CAN DISSOLUTION PREDICT FOOD AND ALCOHOL EFFECT?

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QUIDELINES ON THE INVESTIGATION OF DRUG INTERACTIONS

2012 FDA

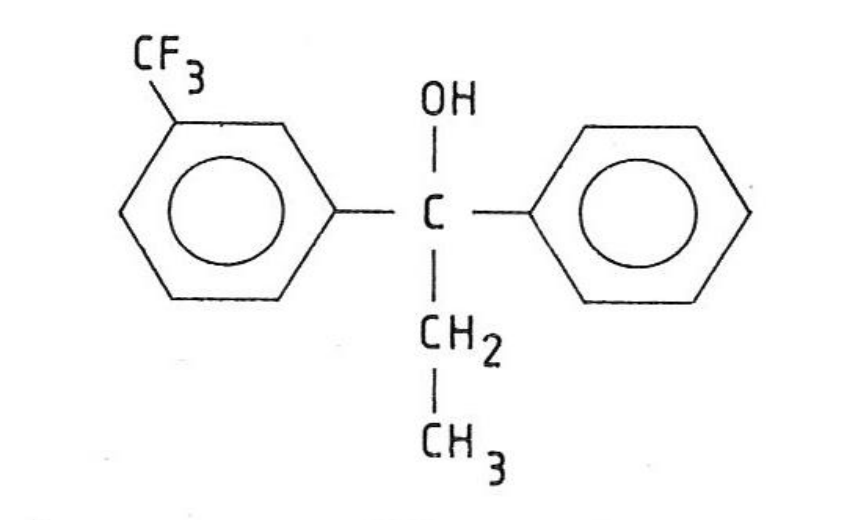
- http://www.ema.europa.eu/docs/en_GB/document library/Scientific_guideline/2012/07/WC500129606.pdf

2013 EMA

- http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/ucm292362.pdf

COMPARISON ON *IN VITRO* DISSOLUTION AND *IN VIVO* HUMAN ABSORPTION PARAMETERS ON FIVE DIFFERENT ORAL FLUMECINOL PREPARATIONS

CHEMICAL STRUCTURE OF FLUMECINOL (ZIXORYN^{R})

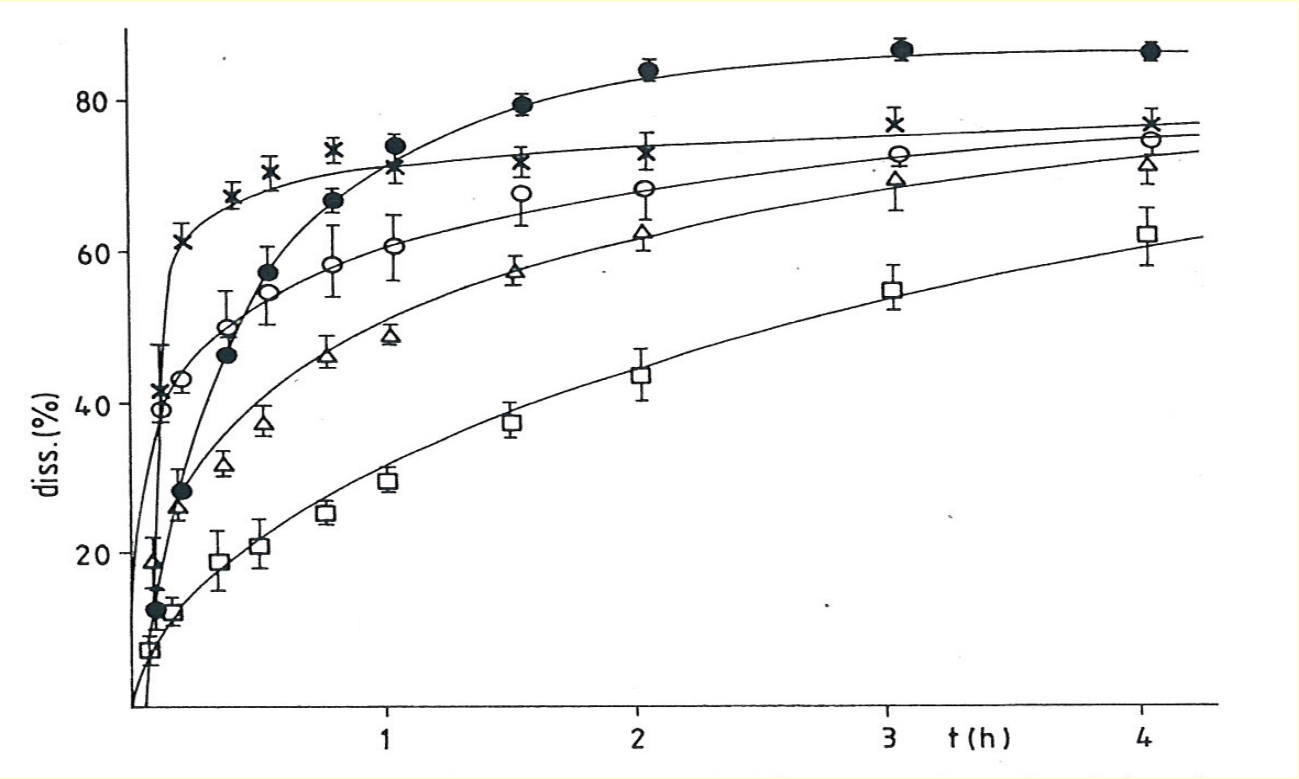


hepatic enzyme inducer (CYP-450 2B1)

METHOD OF FORMULATION OF DIFFERENT ORAL FLUMECINOL PREPARATIONS

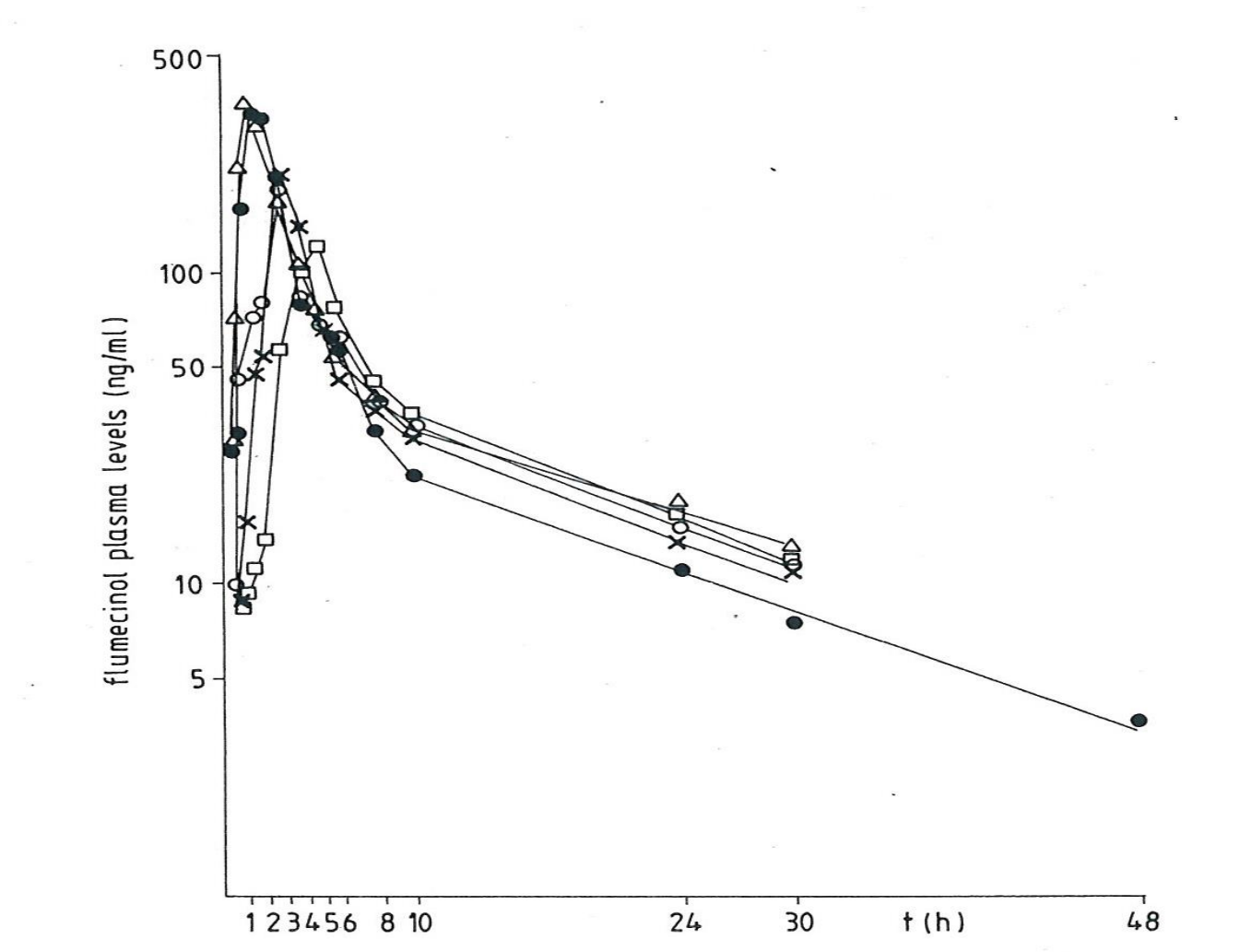
Symbol		Formulation	Method for technology
Adsorbate	o—o	**adsorbate in hard gelatine capsule**	**absorption of flumecinol on the surface of silicium dioxide**
Microcapsules	Δ—Δ	**microcapsules in hard gelaine capsule**	**microencapsulation by coacervation technique**
ß-cyclodextrine inclusion complex	x—x	**tablet**	**inclusion complexation by ß-cyclodextrine**
Micropellets I.	□—□	**micropellets in hard gelaine capsule I.**	**forming of micropellets by a centrifugal granulator**
Micropellets II.	•—•	**micropellets in hard gelaine capsule II.**	**forming of micropellets by a centrifugal granulator**

