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Biodegradable Materials For Improving Oral Absorption Of Carbamazepine: An Eco-sustainable Approach

Eride Quarta, PhD

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Environmental pharmaceutical pollution

Drugs spread in world's rivers

Pharmaceutical pollution of the world's rivers

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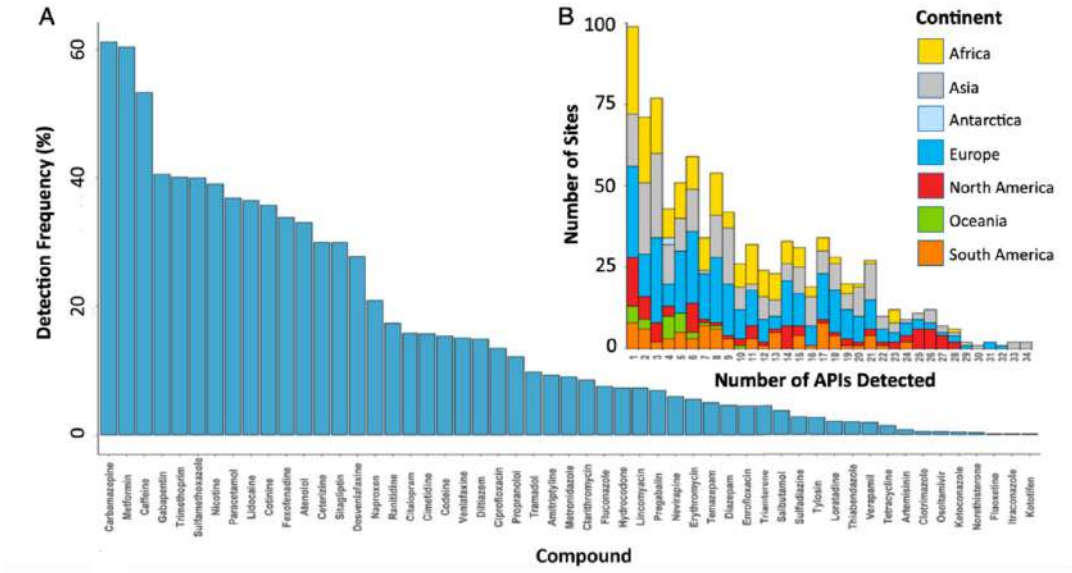


