3978/ j.issn.2078-6891.2012.030

615.015.11:544.351.3

INCREASING WATER SOLUBILITY OF DRUGS, THE PREREQUISITE FOR IMPROVEMENT OF BIOAVAILABILITY

Aleksandar Cvetkovski[1], Elena Drakalska, Bistra Angelovska

Faculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000
Stip, R. Macedonia
**Corresponding Author: aleksandar.cvetkovski@ugd.edu.mk*

Abstract

Many of low water soluble drugs, from the group of small size molecules, once being administered as single therapeutic doses, not oftenmay reach their plasma concentrations to associate to the therapeutics respond. Cyclodextrins (CD), the sugar's cyclized derivatives, that play a role as functionalized excipients in pharmaceutical formulations, enhance the drug solubility toward the formation of inclusion complexes by noncolavelt intermolecular interactions between the molecules of CD and drug. The value of the binding affinity constant of inclusion complex formation imply to the stoichiometric ratio of CD and drug in inclusion complex and its water solubility.

The representative case study relates to binary and ternary solid systems formed of β-CD and anti epileptic drug carbamazepine (CBZ), and β-CD and CBZ, respectively. Both solid systems are formed by using each of two polymorphic form of CBZ, form I and form III, respectively.

The dissolution profiles, gained by performing the test for the Intrinsic Dissolution rate (IDR), and contributes by the thermodynamic data from the thermal analyses, indicate that β-CD and HPMC influence the phase transition of metastable CBZ form I to stable CBZ form III. Though the CBZ form I exert higher water solubility then CBZ form III, both polymorphic forms in water medium undergo to transformation in CBZ dehydrate, that water solubility is lower comparing to solubility of a both anhydrous CBZ polymorphs.

Keywords: Solubility, Inclusion Complexes Cyclodextrins, polymorphs, phase transition

Introduction

Due to drawbacks of many drugs, perceived during the clinical trials, when they fail, and thus not being pursued by further regulatory approval and post-marketing procedures, the immense of investment cost (DiMasi *et al*, 2016) during the drug development life-cycle cannot be reimbursed with historically low return rate of investment of new launched therapies (Smietana *et al*., 2015). The main reason for erratic pharmacokinetics profiles for 40% drugs that have been withdrawn from the clinical trials mainly is caused by inconsistence of ADME (Absorption, Elimination, Metabolism & Elimination) properties, directly related to drug solubility – absorption correlation, that is the first line criteria for assessment of drug bioavailability.

Among the NEC (New Chemical Entities) that enter as drug candidate in pipeline of pre-clinical drug development, nearly 70% of them belong to the Class II (poor solubility and good permeability) of the Biopharmaceutics Classification System (BCS). Inconsistent therapy regimens with these drugs, because of their poor bioavailability, variable pharmacokinetics, that are affected by food intake, are directly related to low water solubility. Subject to food effects. Therapies from non-optimized drug products developed with these compounds can range from sub-therapeutic pharmacotherapy, to cases where patients can be exposed to toxic levels of the drug (Benet, 2010). In order to rationally select the technology for enhance the drug solubility Butler & Dressman (2010) proposed the Developability Classification System (DCS) as a regulatory assessment tool that encompassed drugs whose absorption is dissolution rate-limited (IIa), and for those whose absorption is solubility-limited (IIb).

Carbamazepine, widely spread antiepileptic drug, known by trademark Tegretol® (Ciba-Geigy), due to its lipophilicity, determined by its molecular structure, in solid-state, exerting as three polymorphic forms (Lowes *et al*., 1987; Kobayashi *et al.,* 2000; Grzesiak *et al.,* 2003) and one dehydrate (McMahon *et al.,* 1996), exhibit good permeability and low water solubility that are hurdle for its passage through blood-brain-barrier, and reaching the receptor sites (Alavijeh S.A. *et al,* 2005; Marchi, N., *et al*., 2009; Upadhyay, 2014).