MEAN CUMULATIVE PERCENT OF FLUMECINOL *IN VITRO* DISSOLVED AT PH 1.2 OF FIVE FORMULATIONS

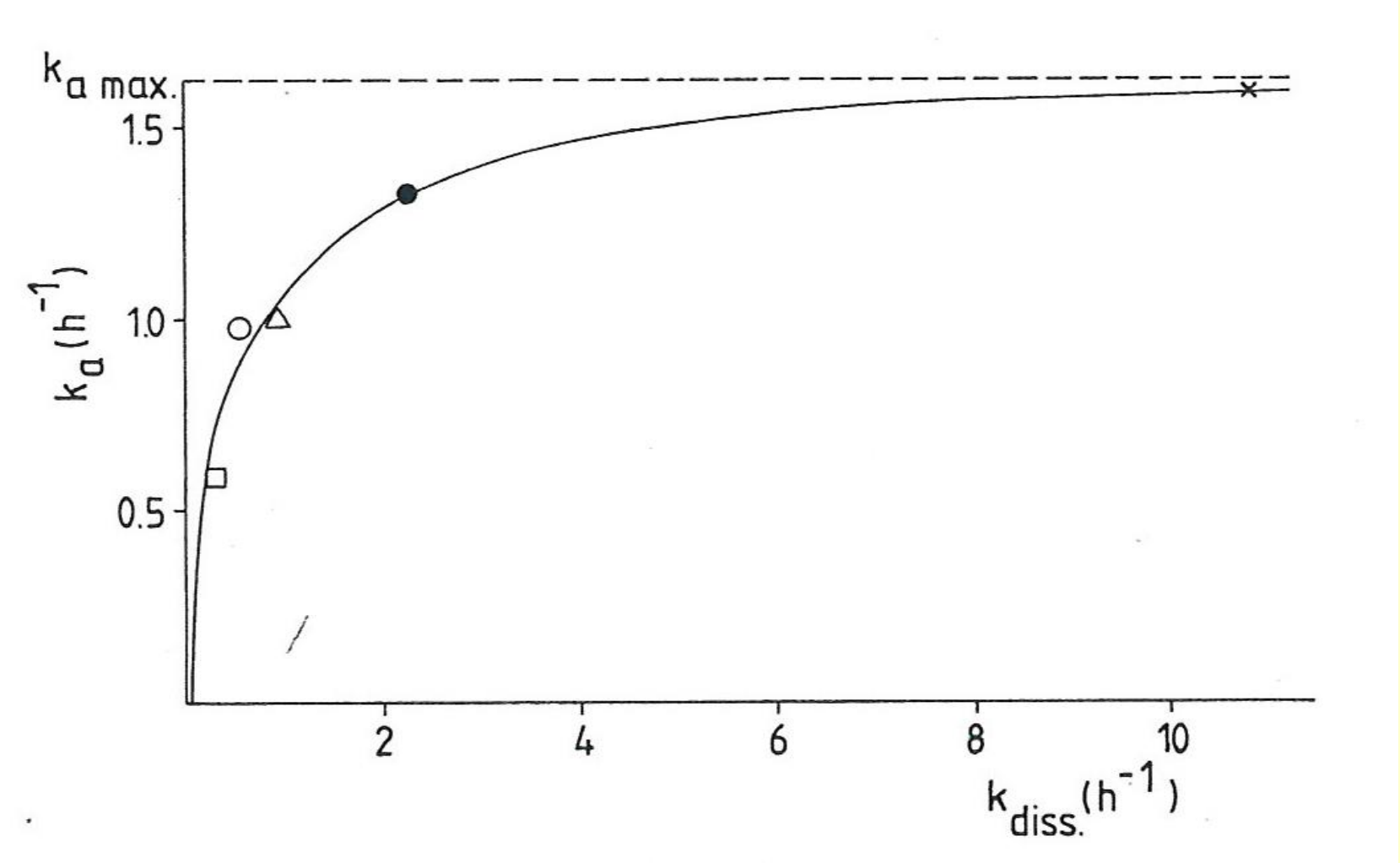


PHARMACOKINETIC CURVES OF FLUMECINOL IN HUMAN

AFTER 100 MG SINGLE ORAL ADMINISTRATION OF 5 DIFFERENT FORMULATIONS



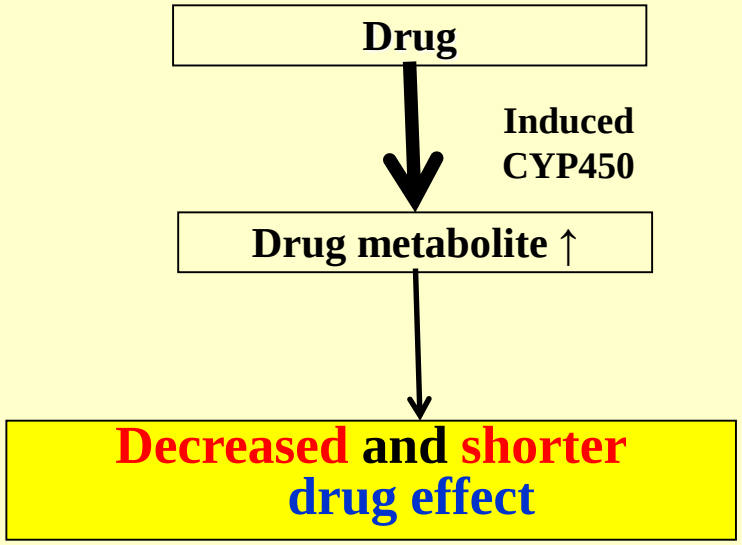
THE RELATIONSHIP OF *IN VIVO* ABSORPTION TO *IN VITRO* DISSOLUTION RATE CONSTANTS



DRUG – ALCOHOL INTERACTION

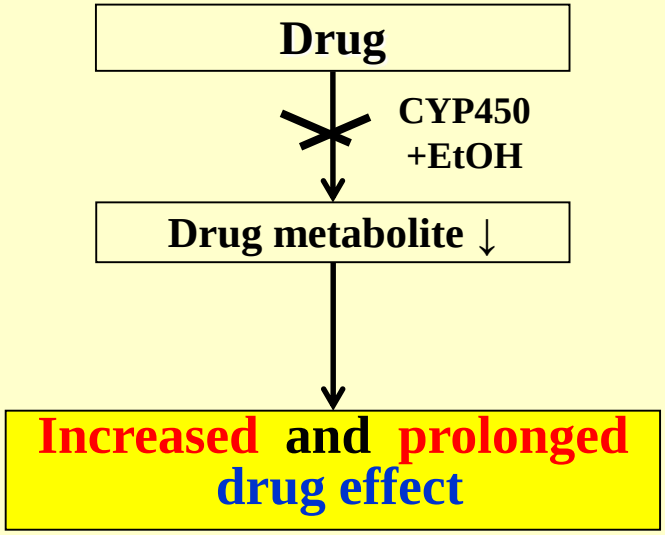
THE INFLUENCE OF *ACUTE* AND *CHRONIC* ALCOHOL CONSUMPTION ON THE CYTOCHROM P450 ENZYMES AND ON THE DRUG EFFECT

