# The Link Between the Human Gastrointestinal Tract and Oral Drug Absorption: Theory and Case Example

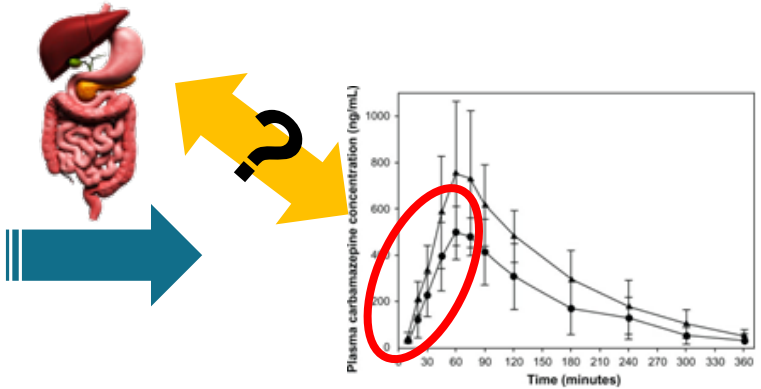

5th FDA/PQRI Conference on Advancing Product Quality: Advancing Quality & Technology of Future Pharmaceuticals– **December 1st, 2021 – Bart Hens**
Bart.hens@pfizer.com

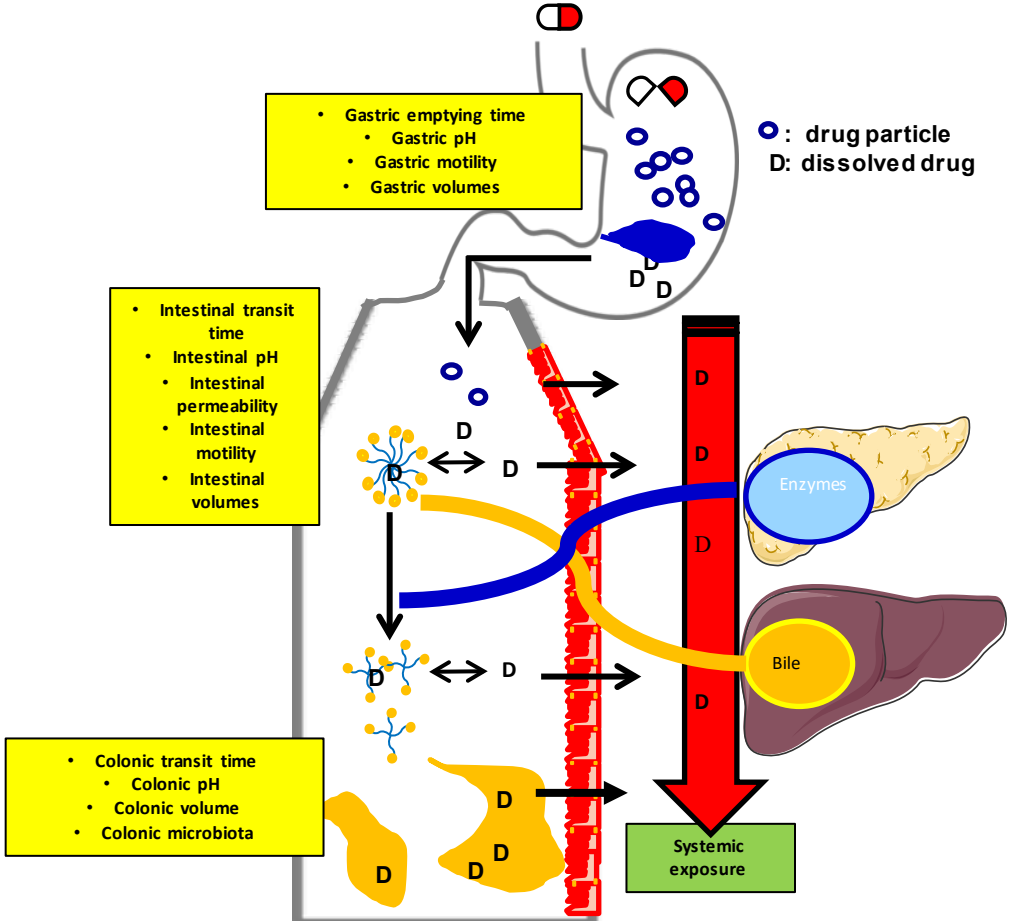
## Outline

- The aspiration technique to link luminal and systemic behavior of orally administed drugs
- Impact of physiology on the behavior of the poorly soluble drugs (class 2):
    - Atazanavir (weak base)

