Biodegradable materials for improving oral absorption of carbamazepine: an eco-sustainable approach

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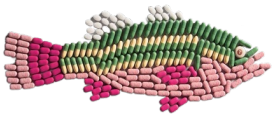
Background

The main source of environmental pharmaceutical pollution is the excretion of drugs. The drug most often detected worldwide is carbamazepine (CBZ) [1], an antiepileptic drug that due to its low solubility belongs to class II of the BCS.



Aim

A pre-formulative study to increase the apparent solubility by improving the bioavailability of CBZ studying their interaction with six different natural and synthetic cyclodextrins (CD), biodegradable materials, was investigated. The improvement of drug solubility and their bioavailability reduce the drug dose to be administered and consequentially the environmental spread of unmetabolized drug.

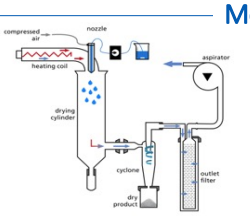
Methods

Preformulation study

The Phase solubility studies to evaluate the affinity between α, β, γ, Methyl-β, Hydroxypropyl-β, Sulfobutyl Ether-β-cyclodextrin and CBZ were performed in simulated colonic fluid at pH 6.8. The Job's plot has been drawn by UV-vis spectroscopy to determine the stoichiometry of *host-guest* inclusion complex.

Spray-dried complex preparation

The complex solution of CBZ/M-β-CD 1:2 was dried by spray drying (SD) technique at 1%p/v.

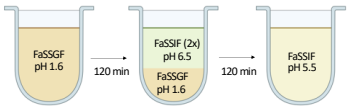


Spray drying parameters	
Inlet T (°C)	120
Outlet T (°C)	65
Feed rate (ml/min)	3.5
Atomization Flow (L/h)	601
Aspiration rate (m^3/h)	35
Nozzle diameter (mm)	1.4

Physicochemical and Biopharmaceutical Characterization

The spray dried complex was compared with the corresponding physical mixture and the raw material by differential scanning calorimetry analysis (DSC), scanning electron microscopy (SEM) and particle size distribution (PSD).

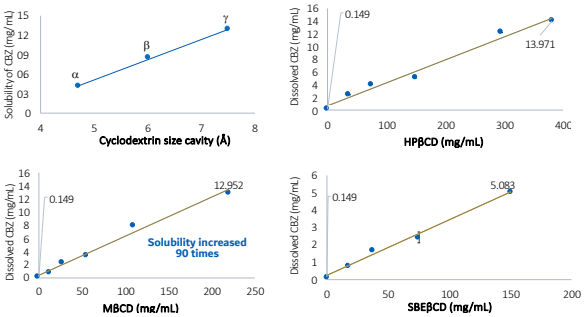
Dissolution in two-step dissolution media containing FaSSGF (pH 1.6) and FaSSIF (pH 6.5) was performed over 4 h under continuous stirring at 100 rpm at 37°C.



To evaluate the *in vitro* safety and permeability, intestinal Caco-2 cells were exposed to increasing concentration (0.49,0.75 and 1.42 mg/ml) of the complex, physical mixture and raw material, based on the amount of unmetabolized CBZ reach the distal colon.

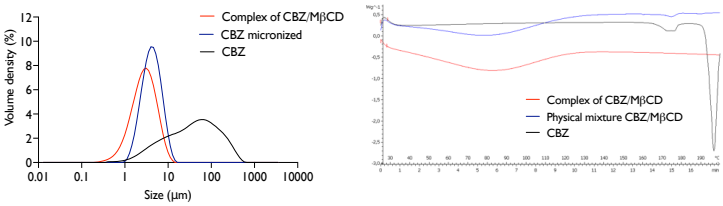
Results

Phase solubility study

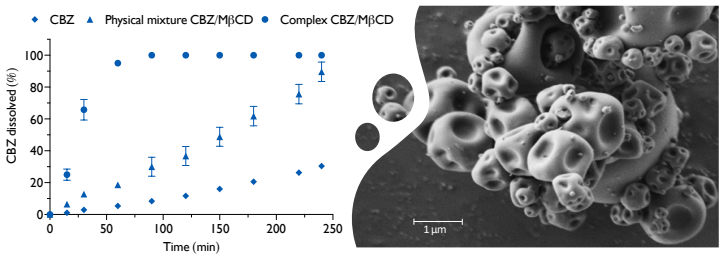


CD	CBZ (mM)	CD (mM)	[CD]/[CBZ]
MβCD	**54.8**	**184.5**	**3.4**
HPβCD	59.1	260.7	4.4
βCD	3.6	15.9	4.5
SBEβCD	21.5	103.5	4.8
γCD	5.4	177.3	32.7
αCD	1.7	143.9	83.3

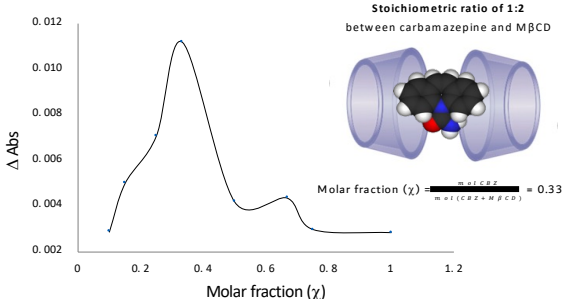
PSD and DSC



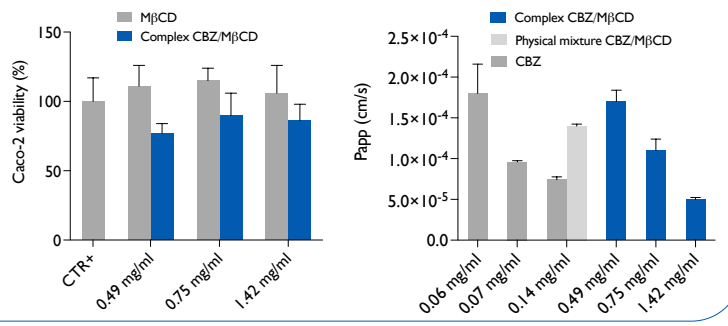
Dissolution and SEM



Job Plot



In vitro safety and permeability



Conclusions

The complexation of CBZ with MβCD improved the dissolution rate of drug by 20-fold in biorelevant fluids and consequently the permeation through Caco-2 cells. The development of a solid oral pharmaceutical form based on the spray dried complex CBZ/MβCD in ratio 1:2 allows the administration of lower dose of CBZ reducing the environmental spread.

[1] Wilkinson, J.L.; Boxall, A.B.A.; Kolpin, D.W.; Leung, K.M.Y.; Lai, R.W.S.; Galbán-Malagón, C.; Adell, A.D.; Mondon, J.; Metian, M.; Marchant, R.A.; et al. *Pharmaceutical Pollution of the World's Rivers*. Proceedings of the National Academy of Sciences of the United States of America 2022, 119, e2113947119 doi:10.1073/pnas.2113947119.