AGE RELATED BIORELEVANT DISSOLUTION TESTING FOR PAEDIATRIC FORMULATIONS

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INTRODUCTION

- Dissolution of oral dosage forms depends on the GI tract physiological conditions, and definition of the dissolution profile in conditions that reflect the *in vivo* GI environment can lead to accurate prediction of the in vivo performance (1).
- Whenever IVIVCs are achieved clinical studies assessing product bioavailability can be reduced in number and size and this aspect is of primary importance for paediatric patients (2). Successful predictions of the in vivo performance of drugs can be achieved based on biorelevant in vitro experiments (2).
- Biorelevant media reflective of age specific paediatric populations (i.e. new born and infant) have been developed (3).

Aim: to develop biorelevant dissolution methods that are representative of the paediatric gastrointestinal tract by applying experimental parameters based on physiological relevant parameters in order to assess the possible effects on dissolution/release proprieties of oral formulations for paediatric patients.

MATERIALS AND METHODS

Tegretol® 200mg tablets (Novartis) traditionally used to treat epilepsy in children and adults have been investigated.

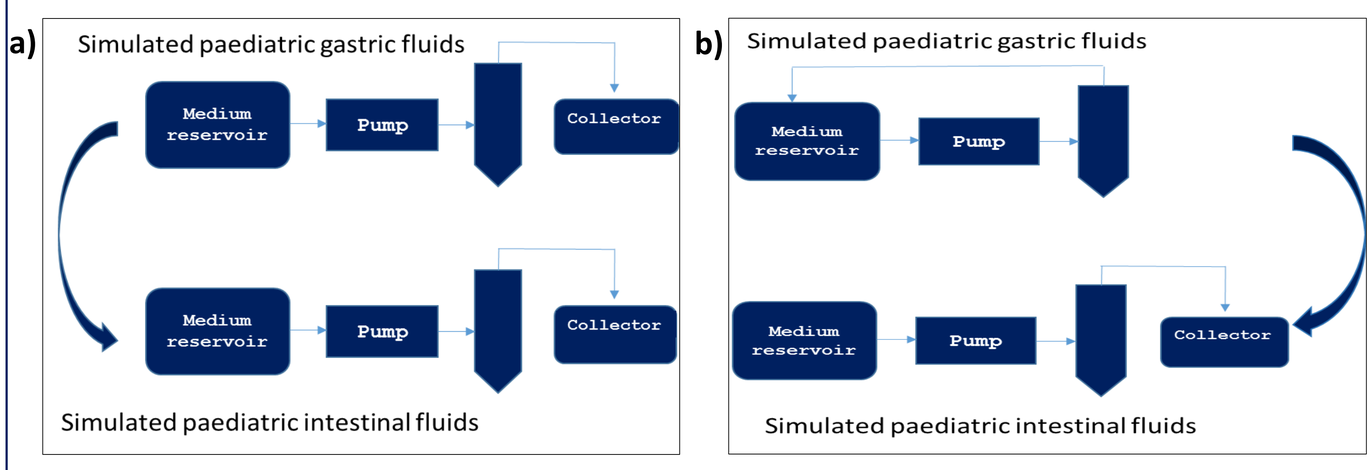
Two paediatric age groups were investigated: namely neonates (0-28 days) and infants (1-12 months). Biorelevant media simulating age specific parameters in GI fluids (i.e. pepsin, bile acids, pH, osmolarity) in the fasted state were used (Table 1).

Table 1: *In vitro* biorelevant dissolution testing parameters based on physiological relevant parameters (i.e. media/hydrodynamics) and used for USP IV apparatus dissolution tests

Age group	Gastric conditions (open mode)			Gastric conditions (closed mode)		
	Media	Time (min)	Flow rate (mL/min)	Media	Time (min)	Volume (mL)
Neonates	Pn-FaSSGF	45	3	Pn-FaSSGF	45	135
Infants	Pi-FaSSGF	30	4	Pi-FaSSGF	30	120
Intestinal conditions (open mode)						
	Media	**Time (min)**		**Flow rate (mL/min)**		
Neonates	P-FaSSIF 50%	240		2		
	P-FaSSIF 150%					
Infants	FaSSIF-v2	240		3		

For neonates intestinal fasted fluids composition two different bile salts concentrations have been taken into account, namely P-FaSSIF 50% and P-FaSSIF 150% of adult level (3).