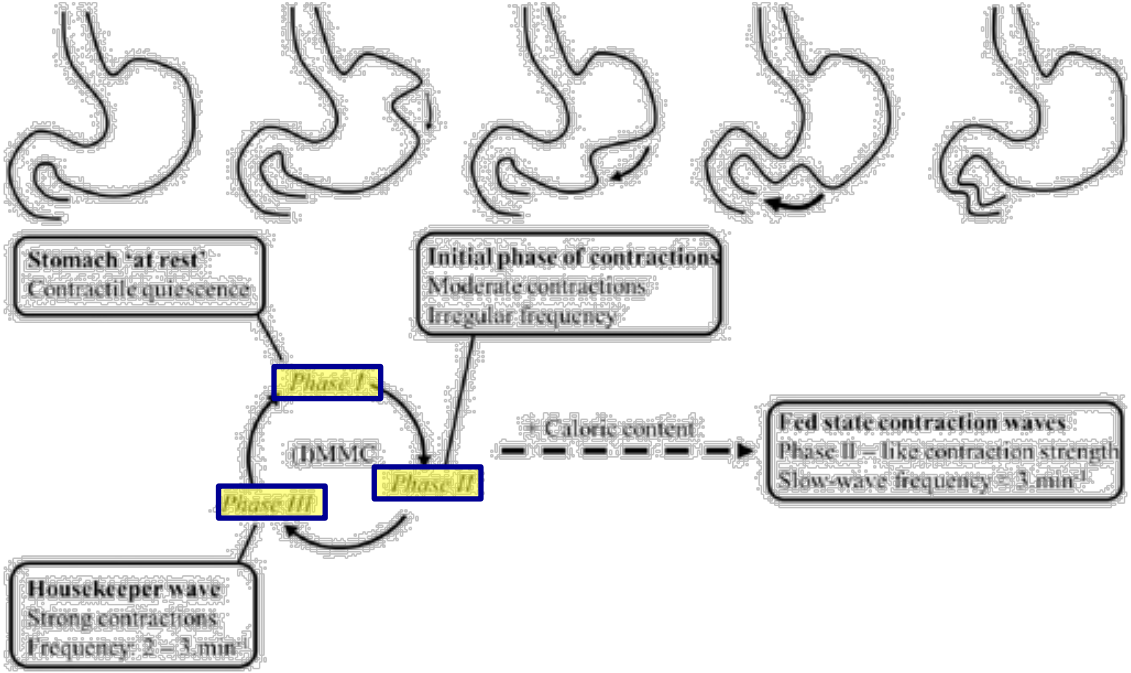
Pfizer

# What happens after oral intake of a drug?




• Gastric emptying time
• Gastric pH
• Gastric motility
• Gastric volumes
: drug particle
D: dissolved drug
• Intestinal transit time
• Intestinal pH
• Intestinal permeability
• Intestinal motility
• Intestinal volumes
Enzymes
Bile
• Colonic transit time
• Colonic pH
• Colonic volume
• Colonic microbiota
Systemic exposure

# Gastric motility

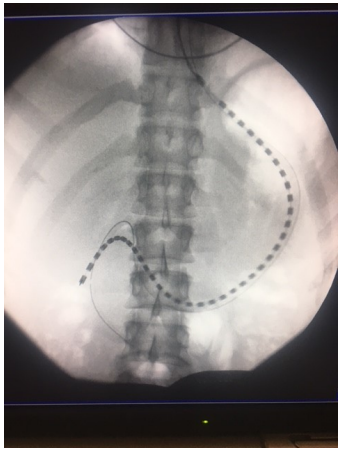



Van Den Abeele et al. - doi: 10.1016/j.ejps.2016.08.060.