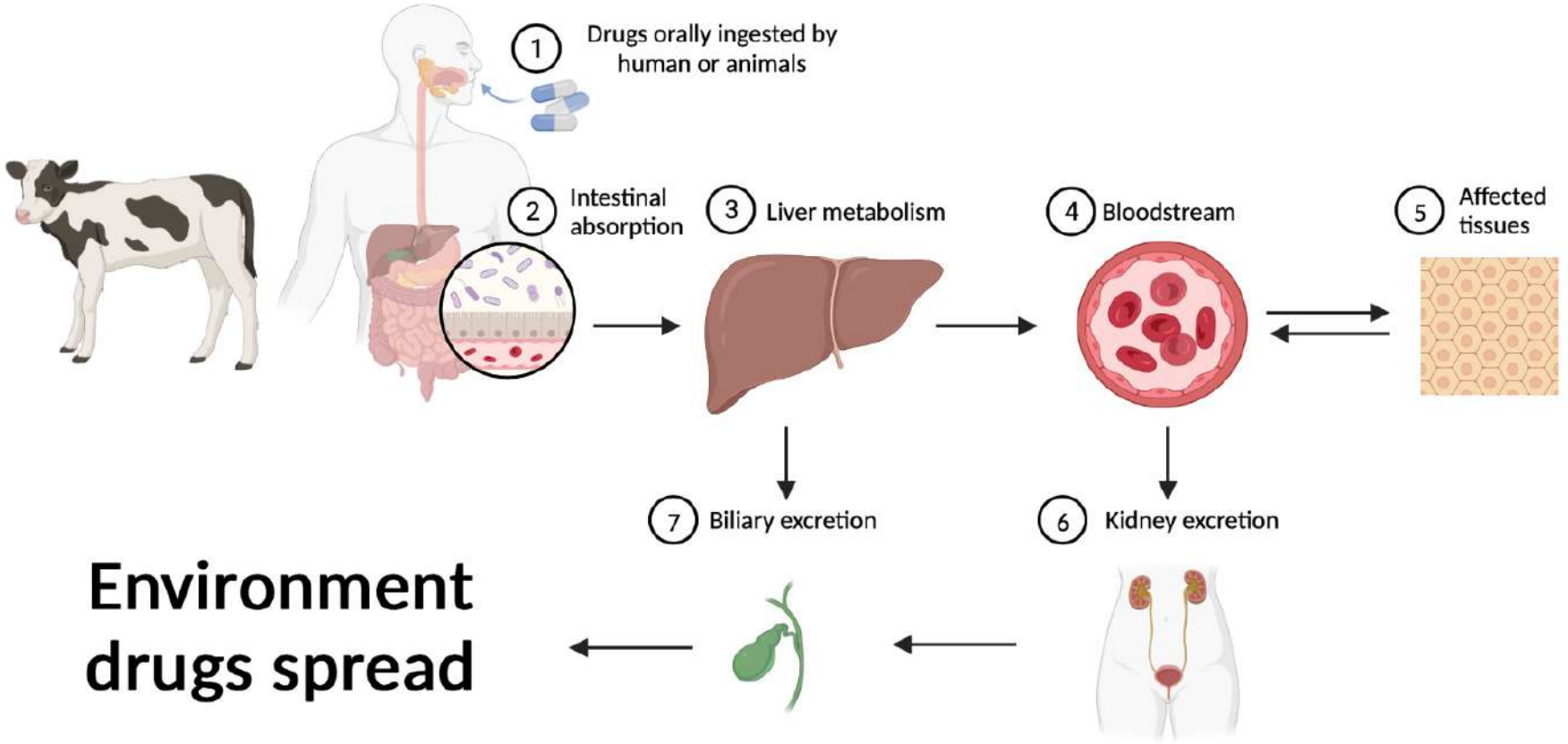
471 milion people

140 geographic regions

Detection frequency %	
Carbamazepine	**62,3**
Metformin	61,1
Caffein	56,1
Gabapentin	41,6
Trimethoprim	39,9
Sulfamethoxazole	39,7
Nicotine	38,7
Paracetamol	36,8

Wilkinson, J. L. et al. P Natl Acad Sci Usa 119, e2113947119 (2022)

