615.015.11:544.351.3

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

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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 The main reason for erratic pharmacokinetics profiles for 40% drugs that have been withdrawn from the clinical trials mainly is caused by inconsistence of ADME (Absorption, Elimination, Metabolism & Elimination) properties, directly related to drug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.

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