# How to measure intragastric motility? → High Resolution Manometry (HRM)

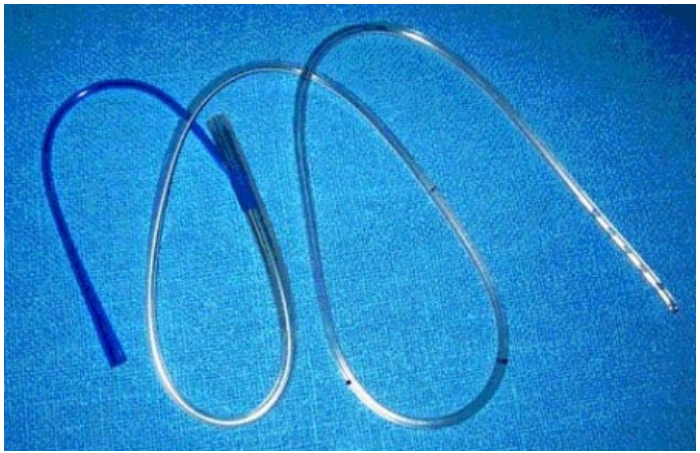
**Intubation**

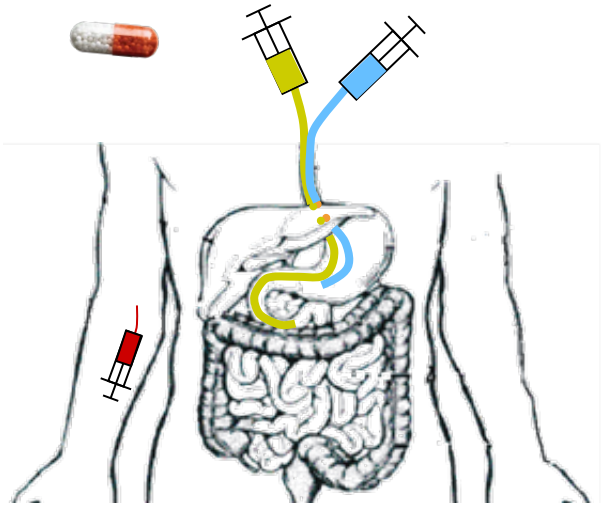

**X-Ray**



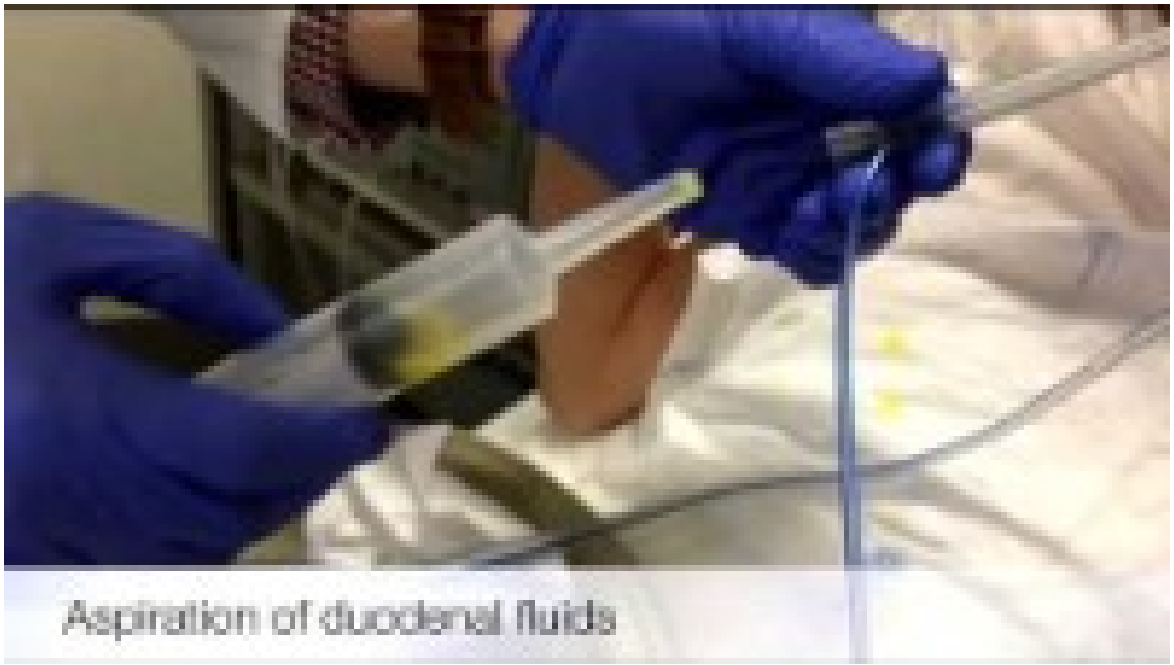
# *In vivo* evaluation?

- Samples in function of time
  - **blood ➔ pharmacokinetics**
  - **stomach- / intestinal samples**
    - **➔ intraluminal drug concentrations**