Chronic alcohol consumption

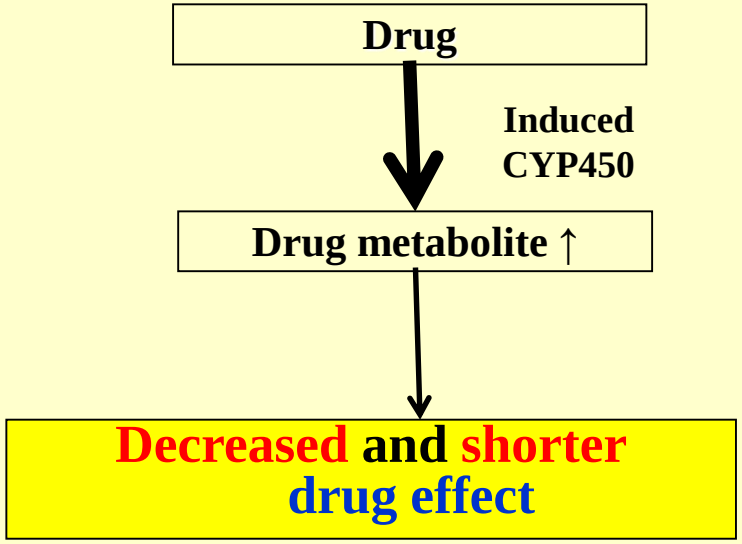


THE INFLUENCE OF *ACUT* AND *CHRONIC* ALCOHOL CONSUMPTION ON THE CYTOCHROM P450 ENZYMES AND ON THE DRUG EFFECT

Acut alcohol consumption



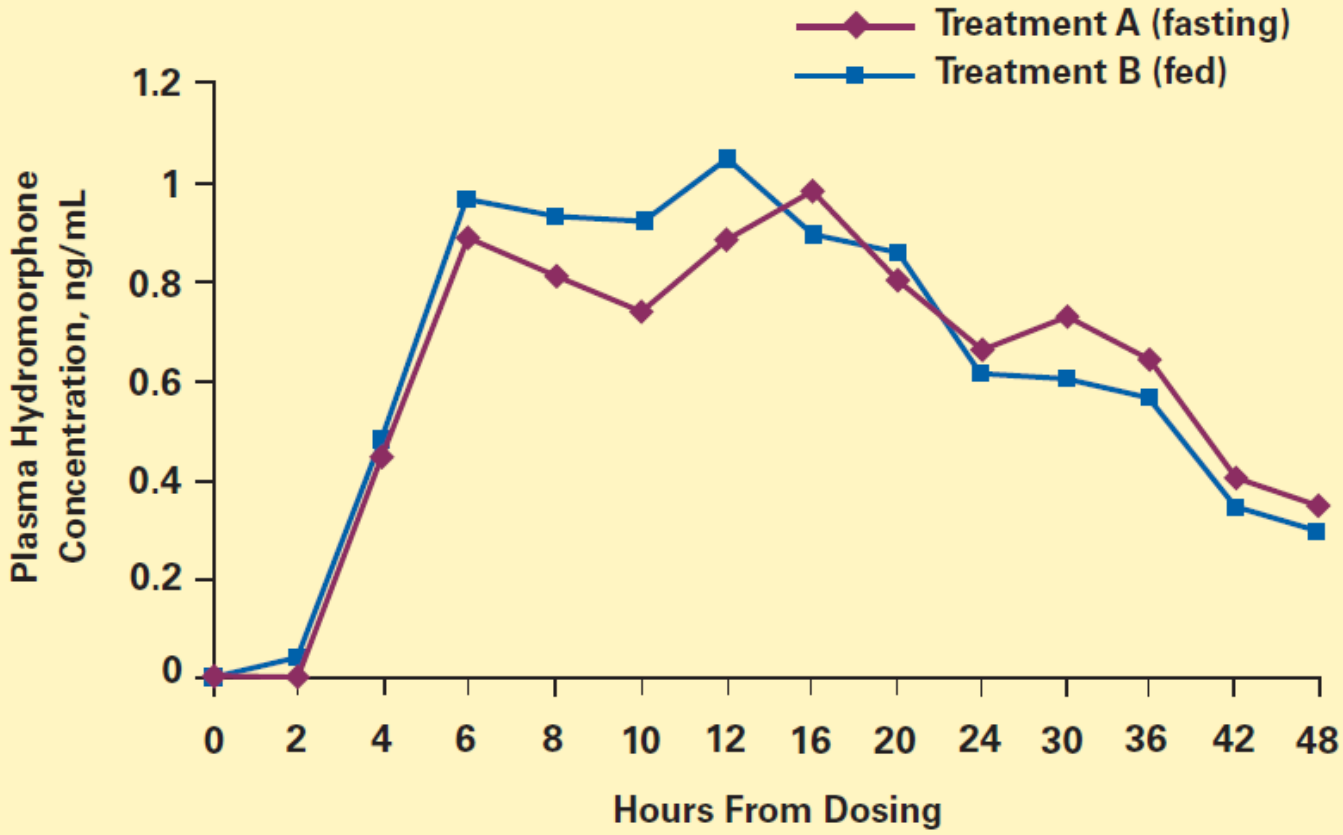
Chronic alcohol consumption



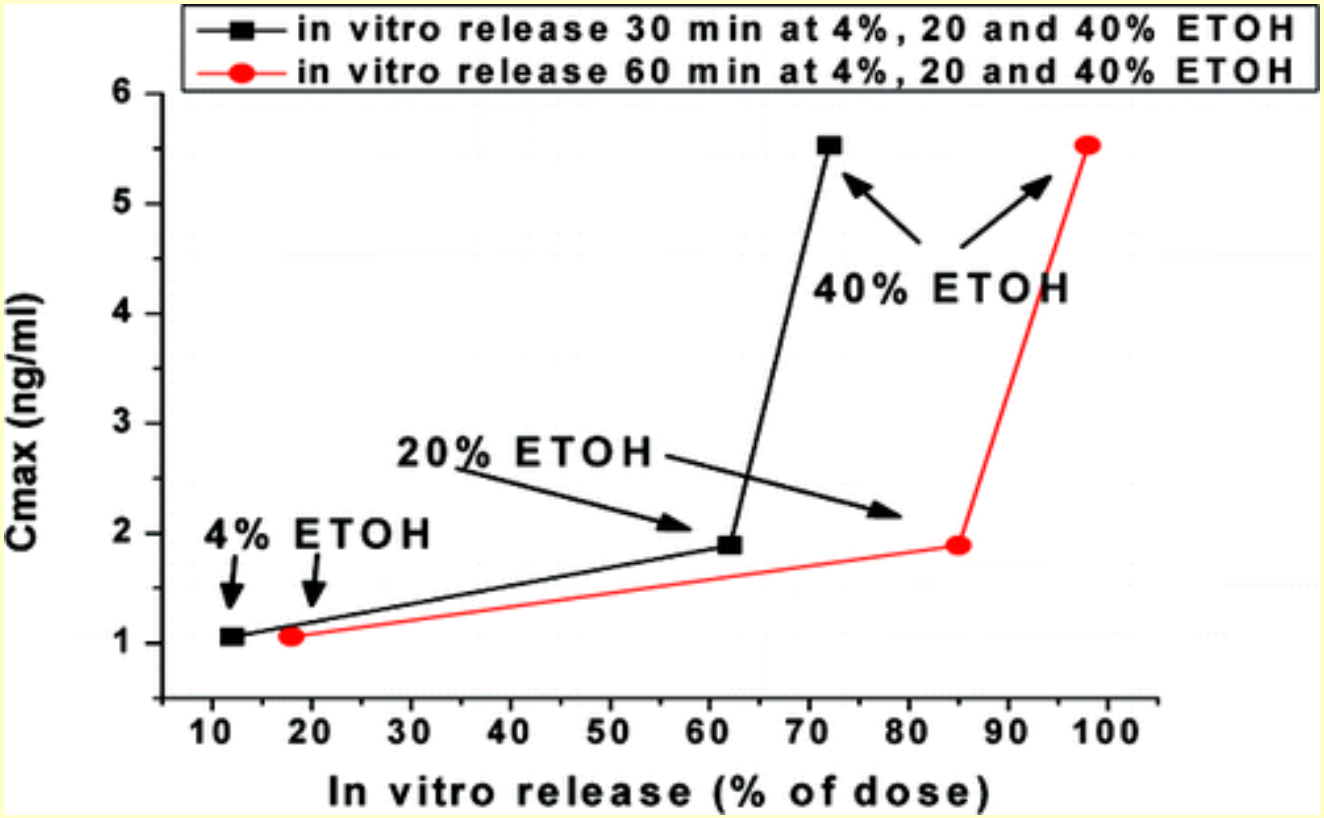
PHARMACOKINETICS OF HYDROMORPHONE (JURNISTA^{R}) IN HUMAN BEFORE AND AFTER THE MEAL

16 mg

. Mean plasma concentration vs time profiles of Treatments A (OROS® hydromorphone 16 mg fasting) and B (OROS® hydromorphone 16 mg fed) in healthy volunteers



IN VITRO DISSOLUTION PROFILE OF A CONTROLLED RELEASE HYDROMORPHONE IN ETHANOL CONCENTRATIONS OF UP TO 40%



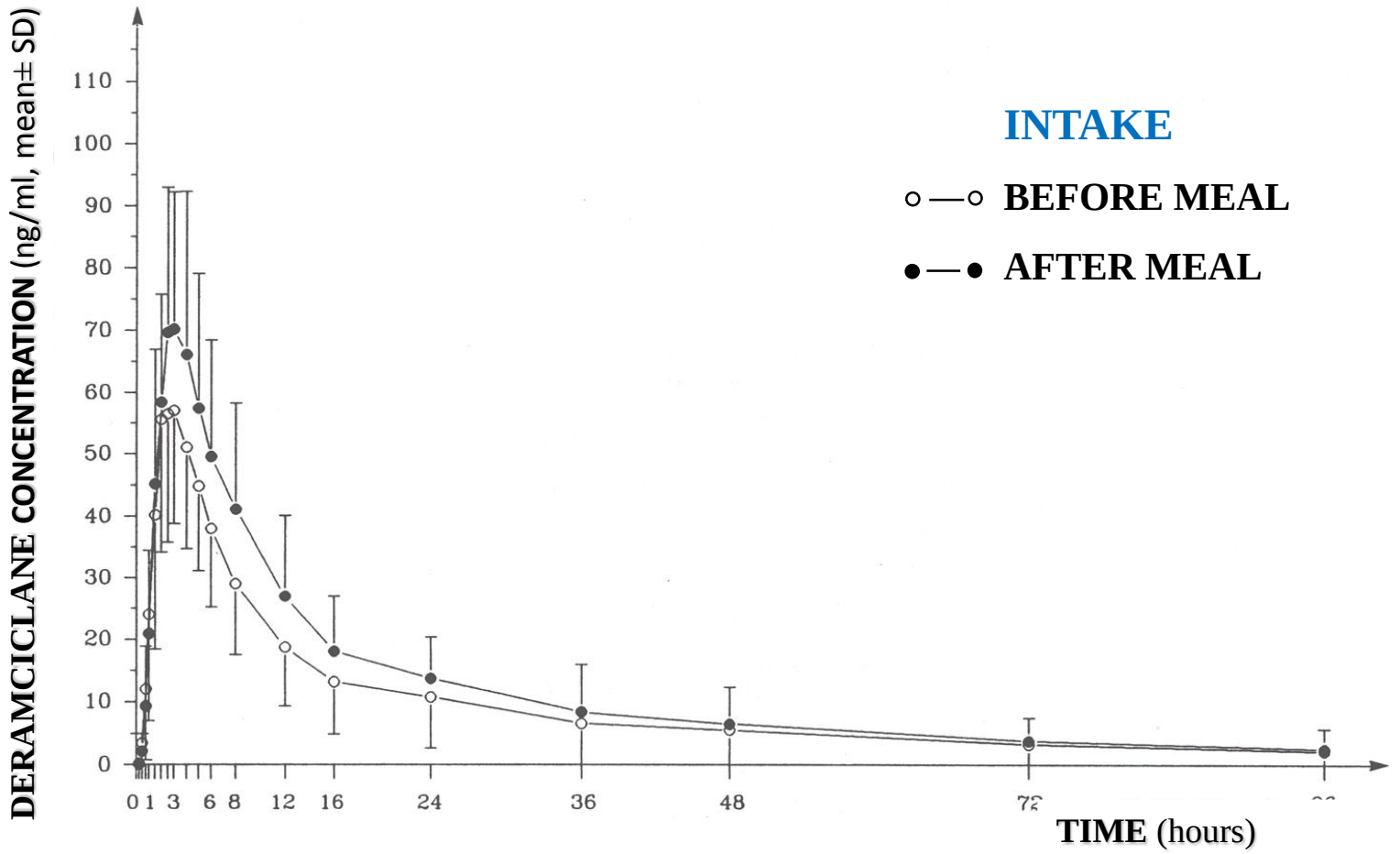
Lennernäs H (2009) Ethanol-drug absorption interaction: potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations. Molecular Pharmacology, 6: 1429-1440.