Experiments were conducted in triplicates with an Erweka Flow-Through-Cell-Apparatus equipped with Ø 22,6 mm cells. The experimental parameters applied are presented in Table 1 (4).



Figures 1a, 1b: The effect of the hydrodynamics on the dissolution was studied with setting **a/** the open mode and **b**/ the closed mode for simulation of the gastric conditions followed by the open mode for simulating the intestinal conditions.

RESULTS

Carbamazepine (CBZ) was not completely dissolved in all the conditions tested. An age dependent dissolution profile of carbamazepine from Tegretol tablet is observed in the two paediatric groups studied (figures 2 and 3), revealing the impact of the gastrointestinal differences (fluid composition and transition times) between the age groups on dissolution.

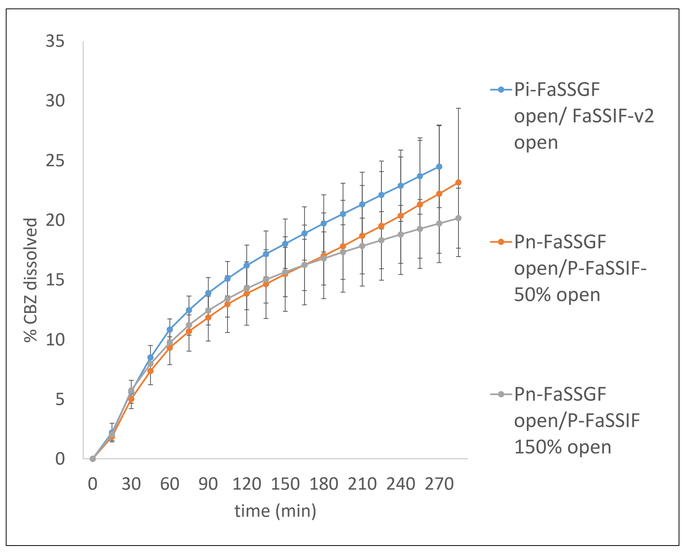


Figure 2: *In vitro* dissolution profiles of carbamazepine from Tegretol in paediatric biorelevant conditions using USP IV apparatus open (gastric)/open (intestinal) mode

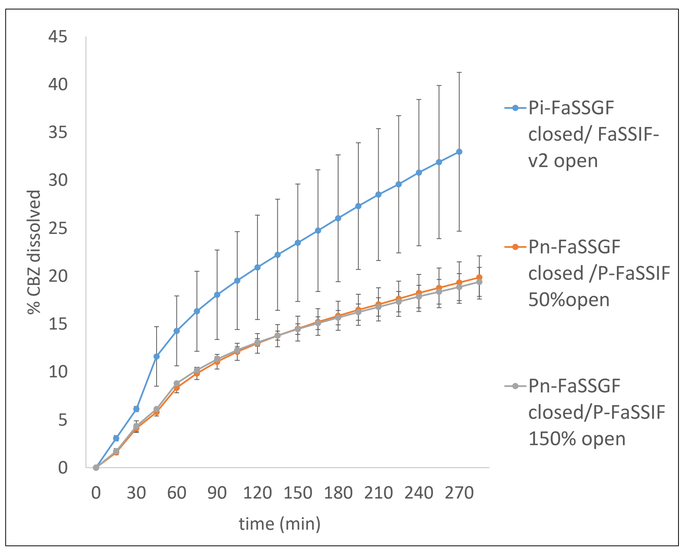


Figure 3 : *In vitro* dissolution profiles of carbamazepine from Tegretol in paediatric biorelevant conditions using USP IV apparatus closed (gastric)/open (intestinal) mode

The use of the closed mode for the dissolution in the stomach resulted in a higher discrimination of the dissolution profiles between the two age groups (figure 3)

CONCLUSIONS

- **Taking into account age related physiological parameters has an impact on dissolution of oral solid dosage forms.**
- **Age related biorelevant dissolution testing can be a valuable tool for the evaluation of paediatric formulations and the assessment of potential implications for paediatric oral drug delivery.**

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