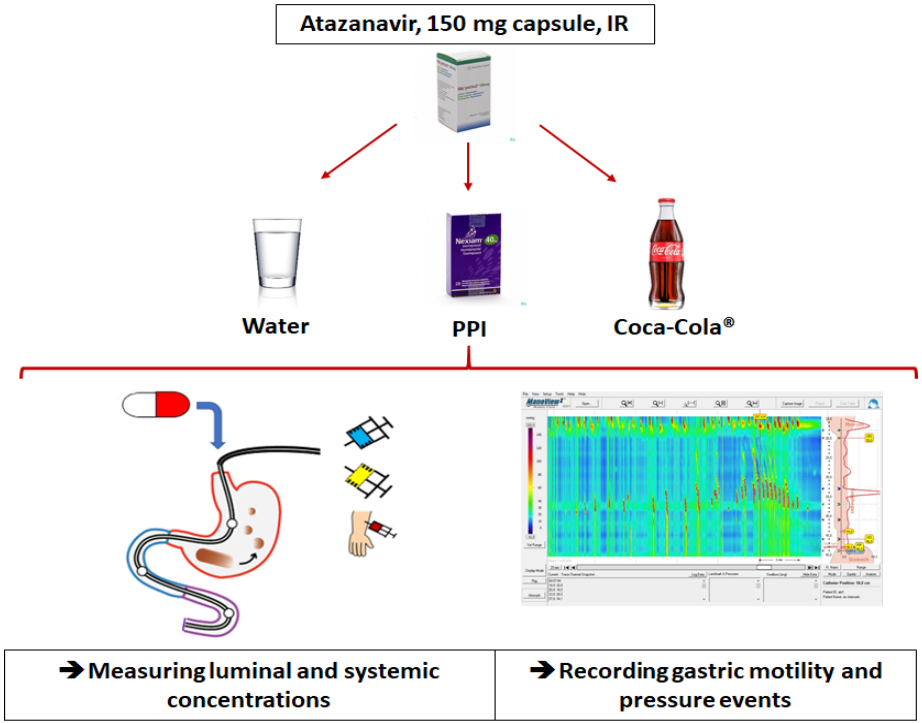


# Aspiration of fluids and determining drug concentrations to evaluate drug release

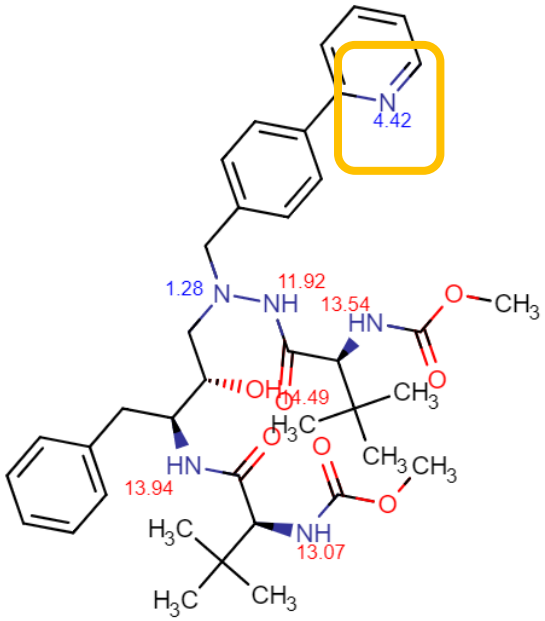


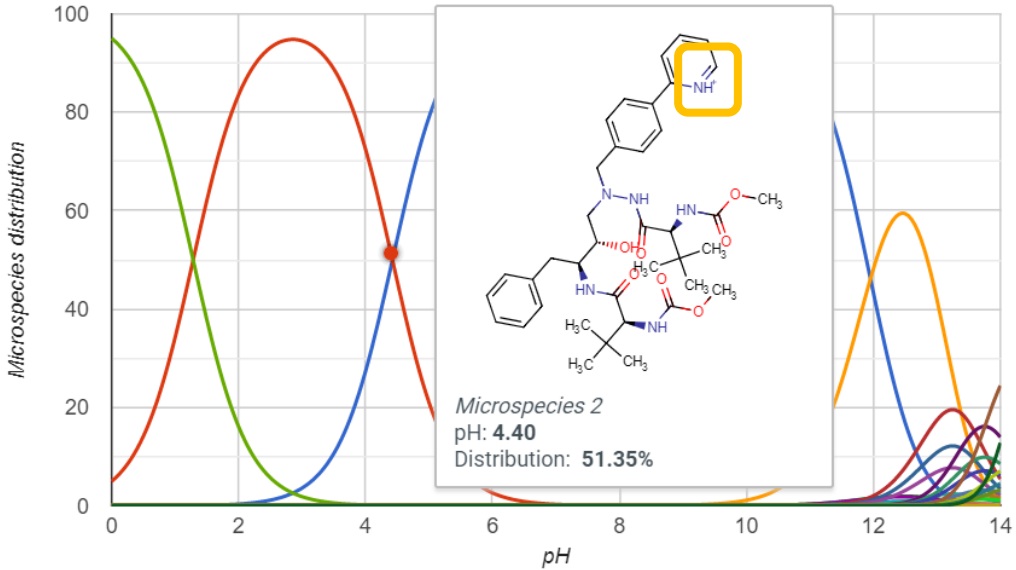
# Case example: Atazanavir – weak base

# Atazanavir: weak basic compound



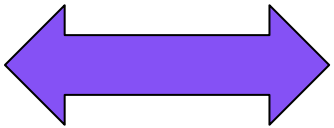
# pKa




| | |
|---|---|
| Strongest acidic pKa | 11.92 |
| Strongest basic pKa | 4.42 |

