Influence of beta-cyclodextrin on the phase transition in carbamazepine polymorphs

Aleksandar Cvetkovski[a], Elena Drakalska [a]

[a] *Faculty of medical science, University Goce Delcev Stip, Krste Misirkov b.b., P. fax. 201, 2000 Stip Republic N. Macedonia ;*

e-mail: aleksandar.cvetkovski@ugd.edu.mk

INTRODUCTION

Carbamazepin (CBZ), a widespread used antiepileptic drug, branded as Tegretol, firstly was launched in form of Active Pharmaceutical Ingredient (API) as a commercially available polymorphic form III. Additionally, crystallographic studies on crystal packing motifs of carbamazepine molecules in crystal lattices, reveal that, a part of the firstly confirmed structure of polymorphic form III, this drug exists in three other polymorphic forms I, II and IV, as well as pseudopolymorph, dihyrdate form. [1] Further solid-state testing confirmed that in terms of thermodynamical stability CBZ III and I are related as enantiotropic pair.

PURPOSE OF THE STUDY

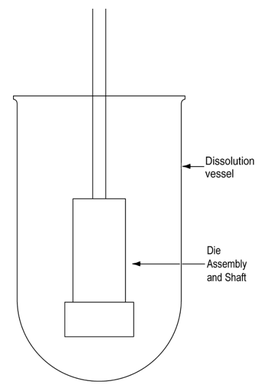
Compromising the differences in crystal packing between CBZ polymorphs III and I that exert differences in density and solubility with the requirements for sufficient plasma concentration available for favorable crossing the blood-brain barrier (BBB) and reaching receptor sites, remain the challenge for crystal engineering CBZ polymorphs with functional excipients which, based on their molecular structures, are appropriate for formation either of inclusion complexes (IC). In terms of processing the CBZ polymorph, either with solvents or by mechanochemical treatments, both technologies impose phase transition; The outlined research objectives address the testing of the influence of beta cyclodextrin (BCD), native cyclic oligosaccharide, on controlling the phase transition of CBZ form III to form I, respectively toward the formation of inclusion complex by non-covalent interactions between nonpolar part of CBZ molecule and hydrophobic CBD cavity that interact each other in stoichiometric ratio [2,3].

METHODS

Mechanochemical treatment (grinded & kneading) of binary systems:
CBZ form I & βCB and CBZ form II & βCB
1/1; 1/1.5 & /2 *M/M*

Rotating disc method

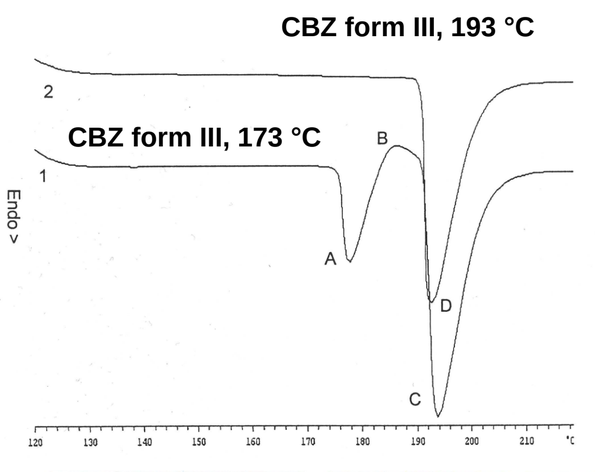
$$DIDR = \frac{dm}{dt}\frac{1}{A_{disc}} = V\,k\,\frac{1}{A_{disc}}$$