FOOD INTERACTION OF DERAMCICLANE

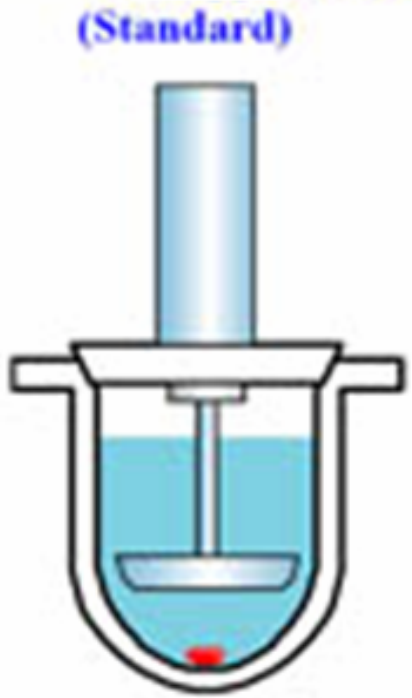
ACID-LABILE DRUGS

- amoxicylline
- penicilline-G
- didanozine
- digoxine
- lanzoprazole
- omeprazole
- deramciclane

PHARMACOKINETICS OF DERAMCICLANE IN HUMAN FOOD-DRUG INTERACTION STUDY, FOLLOWING SINGLE DOSE 30 mg ORAL ADMINISTRATION



IN-VITRO FOOD-INTERACTION STUDY



protein
carbohydrate
fat
(milk)

Dissolution medium

pH= 1.2
pH= 4.5
pH= 6.8

IN -VITRO SIMULATION OF *IN-VIVO* CIRCUMSTANCES

Simulated state before meal

Artifitial gastric juice

- **pH = 1.2**
- **1 N HCl**
- **NaCl**
- **glicine**
- **H_2O**

Simulated state after meal

Food compounds added to artifitial gastric juice

- **pH = 2.98**
- **fatty milk powder**
- **1% methylcellulose**
- **sunflower oil**
- **saccharose**

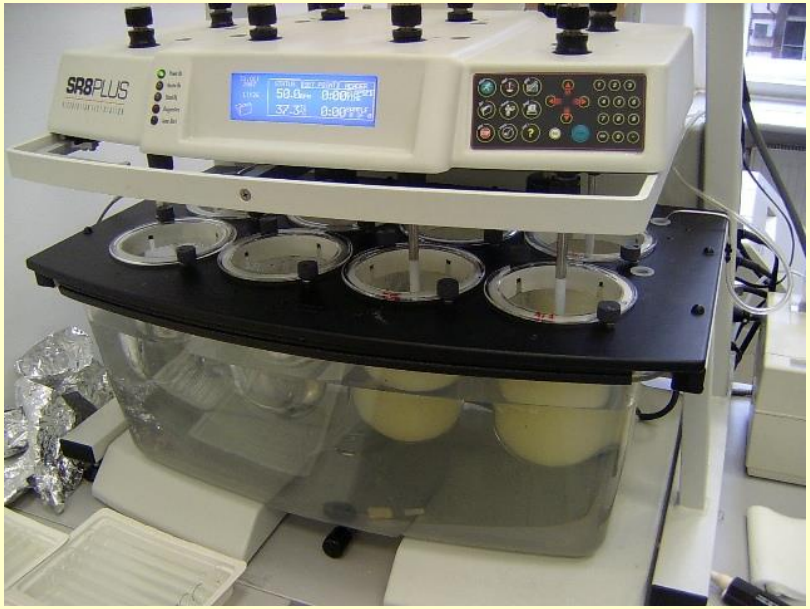
IN-VITRO FOOD EFFECT
SIMULATED 'STANDARD BREAKFAST'

High calorie 'BREAKFAST' 250 ml:

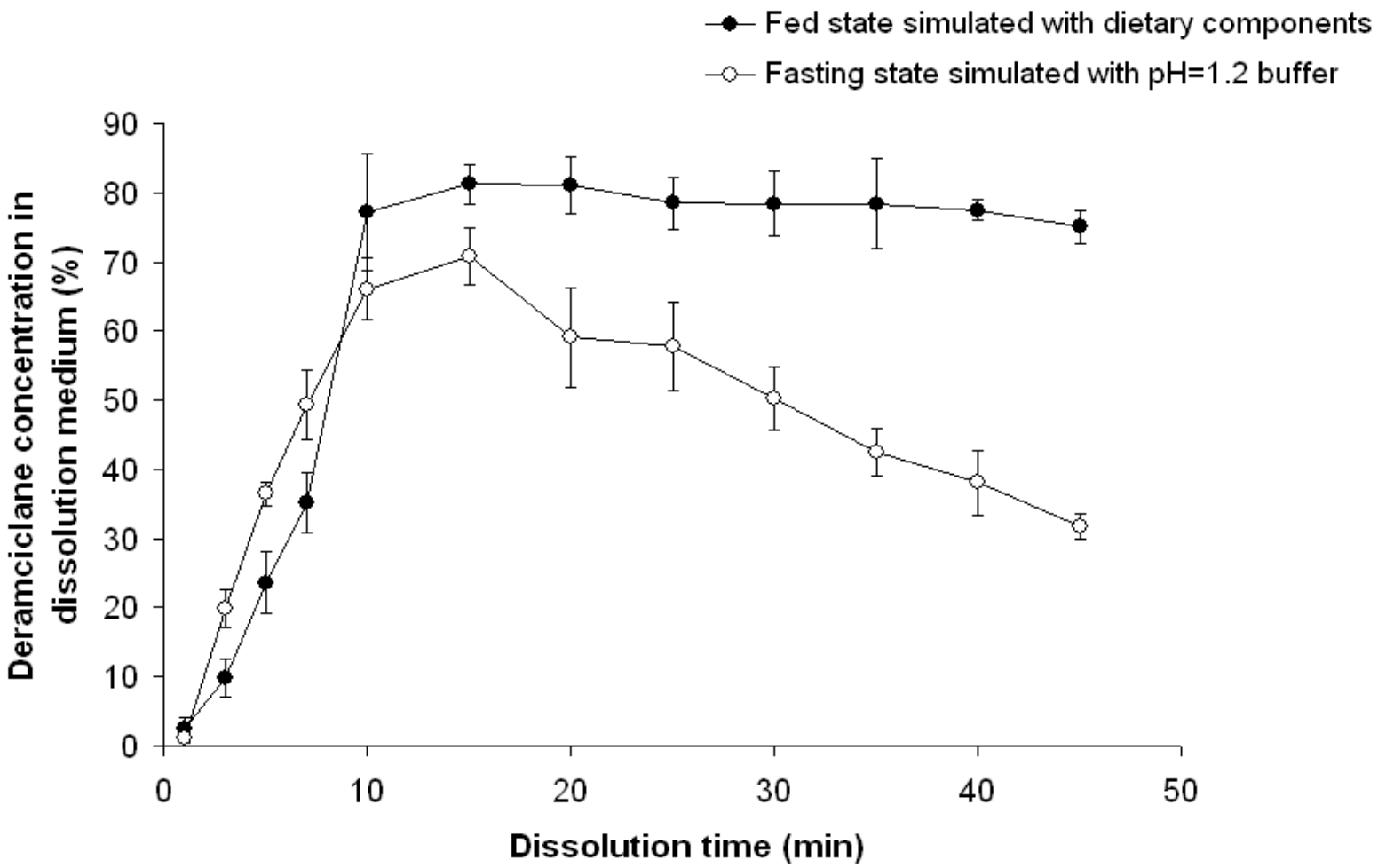
53.8 g oil

31.6 g protein

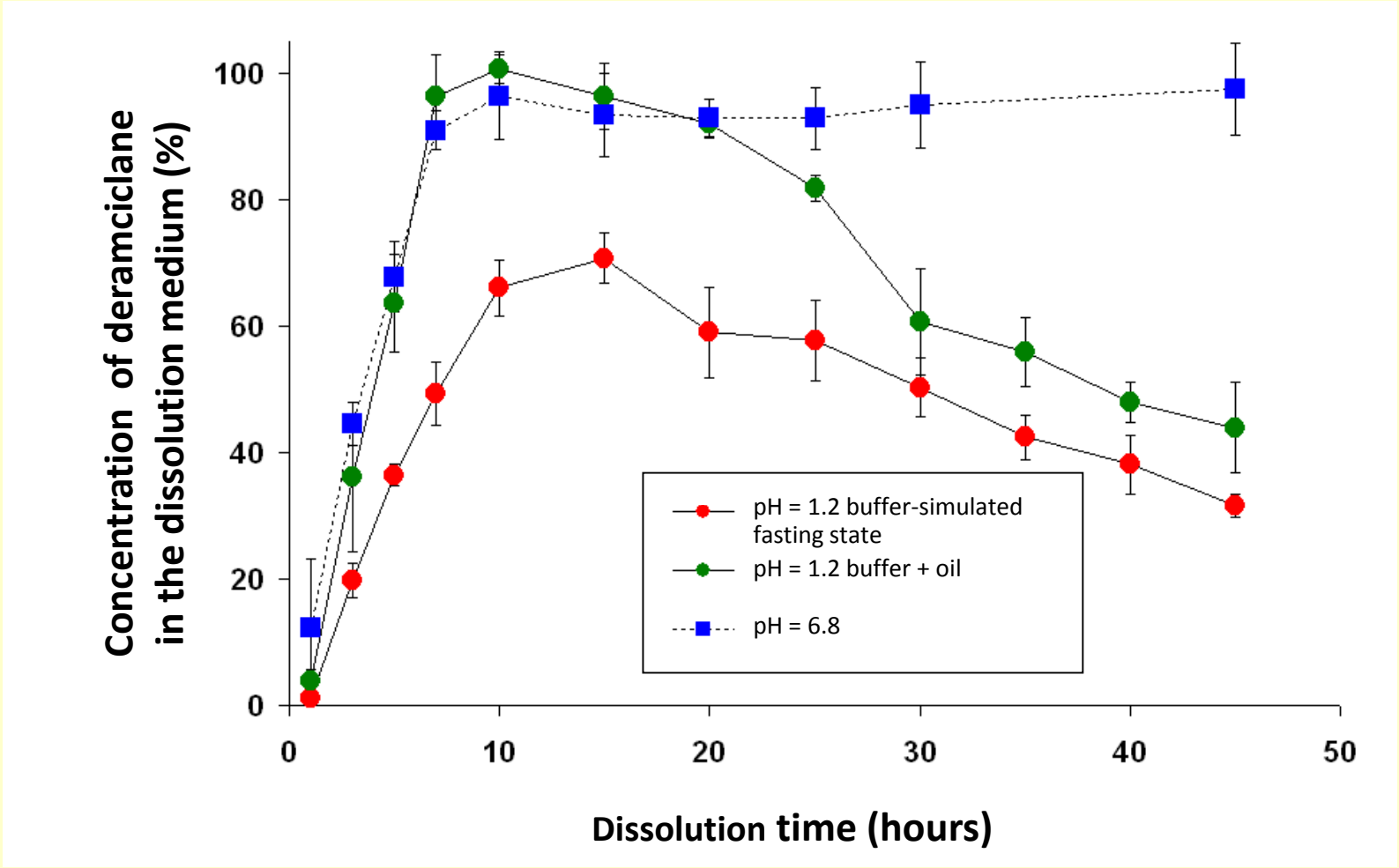
57.4 g carbohydrate



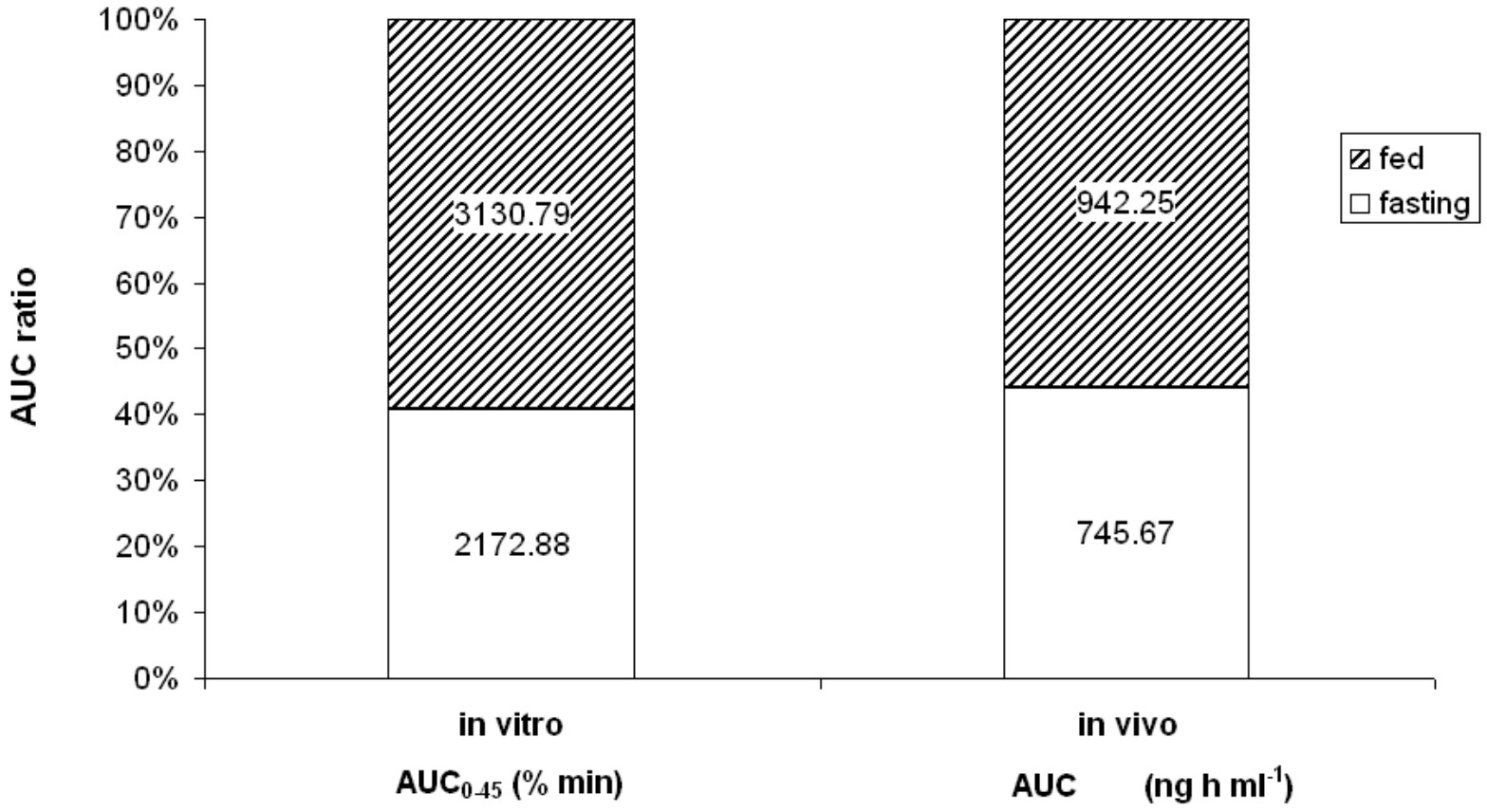
IN -VITRO DISSOLUTION OF DERAMCICLANE (100 mg tabl.)



EFFECT OF OIL ON THE *IN -VITRO* DISSOLUTION OF DERAMCICLANE



IVIVC CORRELATION OF AUC RATIO AFTER FED AND FASTING STUDY



IN VITRO AND *IN VIVO* COMPARATIVE STUDY OF CIPROFLOXATIN IN FED AND FASTING CONDITIONS

Milk

Decreased efficiency

Complex-formation:

- fluorocinolones
- tetracyclines
  (except doxycycline)
- fluconazole
- ketoconazole
- sotalol

- nitrofurantoin

- bisacodyl

Increased efficiency

FOOD-INTERACTION

Bisphosphonates bind the food cations (Ca^{2+}, Fe^{2+}) with geat affinity through chelate formation

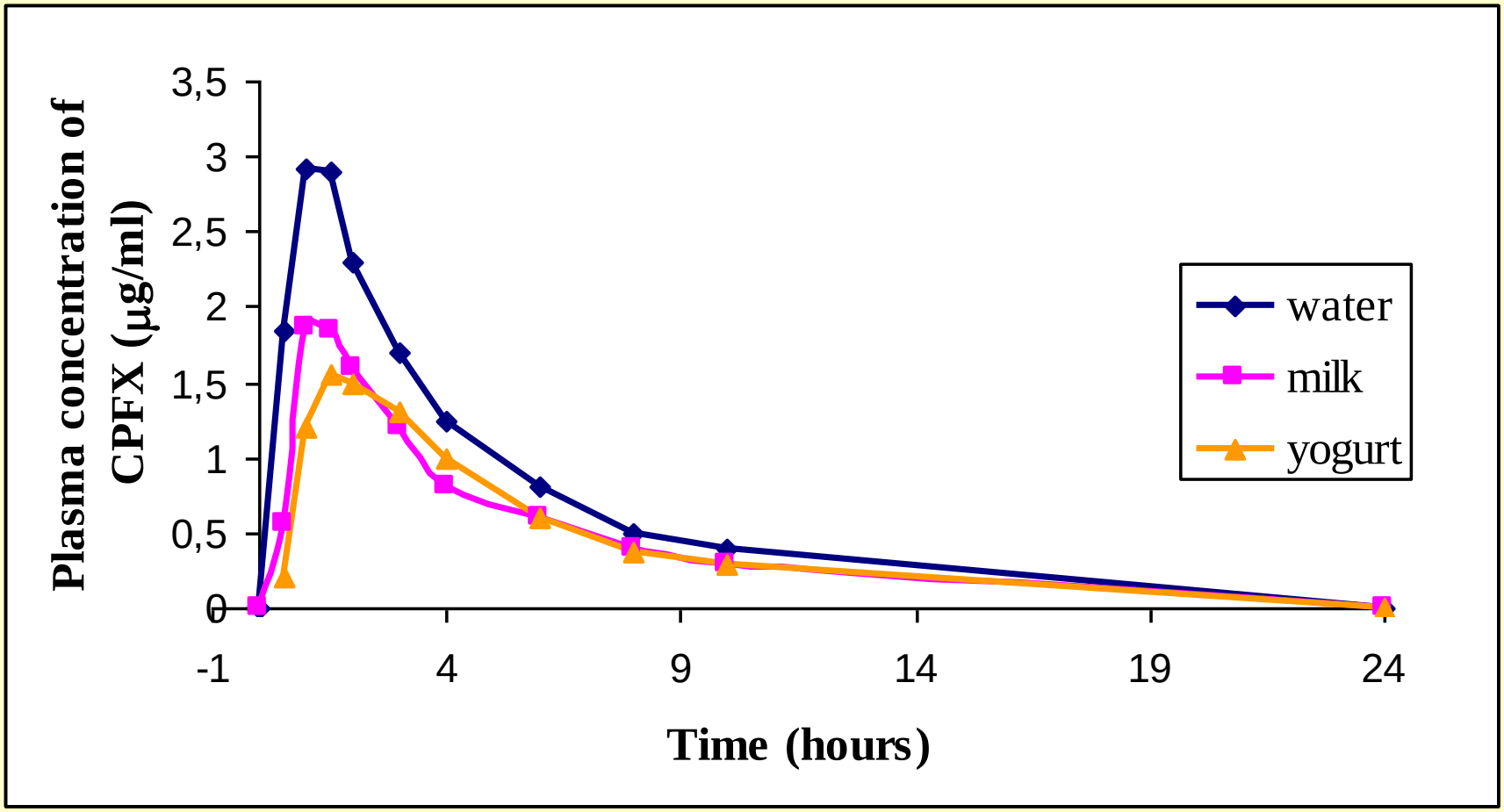
Bioavailability (%):

Clodronate ↓ 31 % (0,5 hour before meal)

Clodronate ↓ 90 % (with meal)

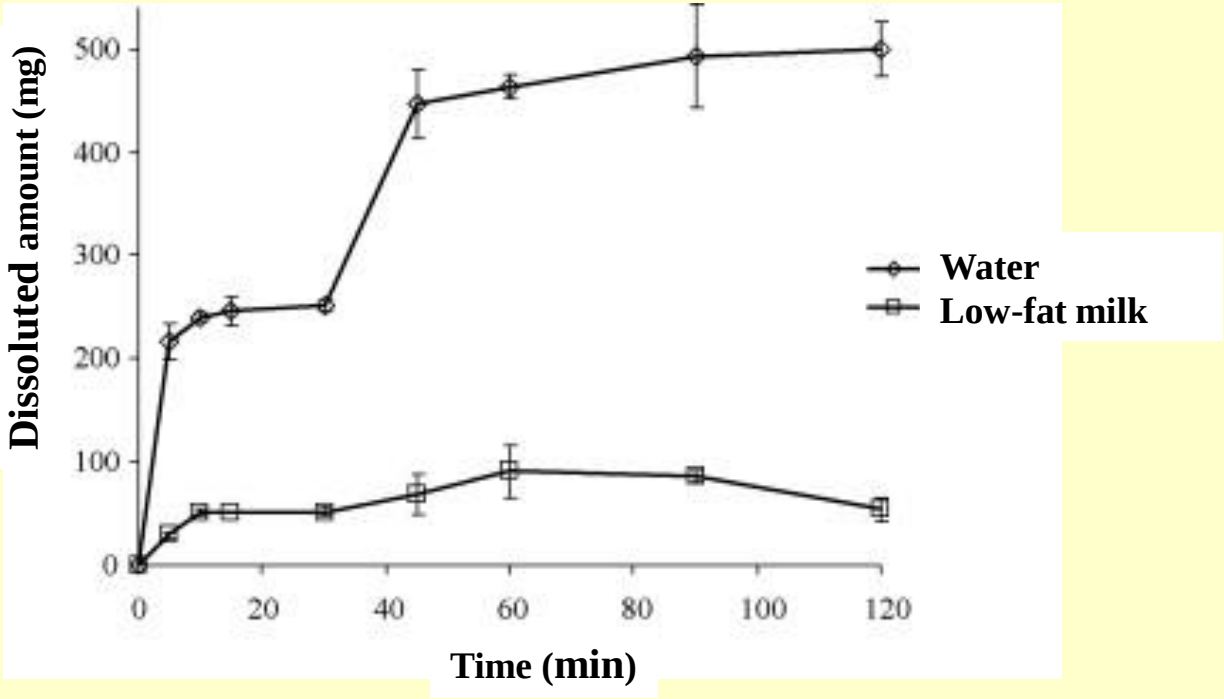
Clodronate ↓ 66 % (2 hours after meal)