Poorly soluble and permeable drugs: an environmental risk

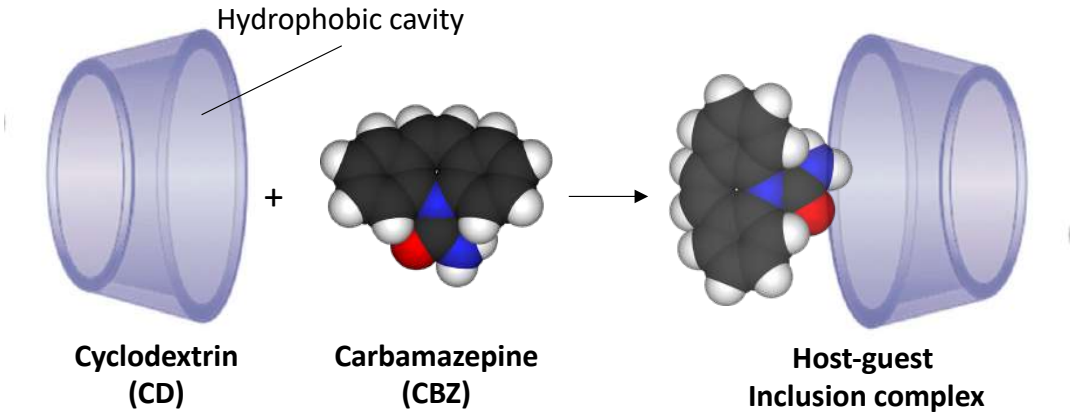


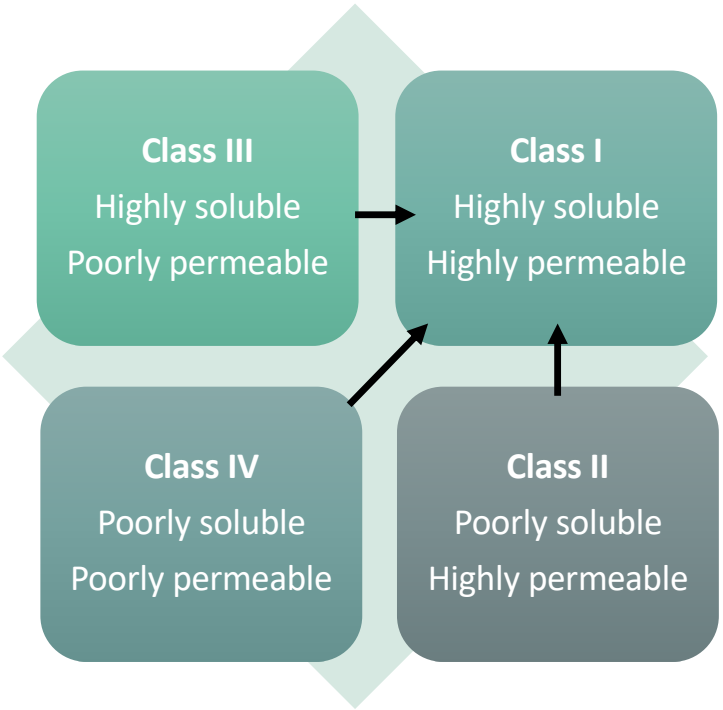
Rzymski, P., et al. *Limnological Rev* **17**, 97–107 (2017)

Biodegradable materials for improving solubility and oral absorption of poor soluble APIs

Cyclodextrins natural or semi synthetic:

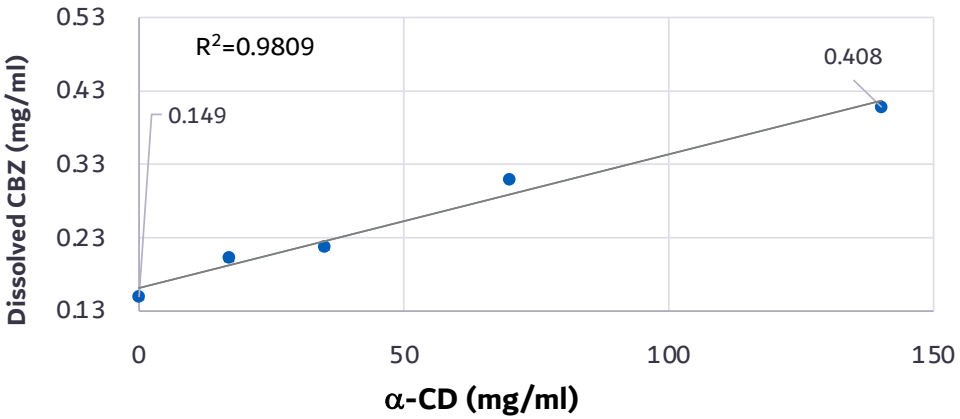
- biodegradable cyclic glucopyranose oligosaccharides
- drug solubility and bioavailability enhancer
- reduced administered doses of complexed drug
- low environmental spread