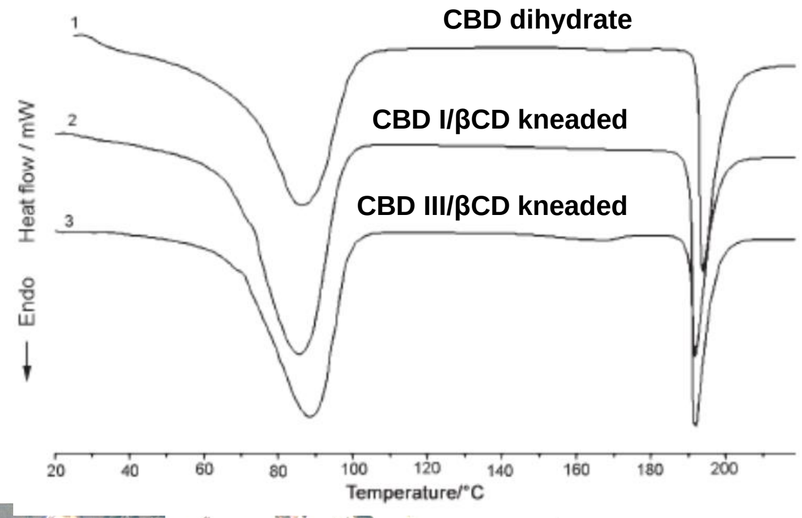


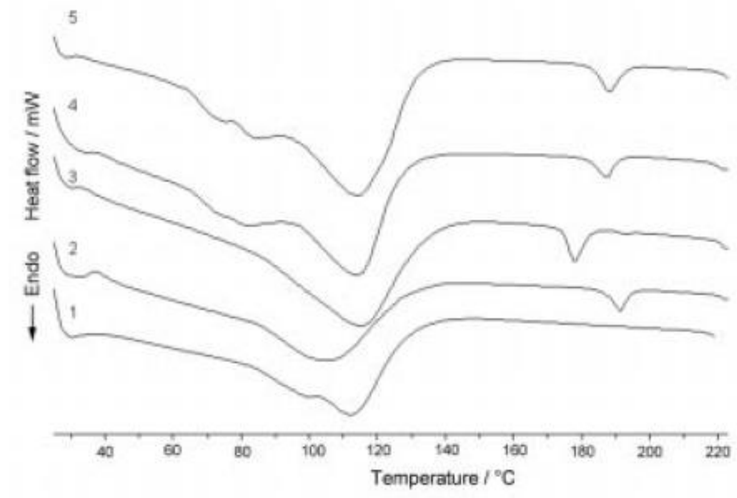
DIDR- disc dissolution rate $\mu g/cm^2 min^{-1}$
m - mass (μg),
t - time (min),
A_{disc} - the disc surface area (cm^2),
V - the volume of the medium (mL),
k - the slope of the straight line from the dissolution profile (μg/(min × mL)