IN VIVO HUMAN STUDY OF CIPROFLOXACIN (CPFX) 500 mg TABLETS (n = 24)



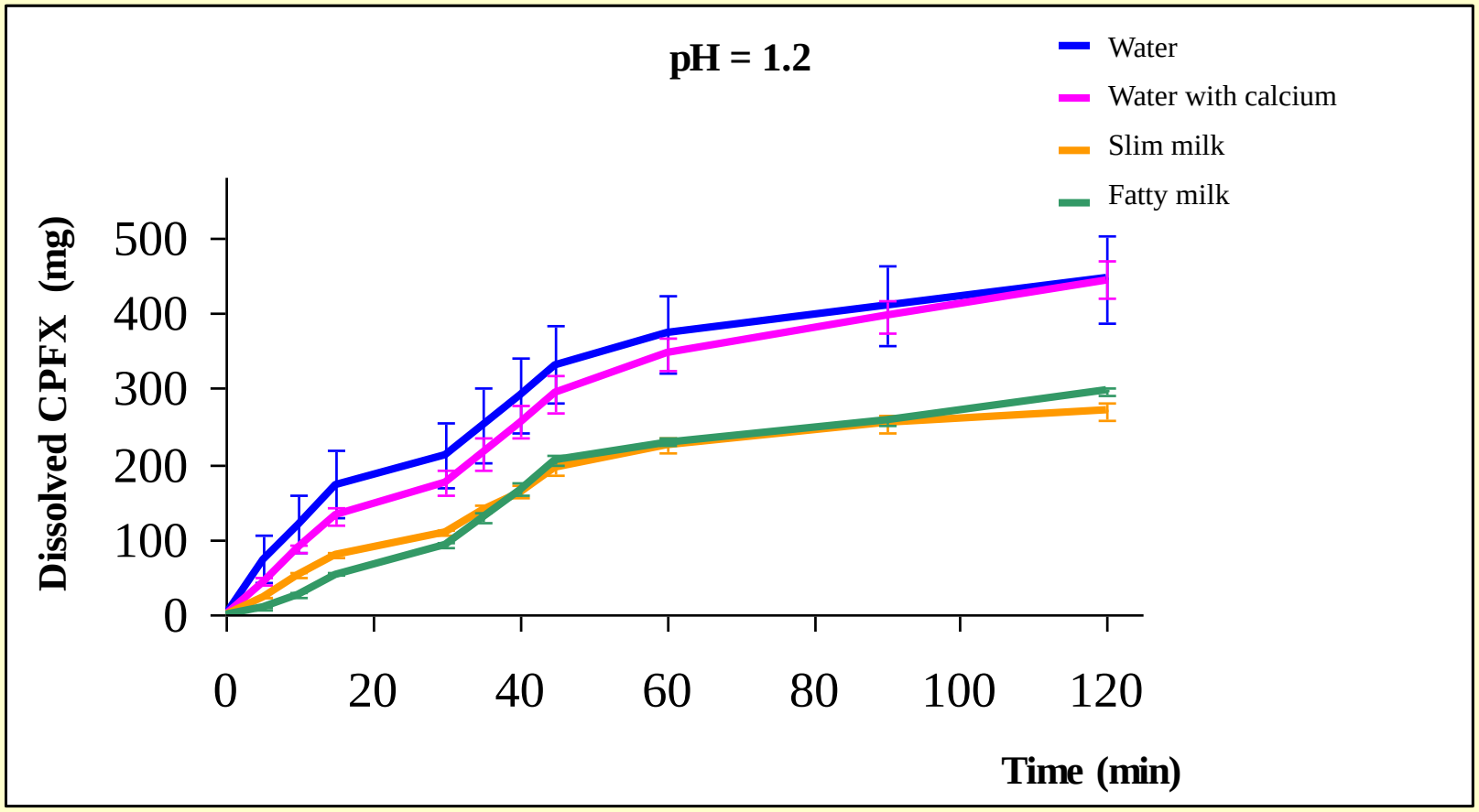
Neuvonen et al. Clin. Pharmacol. Ther., 50, 498-502 (1991).

EFFECT OF MILK ON THE DISSOLUTION OF CIPROFLOXACIN



K. Pápai, M. Budai, K. Ludányi, I. Antal, I. Klebovich: In vitro food–drug interaction study: Which milk component has a decreasing effect on the bioavailability of ciprofloxacin?
J. Pharm. Biomed. Anal., 52, 37-42 (2010).

IN-VITRO STUDY OF CIPROFLOXACIN (CPFX) 500 mg FILM COATED TABLETS

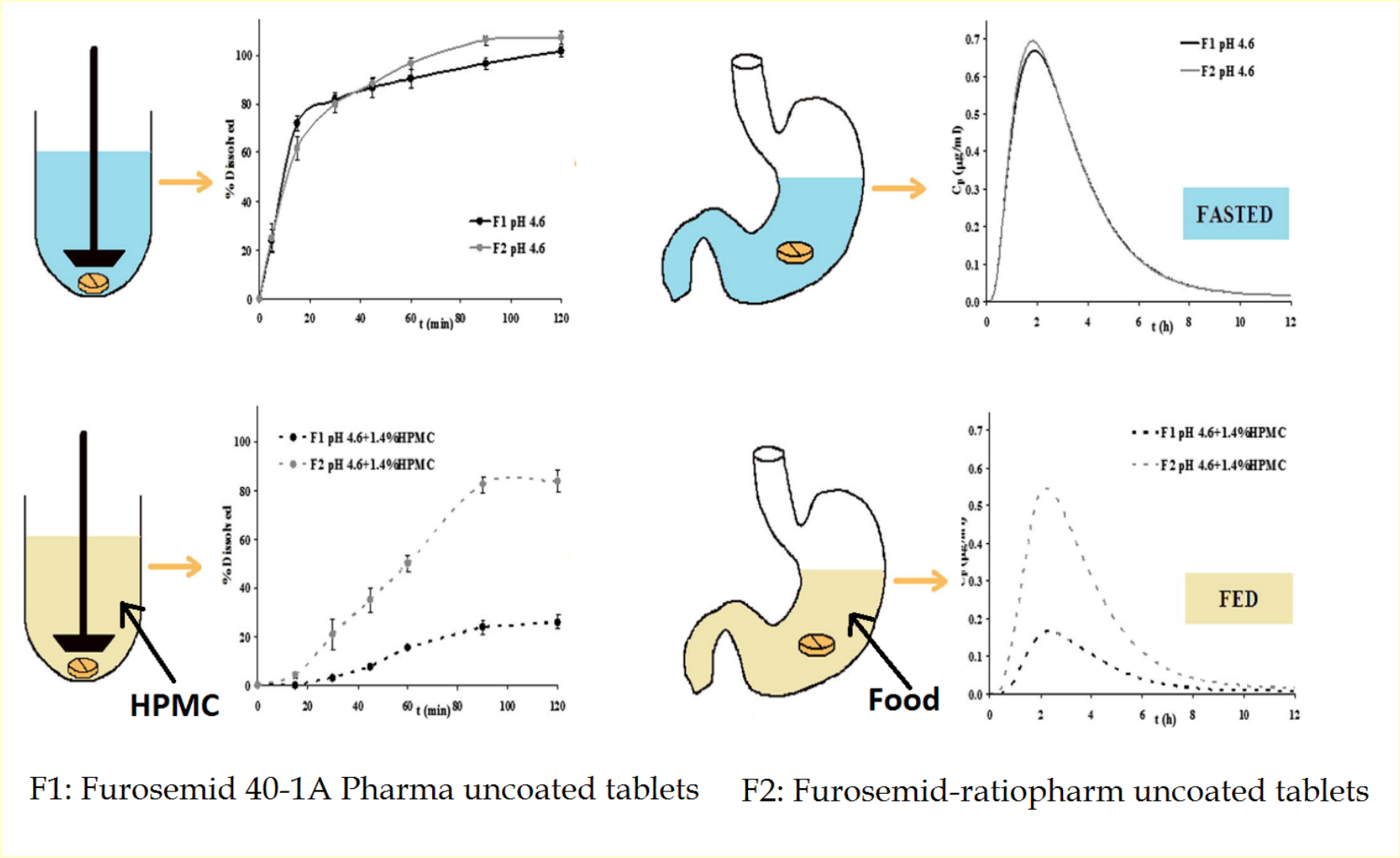


COMPOSITION OF FAT AND SKIMMED POWDERED MILK

Type of the powdered milk	Fat (g/100g)	Protein (g/100g)	Carbohydrate (g/100g)
Skimmed	0.11 ± 0.02	3.13 ± 0.02	4.9 ± 0.01
Fat	2.22 ± 0.01	2.15 ± 0.01	2.74 ± 0.01
$\frac{\text{skimmed}}{\text{fat}}$ = **ratio**	**0.05 X**	**1.5 X**	**1.8 X**

VISCOSITY-MEDIATED FOOD EFFECT WITH HYDROXYPROPYL METHYLCELLULOSE (HPMC)