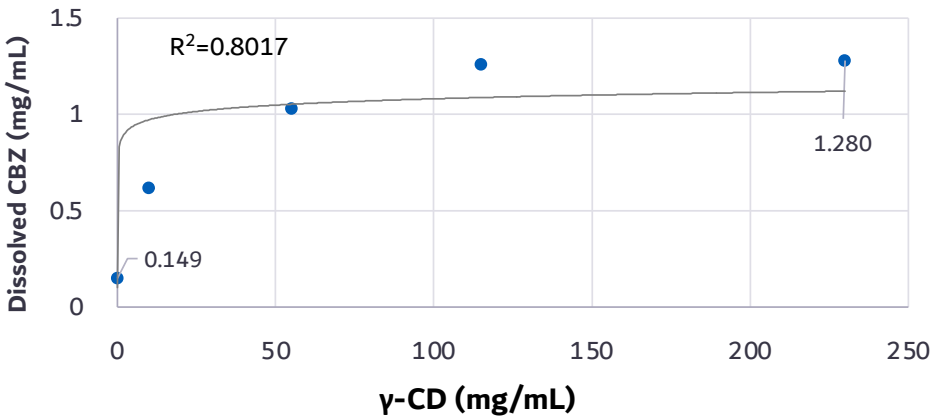


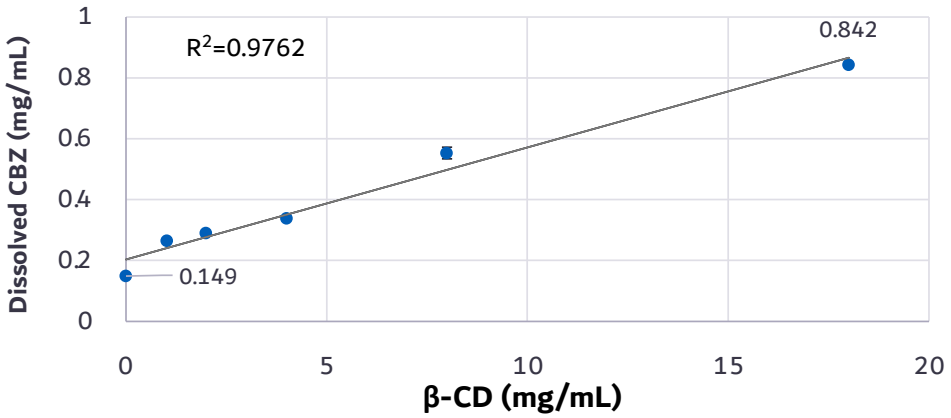


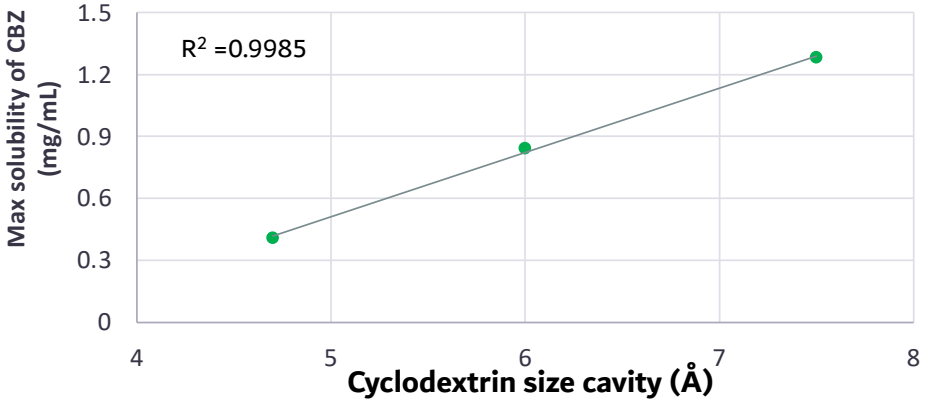
Jambhekar, S. S. & Breen, P. Drug Discov Today 21, 356–362 (2016).

Phase solubility studies of CBZ with natural cyclodextrins in simulated colonic fluid