# Hypothesis: Coca-Cola® may increase the intestinal absorption of atazanavir

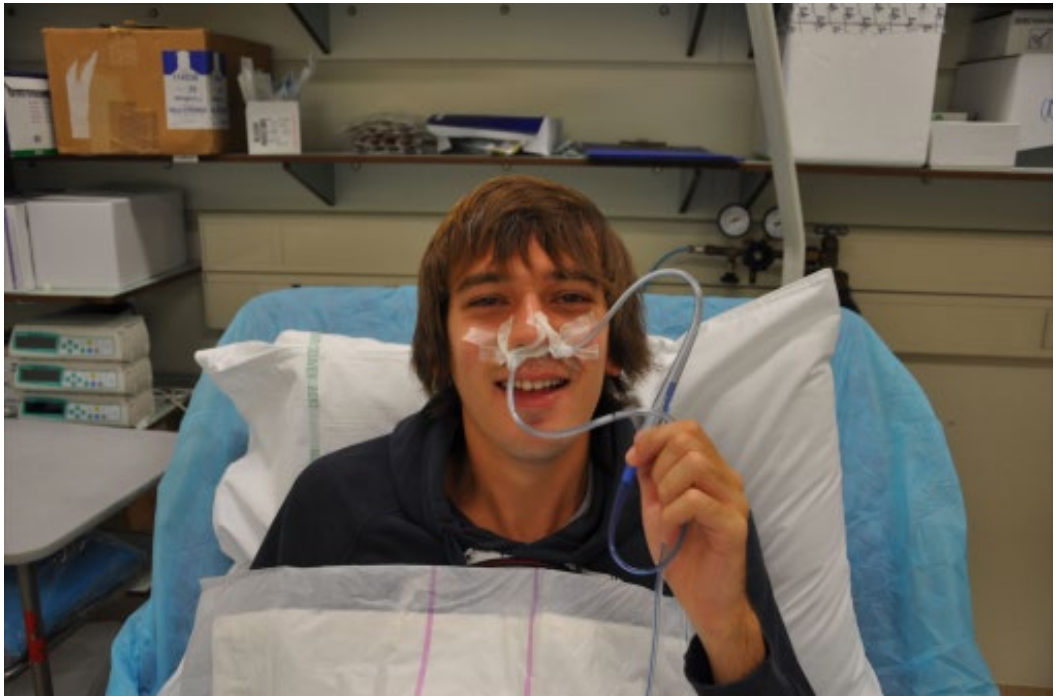



**pH 2.5**
**240 mL – 101 calories**

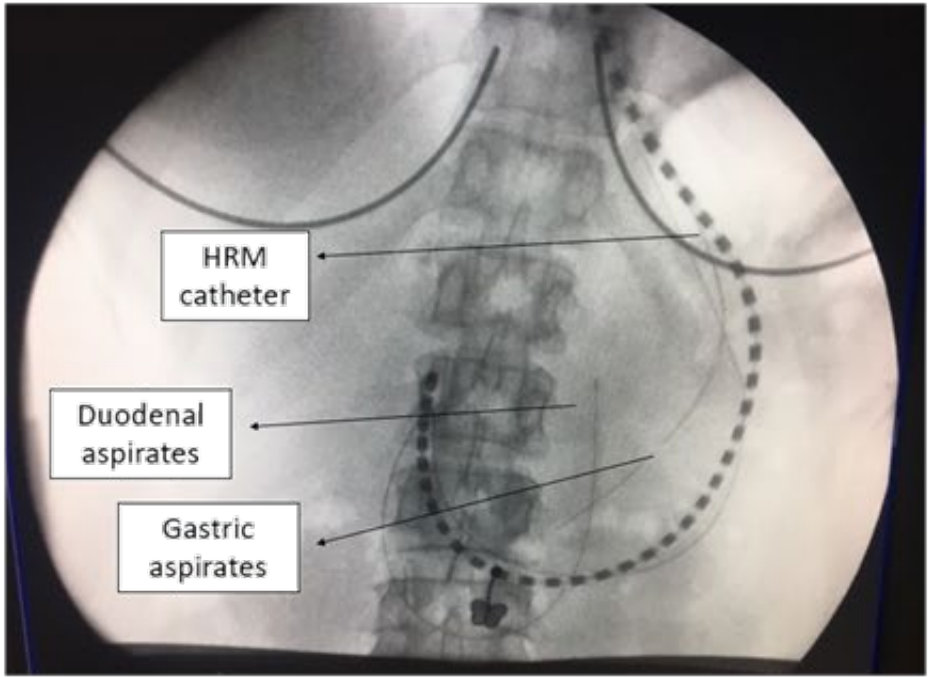
**pH 7**
**240 mL – 0 calories**

- **(i) Acidity and longer gastric residence time due to the calories will increase atazanavir's concentration in the stomach,**
- **(ii) due to the calories, gastric emptying will be delayed resulting in more sustained supersaturated concentrations,**
- **(iii) resulting in higher systemic exposure**

