Dynamic gastrointestinal in vitro model: difference in food effect between two polymorph API forms

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INTRODUCTION:

The behavior of active pharmaceutical compounds (APIs) during transit through the gastrointestinal (GI) tract is critical regarding the release and their subsequent availability for absorption (bioaccessibility). TIM-1 (Figure 1), a dynamic *in vitro* digestion model, mimics the luminal processes in the stomach and small intestine. The system is a useful tool for pre-clinical formulation testing to predict the behavior of a compound in the human GI tract and contributes to the reduction of animal studies, according to the '3R' principle.

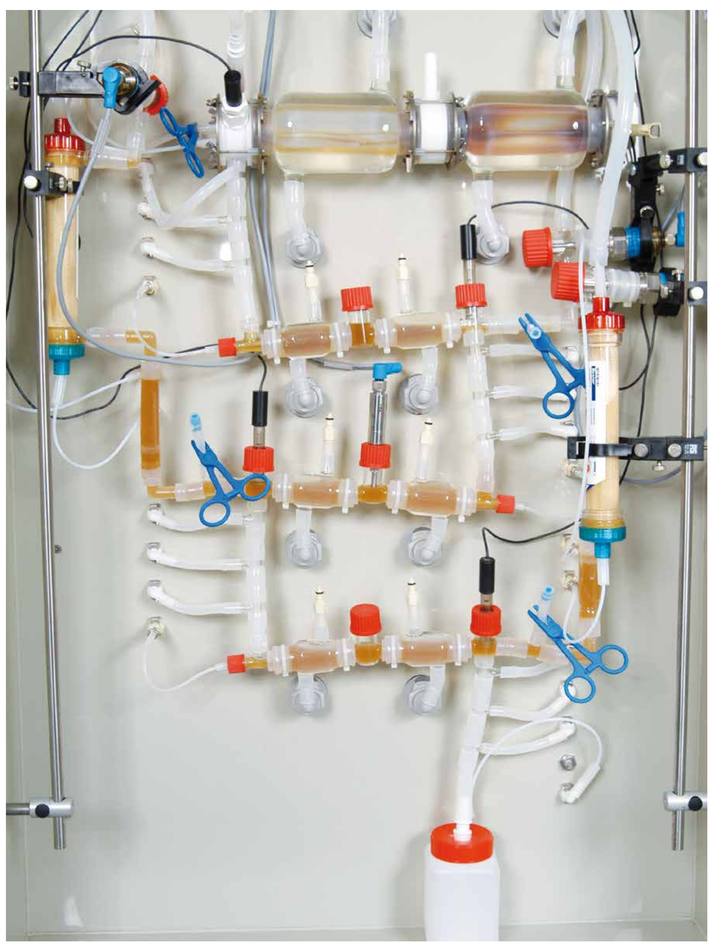

Figure 1. TIM-1 TNO Intestinal model mimicking the stomach and small intestine.

GOAL:

To study the bioaccessibility of an API formulated in two polymorph forms in a dynamic GI model (TIM-1) under fed and fasted state conditions.

METHODS:

TIM-1 (Figure 1) was used in this study (Minekus et al. 1995). The multi-compartmental model mimics body temperature, gastric and intestinal pH, peristaltic mixing, gastric and intestinal transit, secretion of digestive juices, and removal of dissolved low MW compounds and water. The released API is site specifically removed from the ileum, simulating an ileum absorption window. GI conditions of human adults were simulated for fasted and fed state: intake of the API with water or the FDA recommended high fat meal.

Fed and fasted specific parameters were simulated, including specific gastric pH levels, rate of gastric emptying, intestinal pH levels for duodenum, jejunum and ileum and normal or reduced amounts of digestive juices, respectively. The API was added in two polymorph forms, Polymorph X and Polymorph Y, as 150mg IR tablet. The availability for absorption of the API was measured, by analysing TIM-1 ileum samples using HPLC-UV.

RESULTS:

Data show no food effect for Polymorph X; 74.15±0.0 mg vs. 81.86±17.3 mg, collected in 6 hourly aliquots for fasted and fed state, respectively. With Polymorph Y a negative food effect was observed. The ileal bioaccessibility was lower under fed- (36.56±13.2 mg) versus fasted conditions (64.56±7.8 mg). A higher amount of Polymorph Y was retained in the stomach in comparison to Polymorph X (Table 1).

CONCLUSION

- In TIM-1, no food effect was observed for Polymorph X (Figure 2), which was confirmed in vivo, in man (Figure 3).
- The time shift in onset of API release (Figure 2) is caused by the faster gastric emptying during fasted state conditions versus fed state conditions, as found in humans (Figure 3).
- For Polymorph Y a negative food effect was observed in TIM-1, as well as in vivo.
- Based on the TIM-1 experiments, a high gastric retention was identified as reason for the low bioaccessibility of Polymorph Y in the fed state.
- Since the solubility of the API increases with increasing pH values, as during fed state conditions, it is hypothesized that Polymorph Y interacts with ingredients present in the meal matrix.
- TIM-1 gave a first indication for underlying mechanisms (e.g. gastric retention).