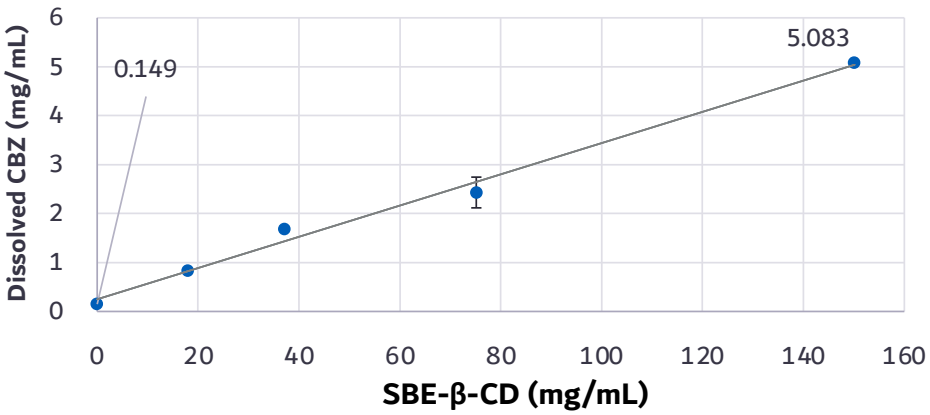


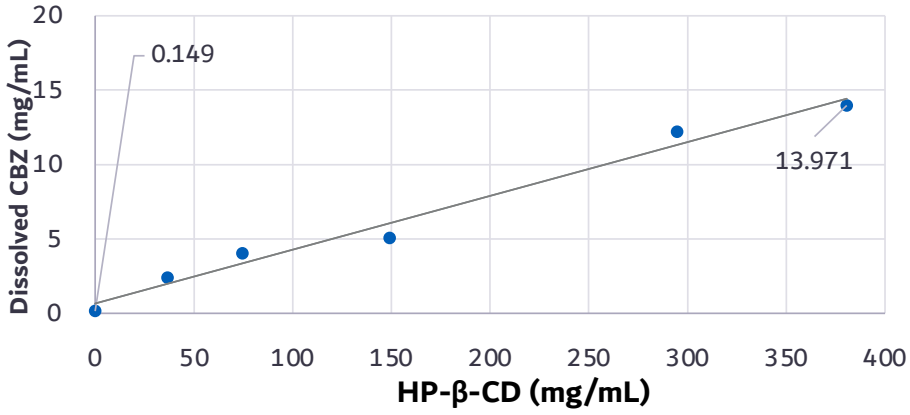


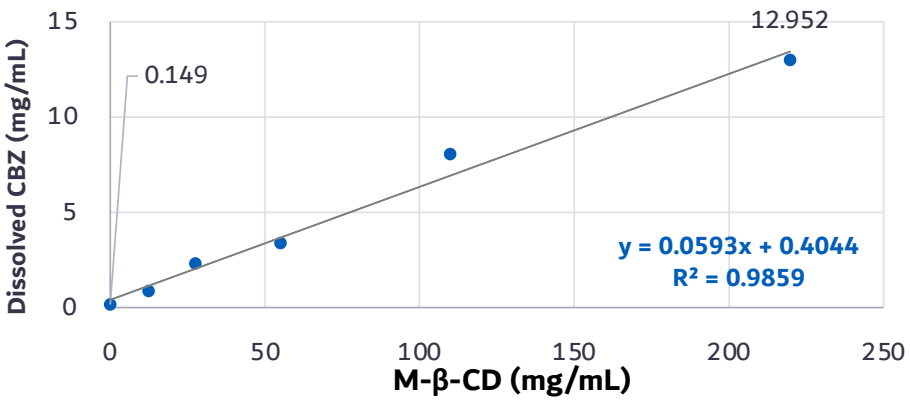




Phase solubility studies of CBZ with synthetic cyclodextrins in simulated colonic fluid