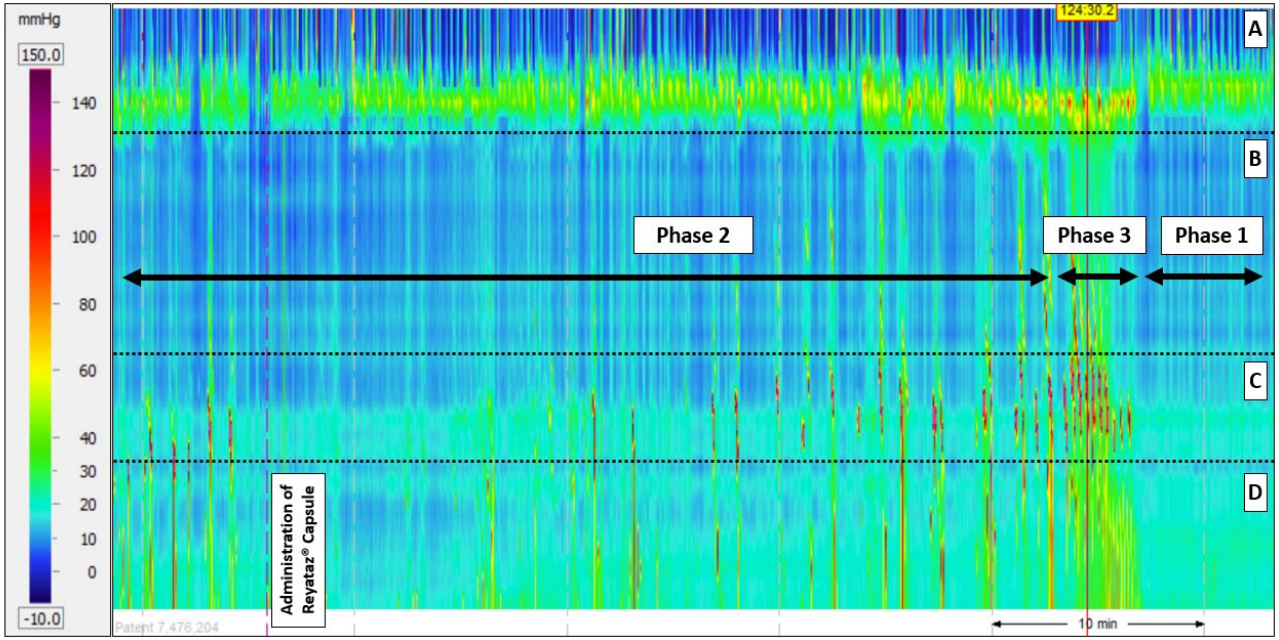
# Positioning of the catheters



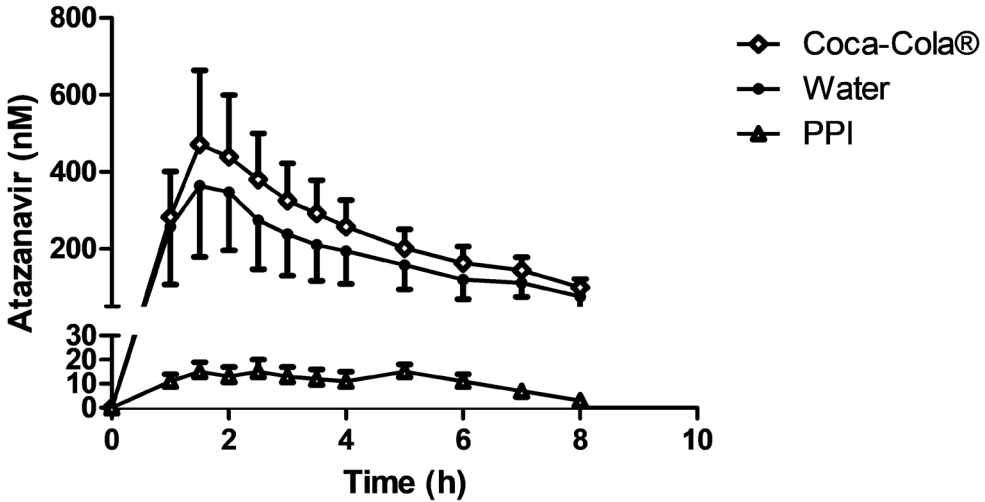
# Positioning of the catheters



# Manometry to record gastric motility



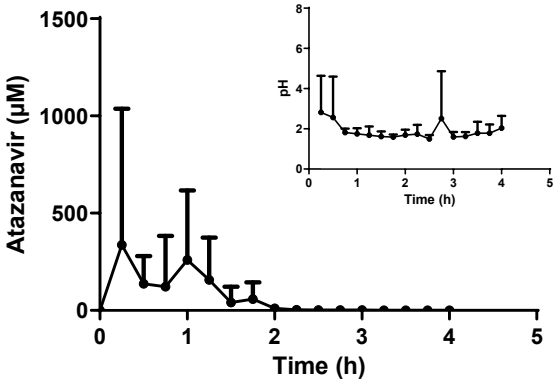
# Systemic plasma exposure



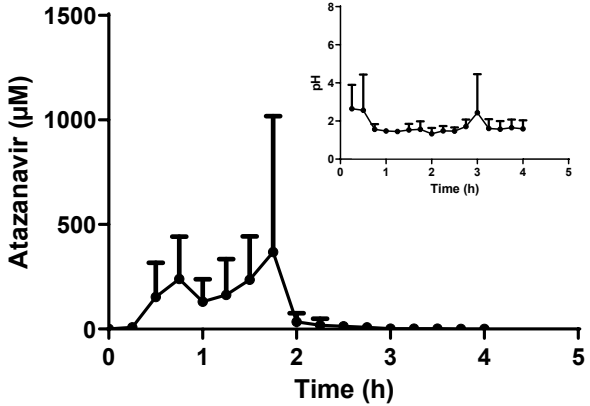

Mean ± SEM, n=5

# Gastric solution concentrations & pH profiles

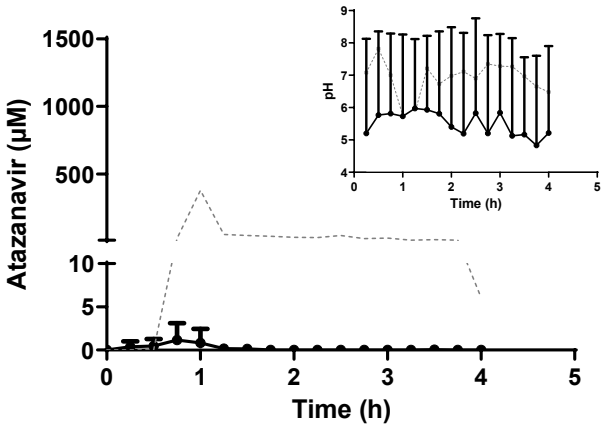
Water




Coca-Cola®



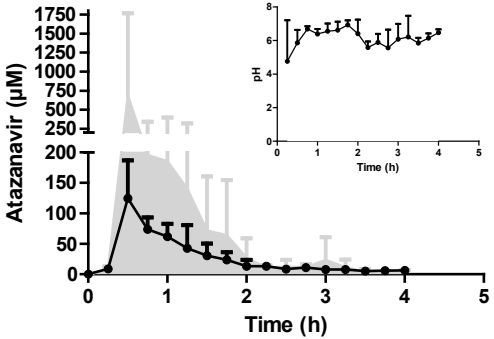

PPI



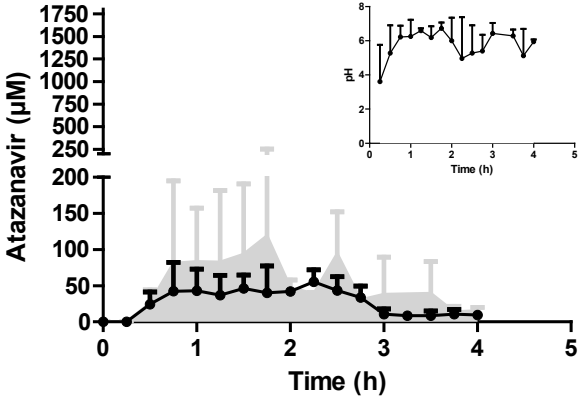

Mean ± SEM, n=5

# Intestinal solution and total concentrations & pH profiles

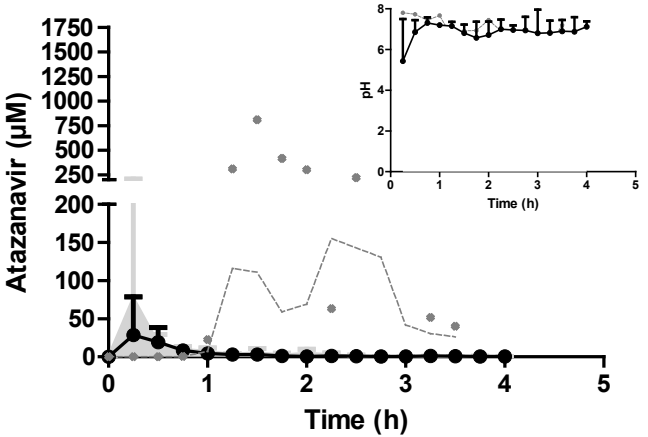
Water




Coca-Cola®



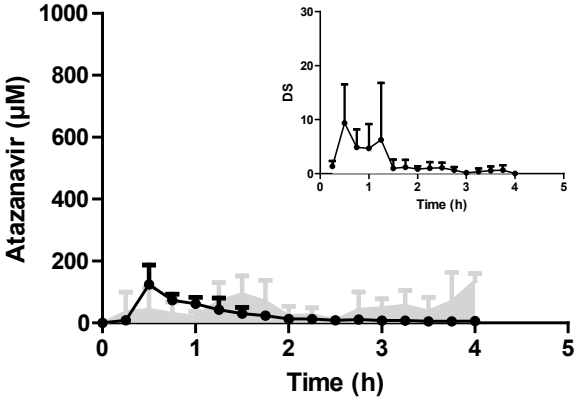

PPI



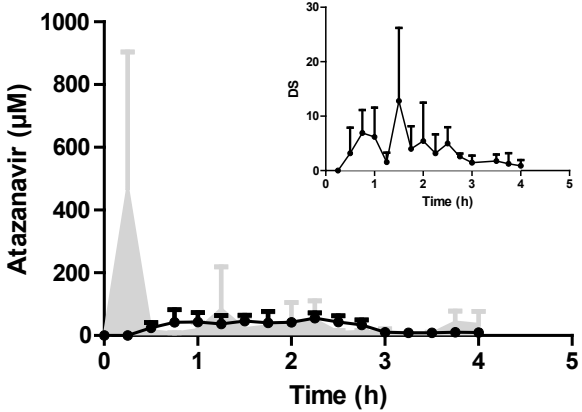