Beside of many previously launched technologies for accelerating water drug solubility that are based on solid dispersion of drug in polymer matrix (Baghel *et al.,* 2016; Qia *et al.,* 2010, Lumar *et al.,* 213), and currently trend for applying cocrystalization for improving the drug performance (Sun, 2012; Lipert *et al.,* 2015, Box et al., 2015; Kale *et al.,* 2016), technologies that are based on formation of inclusion complexes with sugar derivatives, cyclodextrines (Wenz&Monflier, 2016), have still been utilized, mainly because of wide range of versatile non-covalent interactions between drug model and cyclodextrin, that lead to enhancing the drug solubility (Göktürk *et al.* 2012) and bioavailability (Carrier *et al*. 2007; Beig et al., 2013; Tóth *et al.,* 2017).

The aim of this research is to put examine the influence of native β-cyclodextrin (β-CD) on phase transition of enantiotropically related polymorphs III and I of carbamazepin (CBZ) and their transformation in diydrate forms.

Materials and methods

The solid samples, included in Table 1, have been prepared by mixing the powder component in physical mixtures, kneading the physical mixtures with water/ ethanol solution (50/50 *V/V*), drying and sieving the kneaded samples in form of powders, part of which was used for solid state characterization, and one part for preparing compresses for testing the Intrinsic Dissolution Rate (IDR) of CBZ. Polymorph form III is the commercially available carbamazepin. Polymorph form I was prepared by heating CBZ form III on 180ºC during the 3 hours. Dihydrated CBZ was obtained by filtration and drying the sediment from slurry of CBZ form III in water. All chemicals were supplied by Sigma-Aldrich. The Dissolution test was performed according to *USP 29–NF 24* (US Pharmacopeia) and Different Scanning Caloroimetry is run using the Mettler DSC 821e with STARe software (Mettler Toledo)

Table 1.Bicomponent samples of CBZ polymorphic form/ β-CD, prepared in different molar ratio (*M/M*)

Prepared samples	CBZ polymorphs mol	β-CD mol		
Physical mixtures CBZ Form I/ β-CD	1	1	1.5	2
Kneaded CBZ Form I/ β-CD	1	1	1.5	2
Compressed CBZ Form I/ β-CD	1	1	1.5	2
Physical mixtures CBZ Form III/ β-CD	1	1	1.5	2
Kneaded CBZ Form III/ β-CD	1	1	1.5	2
Compressed CBZ Form III/ β-CD	1	1	1.5	2

Results and discussion

Increasing values of enthalpies of fusion for physical mixtures of CBZ form I/ β-CD in relation to increasing the molar share of β-CD indicate that lower value for the sample of 1:1 *M/M* CBZ Form I/ β-CD is result to decreasing the crystallinity of the system due to higher interaction between molecules of CBZ form I (metastable form at room temperature) and β-CD, that lead to formation of amorphous inclusion complex CBZ Form I/ β-CD during the heating cycle, *in situ* condition in Different Scanning Calorimetry (DSC) measurements (Cvetkoveki *et al*., 2002). However, increasing the molar share of β-CD in physical mixtures with the more stable CBZ form III, at room temperature, indicate that β-CD influence to the decreasing the phase transition of CBZ form III to form I (enantiotropically related pair), before reaching the first melting point of metastable form III, above the transition temperature of 71 ºC (Behme & Brooke, 1991). In both group of kneaded samples, CBZ Form I/ β-CD and CBZ Form III/ β-CD, lower values for enthalpy of fusion for 1:2 *M/M* anticipate to more favorable molar ration for non covalent interactions that lead to formation of amorphous inclusion complex CBZ/ β-CD, in spite of the propensity of both anhydrous polymorphic forms, each with different kinetic to convert to CBZ dihydrat (McMahon *et al*., 1996). These thermodynamic data are contributed with kinetic study for measurements of the Intrinsic Dissolution Rate (IDR), that indicate higher value and high constant (*k*) for kneaded samples CBZ Form I/ β-CD by increasing the molar ration which confirm the decreasing the crystallinity of the systems due to formation of amorphous inclusion complex, that is accompanied by releasing the crystalline water from the cavity of β-CD while CBZ molecule fits within by non covalent interactions. Higher value of IDR and *k* for samples of physical mixtures CBZ Form III/ β-CD compared to that of CBZ Form I/ β-CD are affected to the fact that samples prepared with more stable Form III at

room temperature, undergo to lower kinetics of transformation to CBZ dihydrat with lesser IDR and k then form III and I (Katzhendler *et al*., 1998).