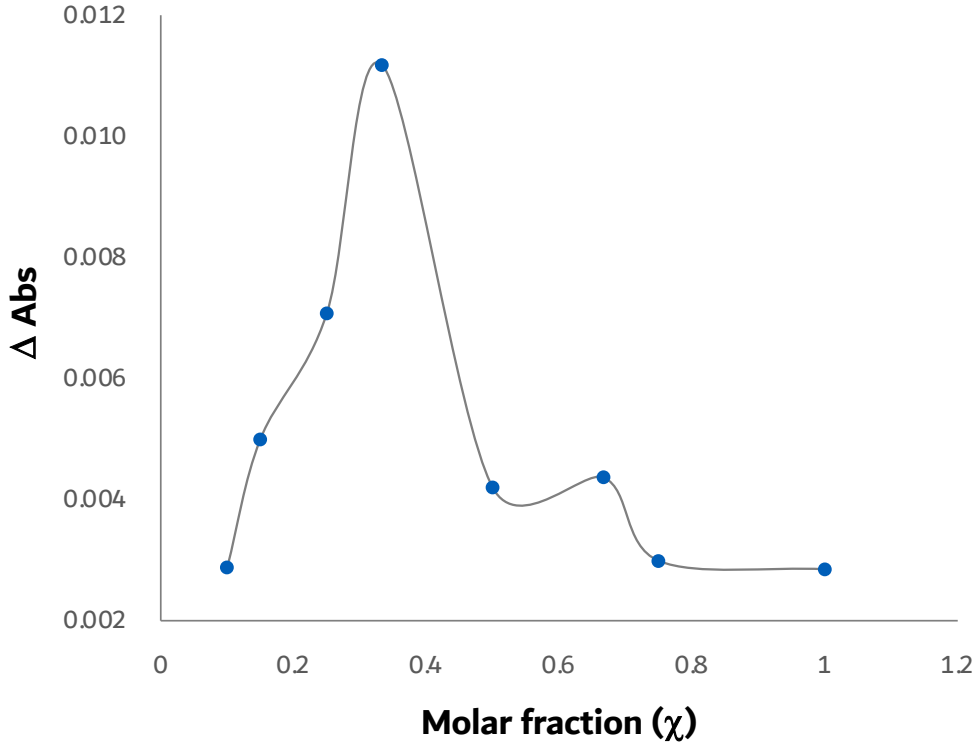




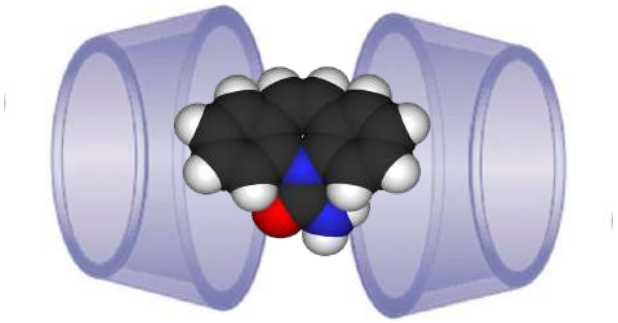


CD	CBZ (mM)	CD (mM)	[CD]/[CBZ]
M-β-CD	**54.8**	**184.5**	**3.4**
HP-β-CD	59.1	260.7	4.4
β-CD	3.6	15.9	4.5
SBE-β-CD	21.5	103.5	4.8
γ-CD	5.4	177.3	32.7
α-CD	1.7	143.9	83.3

Job's plot construction to determine the stoichiometry of *host-guest* inclusion complex



Stoichiometric ratio of 1:2
between carbamazepine and M-β-cyclodextrins

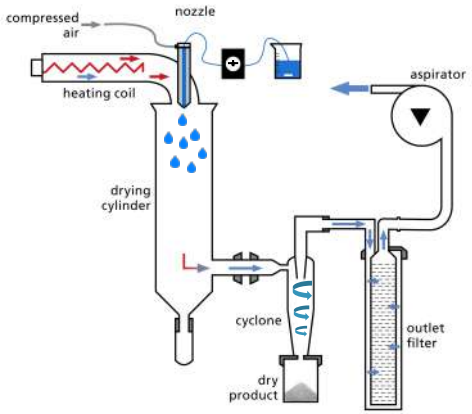


$$\text{Molar fraction } (\chi) = \frac{mol\ CBZ}{mol\ (CBZ+M\beta CD)} = 0.33$$

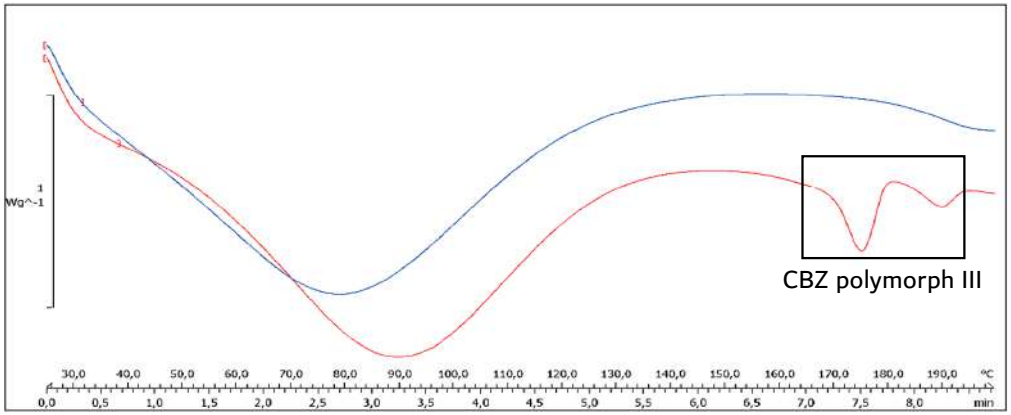
Spray dried CBZ/M-β-CD 1:2 complex characterization by DSC and IR

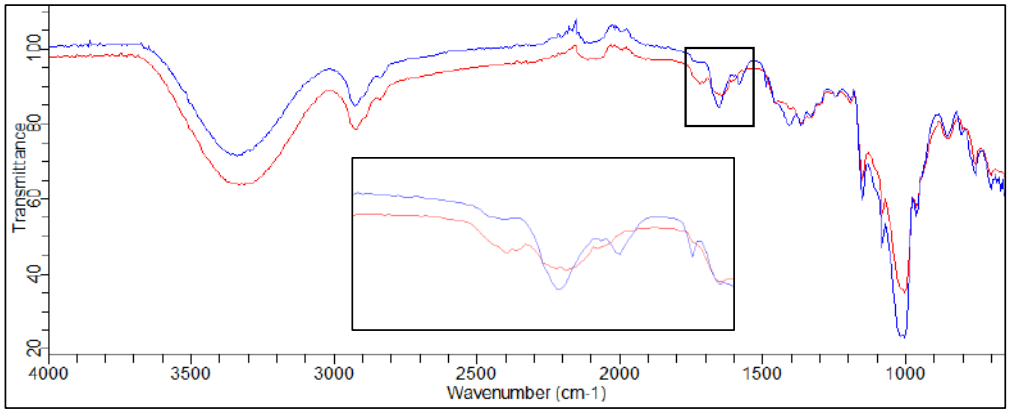
A comparison between spray-dried product and physical mixture:

- conversion from CBZ polymorph form III to that amorphous form is revealed by DSC spectra;
- displacement in IR spectrum of water H-O-H bond within cyclodextrin by CBZ confirms the interaction between CBZ and **M-β-CD.**

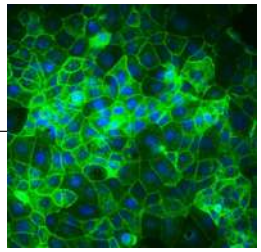


Spray drying Parameters	
Inlet T (°C)	120
Outlet T (°C)	65
Feed rate (ml/min)	3.5
Atomization Flow (L/h)	601
Aspiration rate (m^3/h)	35
Nozzle diameter (mm)	1.4



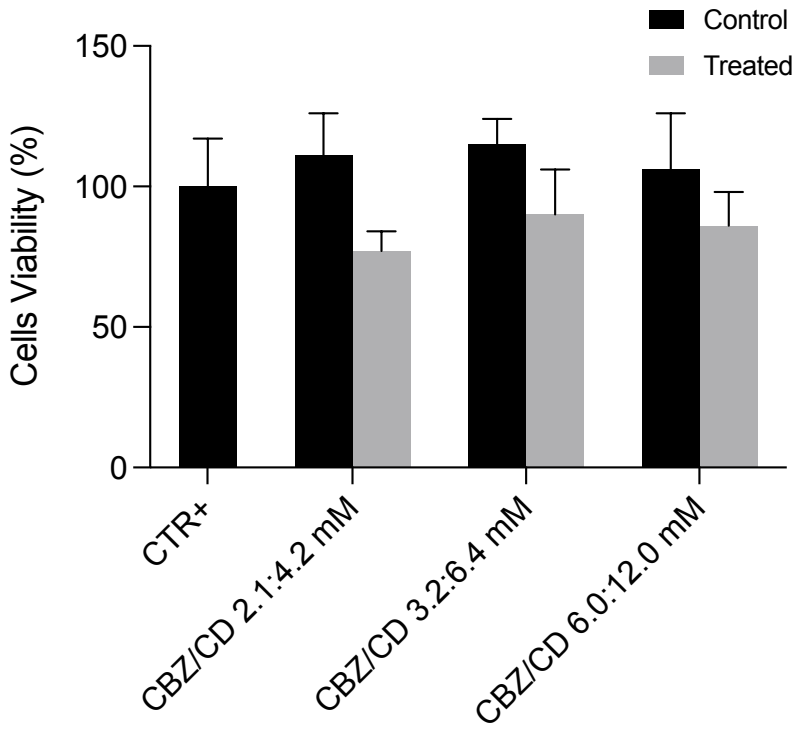


Safety of CBZ/M-β-CD complex on intestinal Caco-2 cells



- CBZ is marketed as Tegretol® tablet 400 mg;
- **120 mg** (*i.e.,* 30%) of unmodified CBZ is excreted as faeces;
- Descending colon fluid volume is **160 ± 85 ml**.

Unmodified CBZ excreted as faeces (mg)	Descending colon fluid volume (ml)	Concentration of CBZ (mM)	Concentration of CD (mM)
120	245	2.1	4.2
	160	3.2	6.4
	75	6.0	12.0



p value > 0.5

Conclusions

- The **CBZ:M-β-CD inclusion complex** is the most promising in terms of solubilization efficacy: apparent **solubility 90 times greater** than the initial CBZ solubility was obtained.

- The **amorphous spray dried** *host-guest* 1:2 complex was successfully manufactured and demonstrated to be **safe in Caco-2 cells**.

- The CBZ therapeutic effect can be obtained by administering a **lower drug dose by reducing the concentration in surface waters**.

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