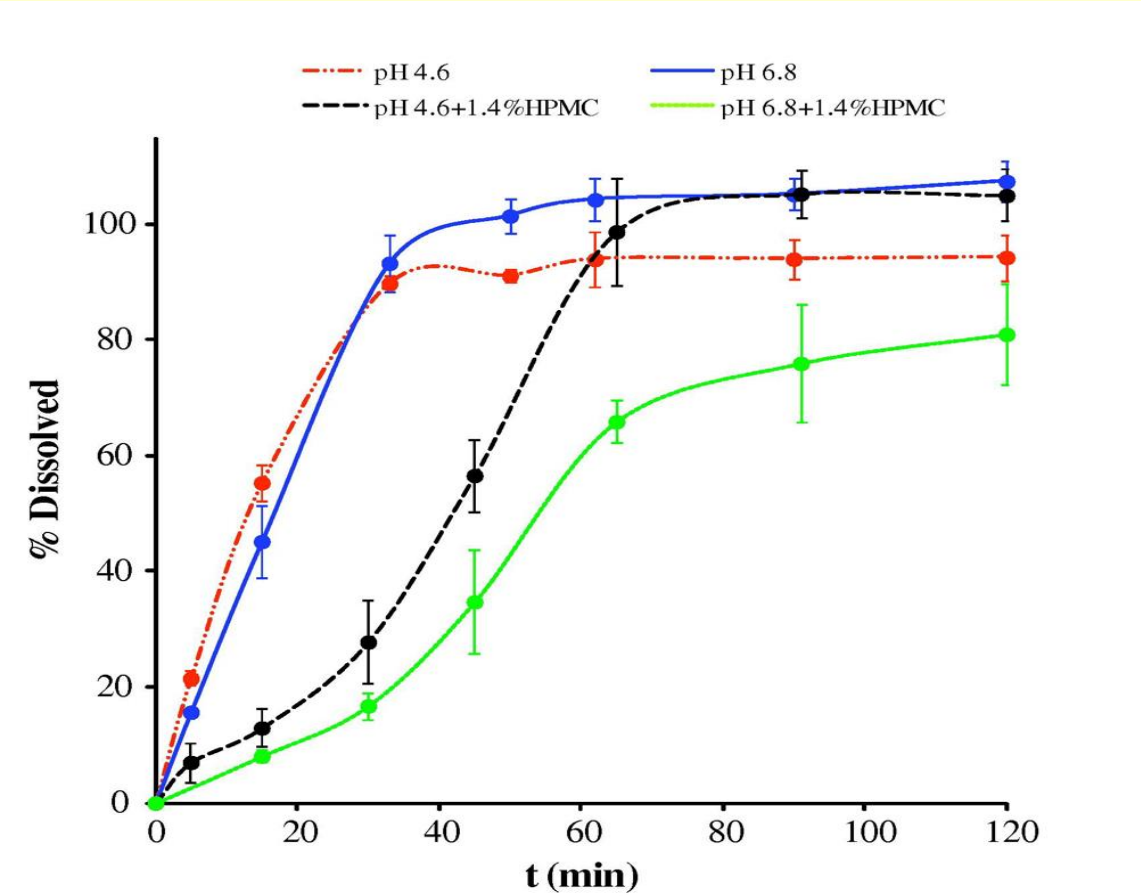
VISCOSITY-MEDIATED NEGATIVE FOOD EFFECT ON ORAL ABSORPTION OF TWO DIFFERENT FUROSEMIDE (BCS IV.) PREPARATIONS (F1, F2)



F1: Furosemid 40-1A Pharma uncoated tablets F2: Furosemid-ratiopharm uncoated tablets

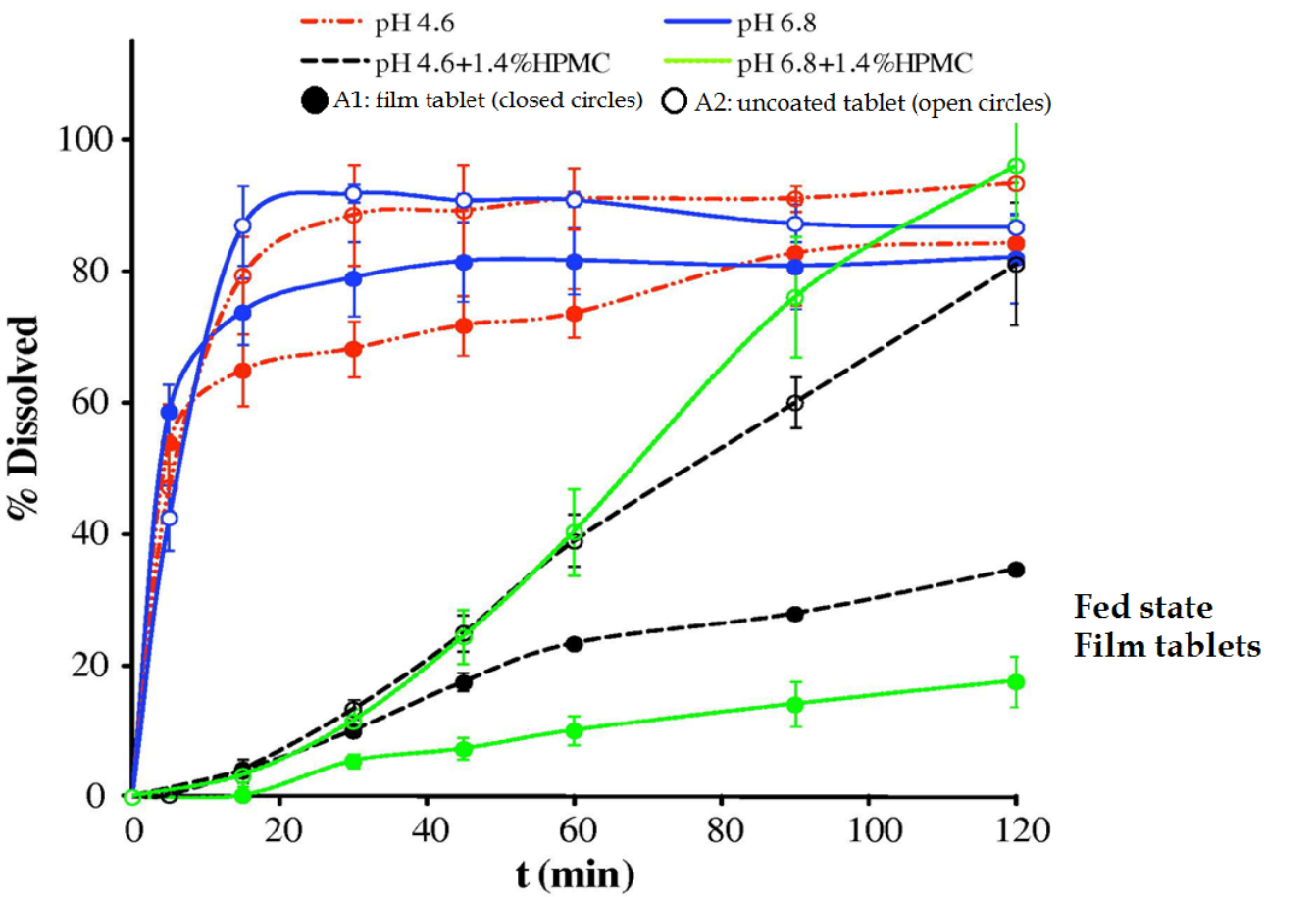
Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Sandra Cvijić et al. Eur J Pharm Sci. 2014 Sep 30;61:40-53.*

DISSOLUTION DATA OBTAINED IN VARIOUS MEDIA FOR METOPROLOL TARTRATE (BCS I.)



Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Sandra Cvijić et al. Eur J Pharm Sci. 2014 Sep 30;61:40-53.*

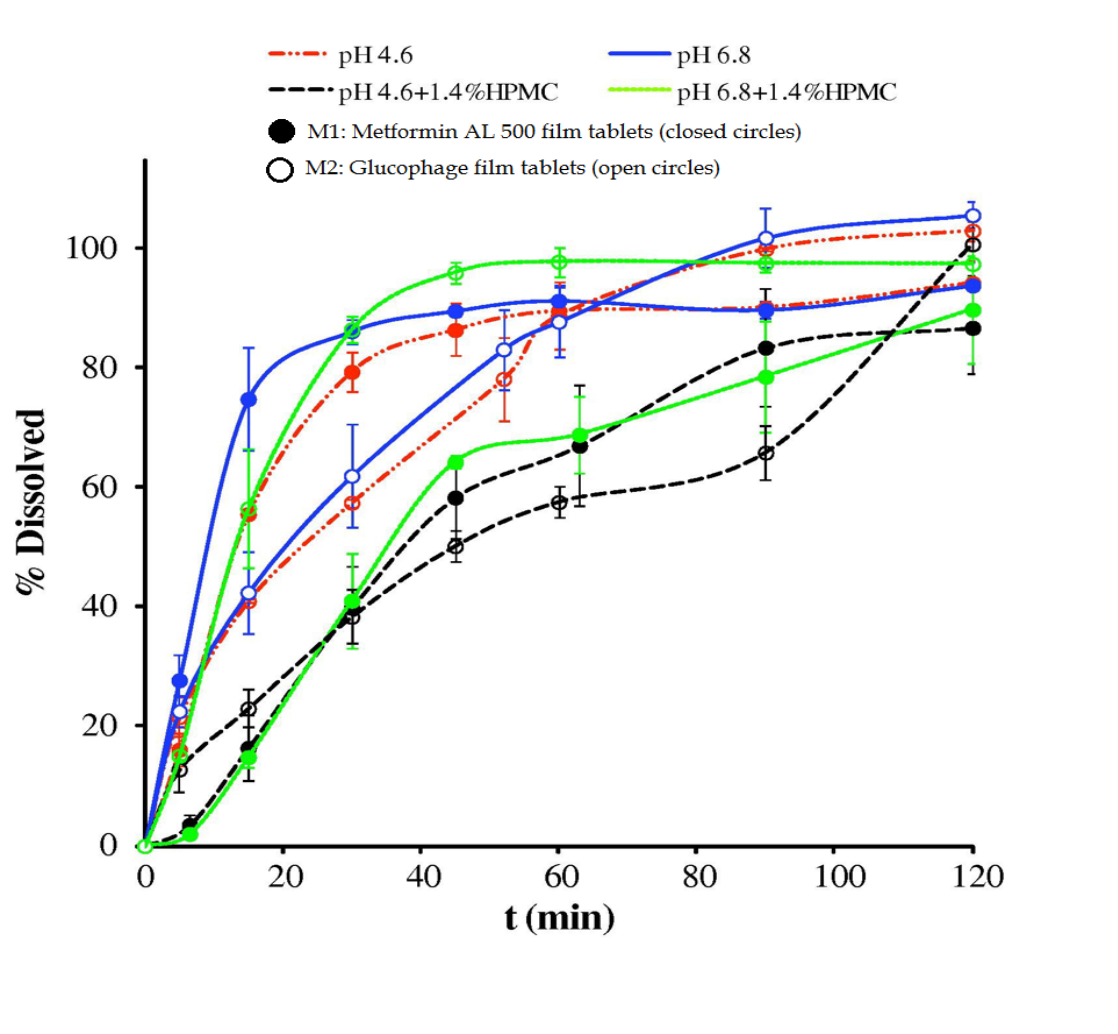
DISSOLUTION DATA OBTAINED IN VARIOUS MEDIA FOR TWO DIFFERENT ATENOLOL (BCS III.) PREPARATIONS