RESULTS

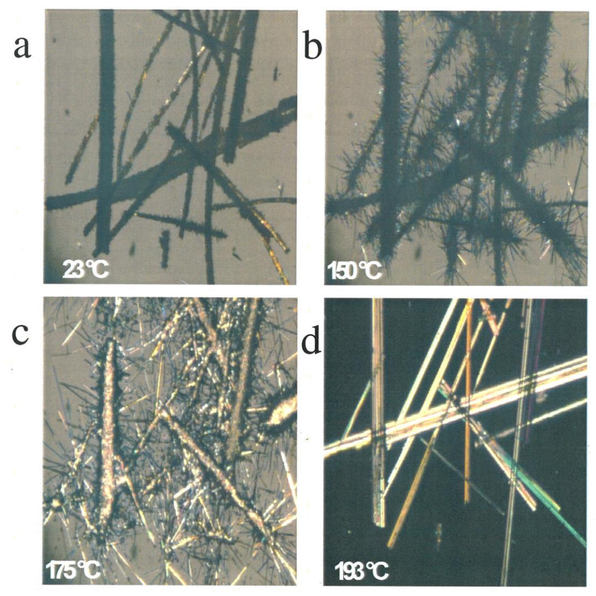
DSC Thermograms

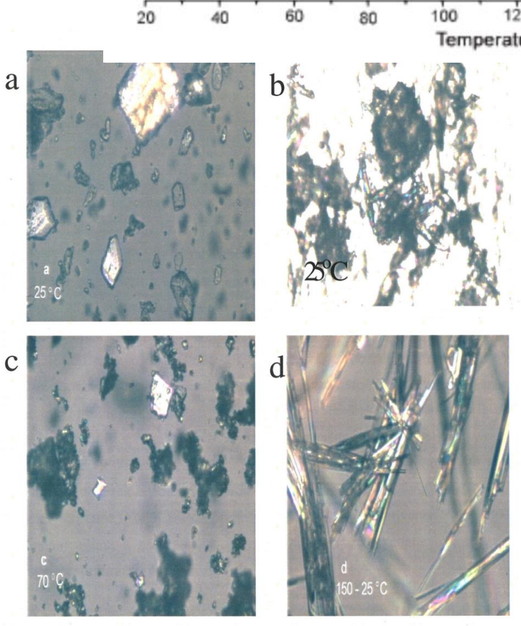


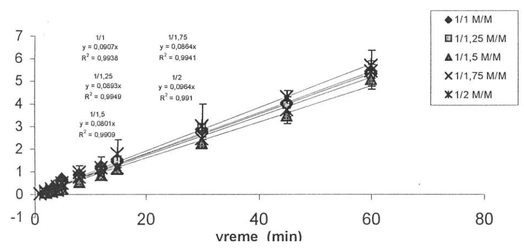


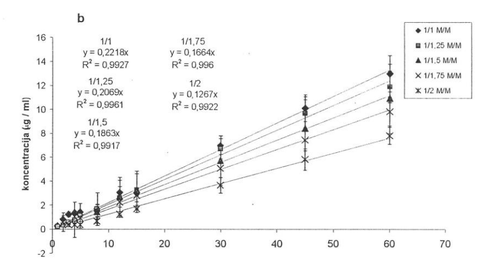


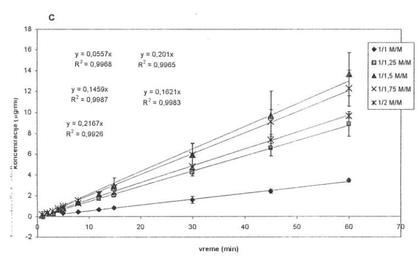
1. βCD 2. CBD I/βCD grounded, 3. CBD III/βCD grounded 4. CBD I/βCD kneaded 5. CBD III/βCD kneaded

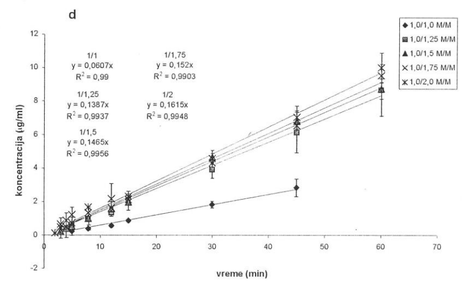












CBZ form	Treatment	Onset ℃	Enthalpy J/g	Onset ℃	DIDR μg·cm⁻².min⁻
III	Grinded	173.6	101.7(2.4)	188.6	77.11
III	Kneaded			181.5	
I	Grinded			186.3	
I	Kneaded			181.9	72.02

Hot-Stege Microscopy; phase transitions

Intrinsic Dissolution Rate Measurements

LITERATURE

1. Grzesiak AL, Lang M, Kim K, Matzger AJ. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J Pharm Sci. 2003 Nov;92(11):2260-71
2. Li Y, Han J, Zhang GG, Grant DJ, Suryanarayanan R. In situ dehydration of carbamazepine dihydrate: a novel technique to prepare amorphous anhydrous carbamazepine. Pharm Dev Technol. 2000;5(2):257-66
3. Cvetkovski, A., Bettini, R., Tasic, Lj., Stupar, M., Casini, L, Rossi, A, Giordano, F., Thermal properties of binary mixtures of β-cyclodextrin with carbamazepine polymorphs. J. Therm. Anal. Cal., 68, (2002) 669–678

CONCLUSION & FURTHER WORK

These results confirm that phase transition of CBZ polymorphs, anhydrous form III and I leading to less water soluble CBZ pseudopolymoprph, dihydrate form during the kneading and formation of IC with BCD occur simultaneously. Less water soluble and stable at ambient temperature CBZ III, thus less favorable for transition in CBZ dihydrate, in grinded binary sample with BCD exerts higher water solubility due to formation of IC. BCD in high extent retains inhibition of phase transition of CBZ III to CBZ I during the DCS heating cycle. ICs as immediate release drug delivery systems offer further opportunities for design modified release formulations that may include IC in combination a polymeric matrix formation compounds for additional control of both the drug release profile and drug phase transition The further work intends to put in evidence biopharmaceutical profiles CBZ form I/βCB and CBZ form II/βCB.

Acknowledgment to pharmaceutical company Replek for supporting the poster presentation of the research data

14th Central European Symposium on Pharmaceutical Technology 28 - 30 of September 2023, Ohrid, R. Macedonia