Mean ± SEM, n=4

# Intestinal solution and solubility & Degree of supersaturation (DS)

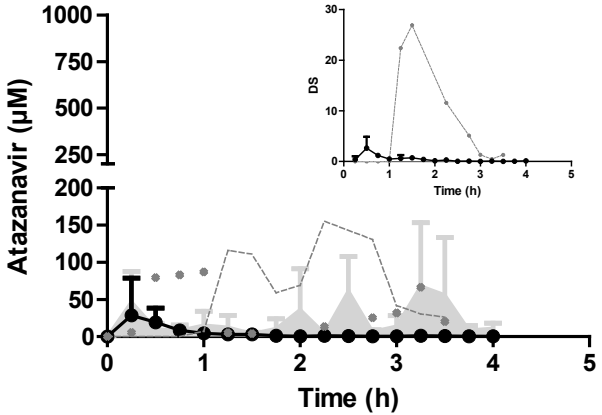
Water




Coca-Cola®

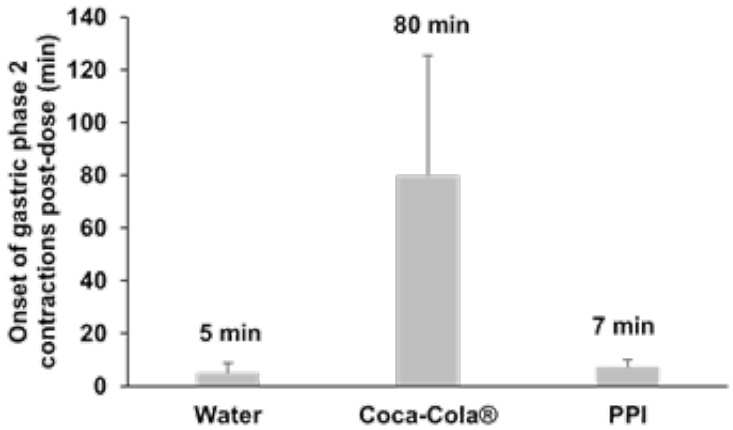



PPI




Mean ± SEM, n=4

# HRM motility data: delayed gastric MMC phase 2 contractions after administration of Coca-Cola®

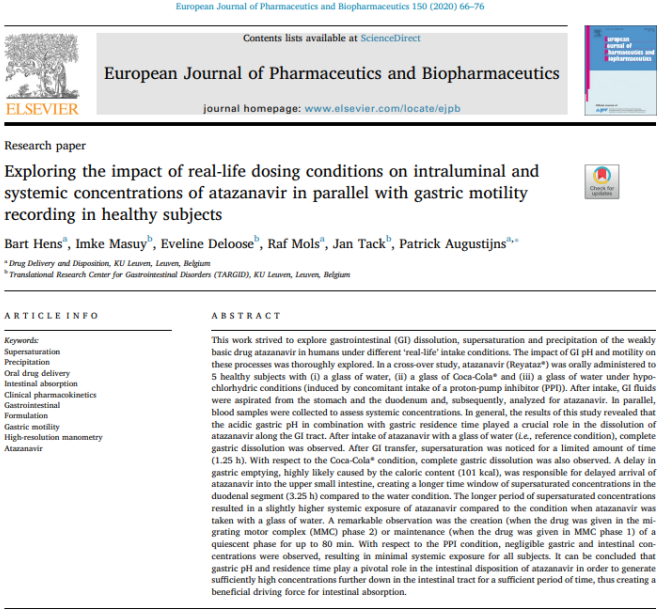



Mean + SD, n=5

## Take-home message

- The aspiration technique reveals the luminal behavior of orally administered drug products and can link this with systemic exposure
- Suitable for different prandial states, different formulations and in combination with co-administered drug products
- Data can be used to optimize and validate *in vitro* and *in silico* tools

