Impact of Sorbitol in the Regional Absorption of Eslicarbazepine Acetate by PBPK Modelling
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Purpose
To assess the effect of sorbitol on the regional absorption of eslicarbazepine acetate (ESL) formulated as an oral liquid for pediatric indication, by using a PBPK model

Methods
Gastroplus®, was used to create a PBPK model. In vivo data retrieved from a paediatric clinical trial dose of 15 mg/kg (formulation with sorbitol) was selected as reference. The developed model showed a fit to the in vivo PK profile > 0.9.
Sorbitol effect was simulated by challenging the model for transit time based on the data described by Adkins to simulate the sorbitol effect:
- Stomach transit time increased by 27%
- Intestinal transit time reduced by 35%

In order to simulate the osmotic effect of sorbitol the percentage of fluids was increased as follows:
- Intestine: 40 → 80%
- Colon: 10 → 20%

Three doses, 5, 15 and 30 mg/kg, were studied in this paediatric population (2-6 years). The absence of sorbitol in the formulation was simulated by using the reference transit time and intestinal fluids content.

A regional absorption analysis and in vivo dissolution over time was performed using PBPK modelling.

Results
Regional absorption data was predicted by Gastroplus®.
Figure 1 shows that, despite not having any impact in the PK profile and respective PK parameters, the presence or absence of sorbitol in the formulation induced changes in the levels of absorption of ESL in some of the GI tract regions.
The differences in the percentages of ESL absorbed in each intestinal area can be justified by the sorbitol effect in the residence time of the oral suspension in the small intestine. The shorter residence time justifies the smaller amounts absorbed in the upper intestinal regions and higher amounts absorbed in the lower intestinal regions.

Additionally, formulations with sorbitol presented a shorter T_max (around 30 minutes) which can be justified by the fact that ESL, in a formulation with sorbitol, reaches faster its higher absorption region (jejunum).
In all tested formulations and doses, ESL was completely dissolved in vivo in less than 3h. The time to achieve a complete dissolution increased with the dose. This justifies the observed increase on T_max with the dose increase (Figure 2).
Formulations without sorbitol required longer time to achieve a complete drug dissolution, which can be justified by the osmotic effect of sorbitol. This was more evident for higher doses.

Transit time effect of sorbitol did not appear to impact in vivo ESL dissolution, which could be justified by the pH independent solubility of the drug.

Conclusion
Based on the developed PBPK model, the following conclusion can be taken with regards to ESL:
- Preferable absorption area is jejunum, followed by duodenum,
- Absorption can occur over the whole small intestine and colon,
- Completely dissolved in vivo within 3h.
The presence of sorbitol impacted the regional absorption and in vivo drug release but did not impact the ESL PK profile. This can be justified by the pH independent solubility of ESL and the fact that drug absorption can occur over the whole small intestine and colon.

![Figure 1](image1.png)
![Figure 2](image2.png)