A1: Atenolol 50-1A Pharma film tablets A2: Atenolol AL 50 uncoated tablets

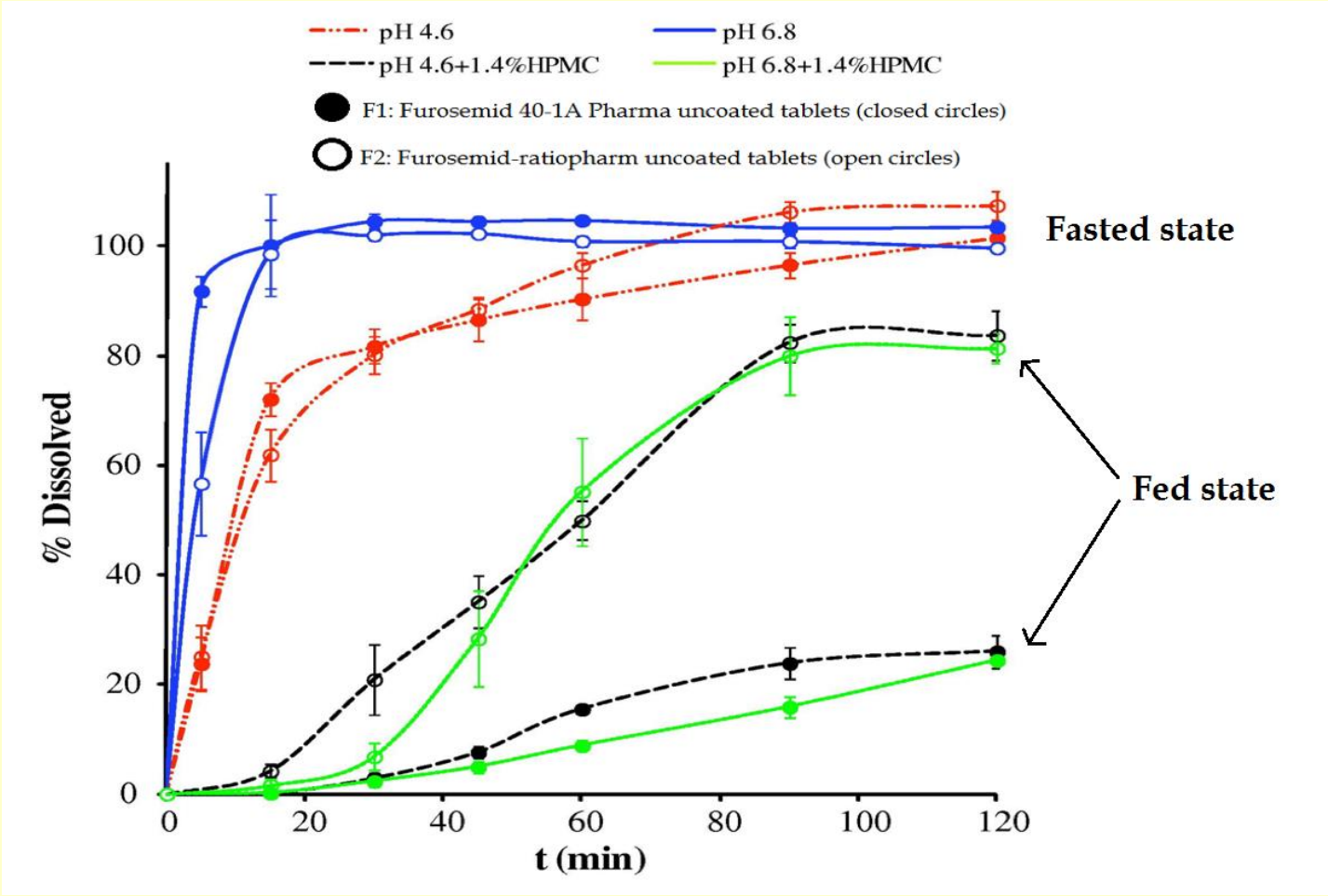
Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Sandra Cvijić et al. Eur J Pharm Sci. 2014 Sep 30;61:40-53.*

DISSOLUTION DATA OBTAINED IN VARIOUS MEDIA FOR TWO DIFFERENT METFORMIN HYDROCHLORID (BCS III.) PREPARATIONS (FILM TABLETS)



Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Sandra Cvijić et al. Eur J Pharm Sci. 2014 Sep 30;61:40-53.*

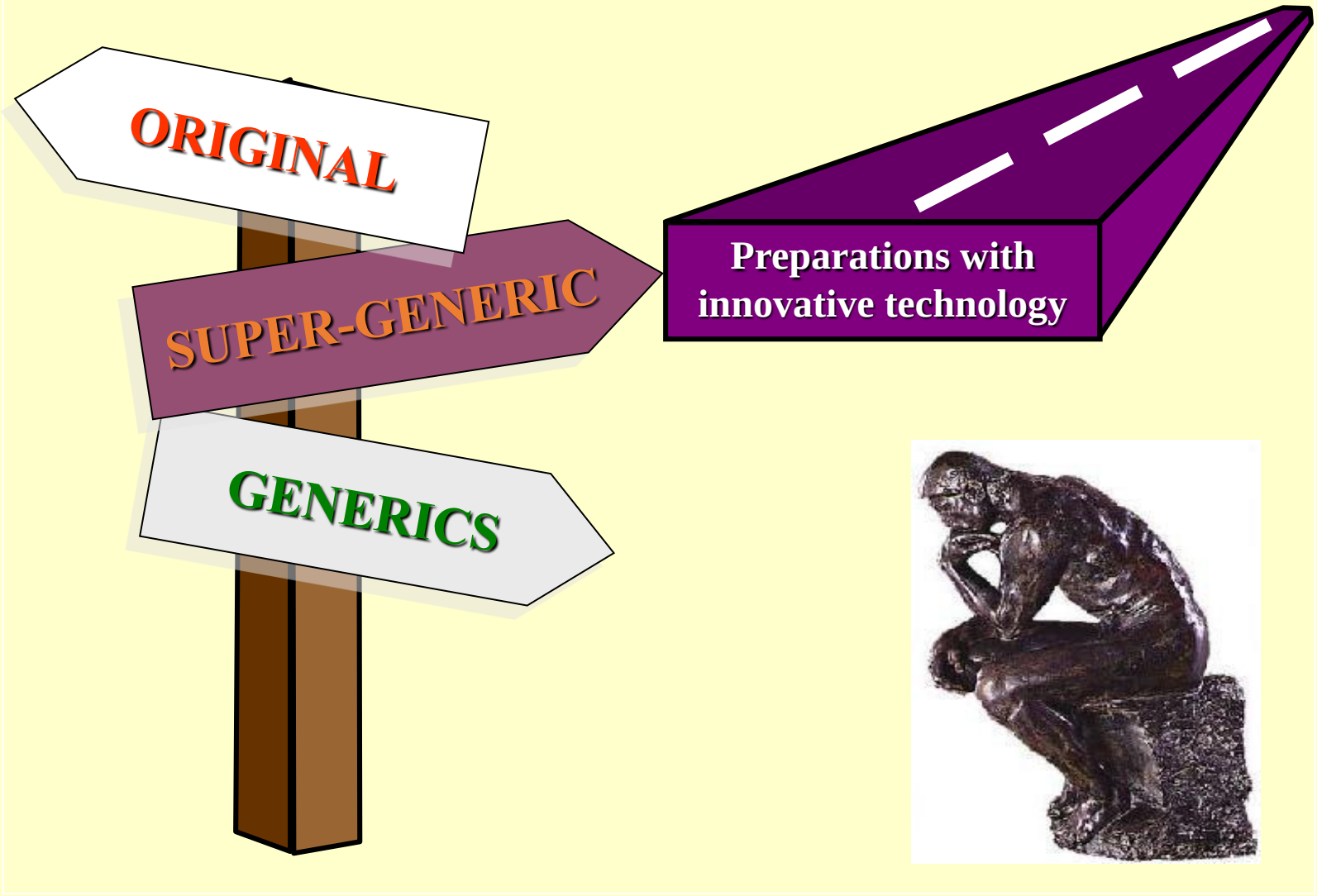
DISSOLUTION DATA OBTAINED IN VARIOUS MEDIA FOR TWO DIFFERENT FUROSEMIDE (BCS IV.) PREPARATIONS (UNCOATED TABLETS)



Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Sandra Cvijić et al. Eur J Pharm Sci. 2014 Sep 30;61:40-53.*

SUMMARY….

TRENDS IN THE ”R+D MAZE” OF PHARMACEUTICAL INDUSTRY



SUMMARY OF MAIN TYPES OF DRUG INTERACTIONS

Drug Interactions

- Drug
- Food
- Alcohol
- Smoking
- Caffeine
- Transporters
- Pharmacogenomics
- Psychoactive drugs
- Antacid and inhibitor of gastric juice secretion

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*** Possibility of prediction with *in vitro* dissolution**

EXPECTATIONS FOR *IN VITRO/IN VIVO* CORRELATIONS FOR IR PRODUCTS BASED ON BCS

BCS class	IVIVC expectations
I. **High S/High P**	No IVIVC until product dissolution becomes slower than gastric emptying
II. **Low S/High P**	IVIVC should be possible to establish provided that **in vitro relevant dissolution test** method is used and **drug absorption is limited by dissolution rate rather than saturation solubility**
III. **High S/Low P**	No IVIVC until product dissolution becomes slower than intestinal permeability
IV. **Low S/Low P**	Low chance for IVIVC

IMPORTANCE OF THE *IN-VITRO* EXAMINATIONS OF FOOD-DRUG INTERACTIONS

- **Fast, „not expensive” information**
- **Fast information about the previously registered drugs, which were not examined to food interaction**
- **Prediction of clinical studies with simulated *in-vitro* examinations**
- **Relative good estimation of IVIVC correlation (BCS II)**
  – biorelevant dissolution medium
  – poorly-permeable drugs (BCS III, IV) with HPMC
- **Prediction of the type and mechanism of food interaction**
- **Prediction of the differences of drug interaction according to the geographic location and culinary tradition**
- ***In-vitro* predictive study of drug-food and/or milk interactions of infant, pediatric and geriatric formulations without ethical consequences**
- **Management of ”ideal therapy” and refined patient’s information**

ACKNOWLEDGMENTS

- **Petra Füredi**
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- **Katalin Pápai**
- **Dávid Virág**
- **Romána Zelkó**

„THE LARGER THE ISLE OF KNOWLEDGE,
THE LONGER
THE LENGTH
OF THE UNKNOWN SHORE.”

Ralph W. Sockman

(1889-1970)

THANK YOU FOR YOUR KIND ATTENTION