# More case examples:



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Research paper

Exploring the impact of real-life dosing conditions on intraluminal and systemic concentrations of atazanavir in parallel with gastric motility recording in healthy subjects

Bart Hens[a], Imke Masuy[b], Eveline Deloose[b], Raf Mols[a], Jan Tack[b], Patrick Augustijns[a,*]

[a] Drug Delivery and Disposition, KU Leuven, Leuven, Belgium
[b] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium

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Atazanavir

ABSTRACT

This work strived to explore gastrointestinal (GI) dissolution, supersaturation and precipitation of the weakly basic drug atazanavir in humans under different 'real-life' intake conditions. The impact of GI pH and motility on these processes was thoroughly explored. In a cross-over study, atazanavir (Reyataz®) was orally administered to 5 healthy subjects with (i) a glass of water, (ii) a glass of Coca-Cola® and (iii) a glass of water under hypochlorhydric conditions (induced by concomitant intake of a proton-pump inhibitor (PPI)). After intake, GI fluids were aspirated from the stomach and the duodenum and, subsequently, analyzed for atazanavir. In parallel, blood samples were collected to assess systemic concentrations. In general, the results of this study revealed that the acidic gastric pH in combination with gastric residence time played a crucial role in the dissolution of atazanavir along the GI tract. After intake of atazanavir with a glass of water (i.e., reference condition), complete gastric dissolution was observed. After GI transfer, supersaturation was noticed for a limited amount of time (1.25 h). With respect to the Coca-Cola® condition, complete gastric dissolution was also observed. A delay in gastric emptying, highly likely caused by the caloric content (101 kcal), was responsible for delayed arrival of atazanavir into the upper small intestine, creating a longer time window of supersaturated concentrations in the duodenal segment (3.25 h) compared to the water condition. The longer period of supersaturated concentrations resulted in a slightly higher systemic exposure of atazanavir compared to the condition when atazanavir was taken with a glass of water. A remarkable observation was the creation (when the drug was given in the migrating motor complex (MMC) phase 2) or maintenance (when the drug was given in MMC phase 1) of a quiescent phase for up to 80 min. With respect to the PPI condition, negligible gastric and intestinal concentrations were observed, resulting in minimal systemic exposure for all subjects. It can be concluded that gastric pH and residence time play a pivotal role in the intestinal disposition of atazanavir in order to generate sufficiently high concentrations further down in the intestinal tract for a sufficient period of time, thus creating a beneficial driving force for intestinal absorption.

Hens B, Masuy I, Deloose E, Mols R, Tack J, Augustijns P. Exploring the impact of real-life dosing conditions on intraluminal and systemic concentrations of atazanavir in parallel with gastric motility recording in healthy subjects. Eur J Pharm Biopharm. 2020 May;150:66-76. doi: 10.1016/j.ejpb.2020.02.014. Epub 2020 Feb 28. PMID: 32113916.

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Unraveling the behavior of oral drug products inside the human gastrointestinal tract using the aspiration technique: History, methodology and applications

Patrick Augustijns[a], Maria Vertzoni[b], Christos Reppas[b], Peter Langguth[c], Hans Lennernäs[d], Bertil Abrahamsson[e], William L. Hasler[f], Jason R. Baker[g], Tim Vanuytsel[h], Jan Tack[i], Maura Corsetti[j,k], Marival Bermejo[l], Paulo Paixão[l], Gordon L. Amidon[f], Bart Hens[a,*]

[a] Drug Delivery & Disposition, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven Herestraat 49, box 921, 3000 Leuven, Belgium
[b] Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Greece
[c] Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Mainz 55131, Germany
[d] Department of Pharmaceutical Biosciences and Technology, Uppsala University, Box 580, 751 23 Uppsala, Sweden
[e] Oral Product Development, Pharmaceutical Technology & Development, Operations, AstraZeneca Gothenburg, 431 83 Mölndal, Sweden
[f] Department of Internal Medicine, Division of Gastroenterology, University of Michigan, Ann Arbor, MI 48109, USA
[g] Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium
[h] NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK
[i] Nottingham Digestive Diseases Centre, School of Medicine, University of Nottingham, Nottingham, UK
[j] Department Engineering Pharmacy Section, Miguel Hernández University, San Juan de Alicante, 03550 Alicante, Spain
[k] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisboa, Portugal
[l] Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109, USA

Augustijns P, Vertzoni M, Reppas C, Langguth P, Lennernäs H, Abrahamsson B, Hasler WL, Baker JR, Vanuytsel T, Tack J, Corsetti M, Bermejo M, Paixão P, Amidon GL, Hens B. Unraveling the behavior of oral drug products inside the human gastrointestinal tract using the aspiration technique: History, methodology and applications. Eur J Pharm Sci. 2020 Dec 1;155:105517. doi: 10.1016/j.ejps.2020.105517. Epub 2020 Aug 18. PMID: 32818656.

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