Table 2. Thermodynamic and Kinetic data for binary systems CBZ / β-CD

Prepared samples	*M/M*	ΔH_f ($J \cdot g^{-1}$)	IDR ($\mu g \cdot cm^{-2} \cdot min^{-1}$)	*k* $cm \cdot min^{-1}$
Physical mixtures CBZ Form I/ β-CD	1/1	91.34 (±5.0)	94.84	0.37
	1/1.5	124.75(±5.0)	103.64	0.41
	1/2	130.71(±3.9)	124.73	0.49
Physical mixtures CBZ Form III/ β-CD	1/1	101.66(±4.8) 7.33(±4.8)	287.36	1.45
	1/1.5	99.82(±4.9) 10.02(±1.9)	241.04	1.22
	1/2	93.39(±0.4) 27.12(±1.6)	163.93	0.83
Kneaded CBZ Form I/ β-CD	1/1	104.23(±1.4)	72.07	0.28
	1/1.5	75.33(±4.1)	209.73	0.83
	1/2	62.6(±1.0)	285.68	1.13
Kneaded CBZ Form III/ β-CD	1/1	100.75(±4.7)	77.11	0.39
	1/1.5	83.55(±3.4)	189.55	0.96
	1/2	72.98(±5.9)	208.31	1.05
CBZ Form I (anhydrous)		138.9(±6.6)	253.46	
CBZ Form III (anhydrous)		40.7(±0.4) 134.1(±1.4)	197.72	
CBZ dihydrat		4.4(±0.05) 122.9(±3.9)	125.9	

Conclusion

β-CD influences the phase transition temperature of enantiotropically related polymorphic pair of CBZ, form III and I, due to differences in kinetics of hydration, leading to transformation of both anhydrous polymorphic forms to CBZ dihydrat.

References

1. Alavijeh S.A., Chishty M, Qaiser MZ, Palmer AM., (2005) Drug Metabolism and Pharmacokinetics, the Blood-Brain Barrier, and Central Nervous System Drug Discovery, *NeuroRx.* Oct; 2(4): 554–571.
2. Baghel S, Cathcart H, O'Reilly J. N., (2016) Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II *Drugs, J.Pham.Sci.* 105 2527 -2544
3. Behme RJ, Brooke D.(1991)Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis.*J Pharm Sci.* Oct;80(10):986-90.