	Polymorph X		Polymorph Y	
Sample fraction	**Fasted***	**Fed**	**Fasted**	**Fed**
bioaccessible fraction (ileum)	74,15 ± 0,0	81,86 ± 17,3	64,56 ± 7,8	36,56 ± 13,2
ileum effluent	30,82 ± 0,0	25,30 ± 5,3	21,27 ± 4,8	11,80 ± 4,5
stomach residue	9,73 ± 0,0	23,50 ± 20,7	30,69 ± 13,9	76,69 ± 14,1
small intestinal residues	10,09 ± 0,0	9,16 ± 2,6	8,22 ± 2,6	7,10 ± 2,8
Recovery	124.8 ± 0,0	139,8 ± 0,7	124,8 ± 0,1	132,2 ± 6,4
[%]	(83,2%)	(93,2%)	(83,2%)	(88,1%)

Table 1. Mean (± range, n=2) API in the sample fraction collected from TIM-1 [mg]. ** n=1*

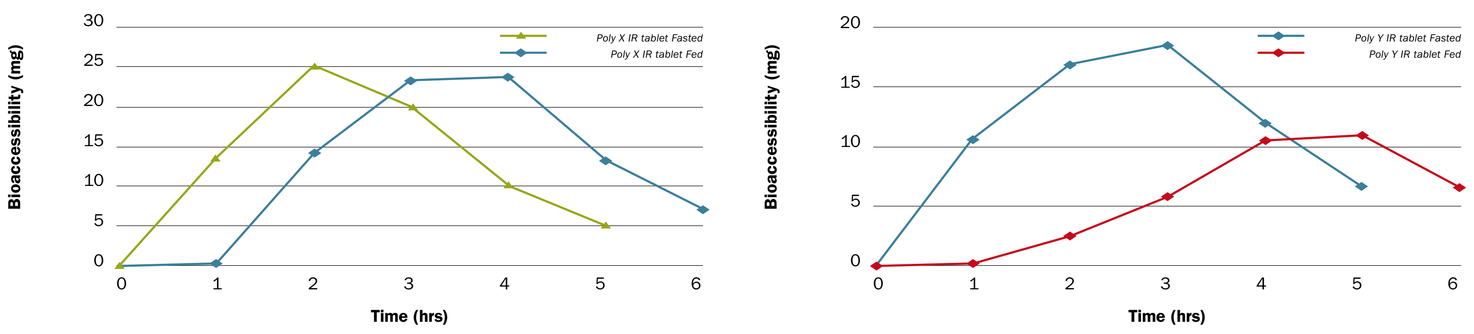

Figure 2. TIM-1: mean (n=2) bioaccessibility in time of API in Polymorph X (left) and Polymorph Y (right) during simulation of fasted and fed state conditions.

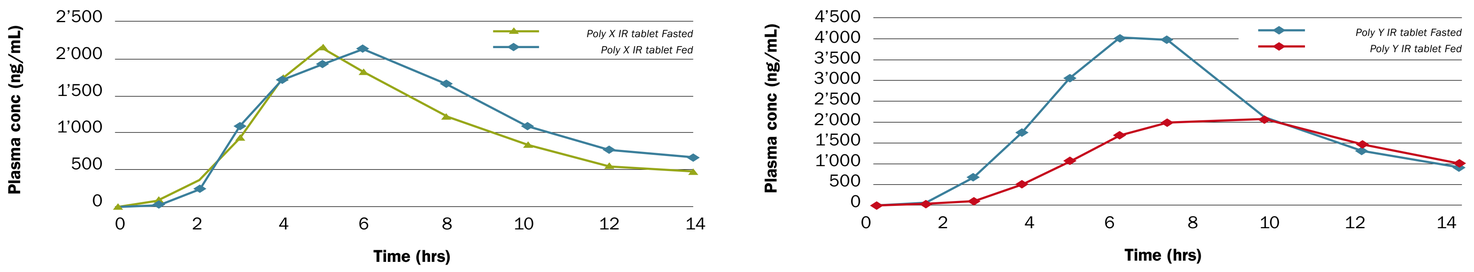

Figure 3. In humans: mean plasma concentration in time of API in Polymorph X (left) and Polymorph Y (right) during fasted and fed state conditions.

	ratio iAUC fed / iAUC fasted	
	in vivo	in vitro (TIM-1)
Polymorph X IR tablet	1,2	1,1
Polymorph Y IR tablet	0,7	0,6

Table 2. Ratio of API available for intestinal absorption (TIM-1) and absorbed in vivo (humans) in the fed state versus the fasted state.