4. Beig, A., Agbaria, R., Dahan, A. (2013) Correction: Oral Delivery of Lipophilic Drugs: The Tradeoff between Solubility Increase and Permeability Decrease When Using Cyclodextrin-Based Formulations. PLOS ONE 8(10): 10.1371 e68237 - e68237
5. Benet, Z.L., (2010) Predicting Drug Disposition via Application of a Biopharmaceutics Drug Disposition Classification System Basic Clin Pharmacol Toxicol. Mar; 106(3): 162–167.
6. Box KJ, Comer J, Taylor R, Karki S, Ruiz R, Price R, Fotaki N. (2016) Small-Scale Assays for Studying Dissolution of Pharmaceutical Cocrystals for Oral Administration.*AAPS PharmSciTech*.;17(2):245-51.
7. Butler JM, Dressman JB. (2010) The developability classification system: application of biopharmaceutics concepts to formulation development. *J Pharm Sci*; 99:4940-4954.
8. Carrier, R.L., Miller, L.A., Ahmed, I. (2007) The utility of cyclodextrins for enhancing oral bioavailability. *J Control Release.* 2007 Nov 6;123(2):78-99.
9. Cheney ML, Weyna DR, Shan N, Hanna M, Wojtas L, Zaworotko MJ. (2010) Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics.J Pharm Sci. 2011 Jun;100(6):2172-81.
10. Cvetkovskii, A., Bettini, R., Tasic, L. et al. (2002) Thermal Properties of Binary Mixtures of β-Cyclodextrin with Carbamazepine Polymorphs, J *ThermAnal Calorim*, 68, 2, 669–678
11. DiMasi JA, Grabowski HG, Hansen RA. (2016) Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics; 47:20-33.
12. Göktürk S., Çalışkan E., Talman R. Y., Var U., (2012) A Study on Solubilization of Poorly Soluble Drugs by Cyclodextrins and Micelles: Complexation and Binding Characteristics of Sulfamethoxazole and Trimethoprim," The Scientific World Journal, vol. 2012:718-791
13. Grzesiak AL, Lang M, Kim K, Matzger AJ. (2003) Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *J Pharm Sci.* ;92(11):2260-71
14. Kale DP, Zode SS, Bansal AK (2017) Challenges in Translational Development of Pharmaceutical Cocrystals.*J Pharm Sci.* 106(2):457-470. 2016
15. Katzhendler I, Azoury R, Friedman M. (1998) Crystalline properties of carbamazepine in sustained release hydrophilic matrix tablets based on hydroxypropyl methylcellulose.*J Control Release.* 54(1):69-85.
16. Kobayashi Y, Ito S, Itai S, Yamamoto K., (2000) Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. *Int J Pharm*. 5;193(2):137-46.
17. Kumar S, Bhargava D, Thakkar A, Arora S. (2013) Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review, *Crit RevTher Drug Carrier Syst*.;30(3):217-56.
18. Lipert, P.M., Roy, L., Childs L.C., Rodríguez-Hornedo, N., (2015) Cocrystal solubilization in biorelevant media and its prediction from drug solubilization, *J Pharm Sci.* 104(12): 4153–4163.
19. Loftsson T, Hreinsdóttir D, Másson M. Evaluation of cyclodextrin solubilization of drugs, (2005) *Int J Pharm*. 30;302(1-2):18-28
20. Lowes, M.M., Caira, M.R., Lötter, A.P., Van der Watt, J.G. (1987) Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepineJ Pharm Sci. Sep;76(9):744-52.
21. Marchi, N., Betto, G., Fazio, V., Fan, Q., Ghosh, C., Machado, A., & Janigro, D. (2009). Blood–brain barrier damage and brain penetration of antiepileptic drugs: Role of serum proteins and brain edema. *Epilepsia*, *50*(4), 664–677.
22. McMahon, L.E., Timmins, P., Williams, A.C., York, P., (1996) Characterization of dihydrates prepared from carbamazepine polymorphs,*J Pharm Sci.* 85(10):1064-9.
23. Qia F, Huang J, Hussain, A.M., (2010) Drug–Polymer Solubility and Miscibility: Stability Consideration and Practical Challenges in Amorphous Solid Dispersion Development, *J.Pharm.Sci.* 99 (7) 2941-2947
24. Smietana K, Ekstrom L, Jeffery B, Moller M. (2015) Improving R&D productivity. Nature Reviews Drug Discovery; 14:455-456.
25. Sun, C.C., (2012) Cocrystallization for successful drug delivery. Expert Opin Drug Deliv. 2013 Feb;10(2):201-13.
26. Tóth G., Jánoska Á., Völgyi G. (2017) Physicochemical Characterization and Cyclodextrin Complexation of the Anticancer Drug Lapatinib," Journal of Chemistry, vol. 2017 Article ID 4537632
27. UpadhyayK.R., (2014) Drug Delivery Systems, CNS Protection, and the Blood Brain Barrier, *Biomed Res Int.;* 2014: 869269.
28. WenzG. &MonflierE. (2016) Superstructures with cyclodextrins: chemistry and applications III *Beilstein J. Org. Chem.*, *12,* 937–938.