PREDICTING DRUG INTERACTIONS FROM DISSOLUTION STUDIES

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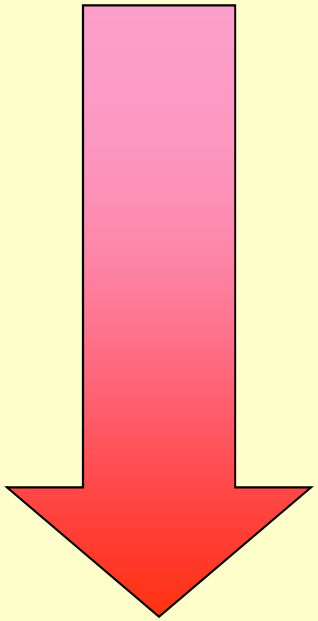
THE BASIC LOGIC OF NOVEL DRUG RESEARCH CONCEPT

in-celebro

in-silico

in-vitro

in-vivo



MAIN TYPES OF DRUG INTERACTIONS

Drug Interactions

- Drug
- Food
- Alcohol
- Smoking
- Caffeine

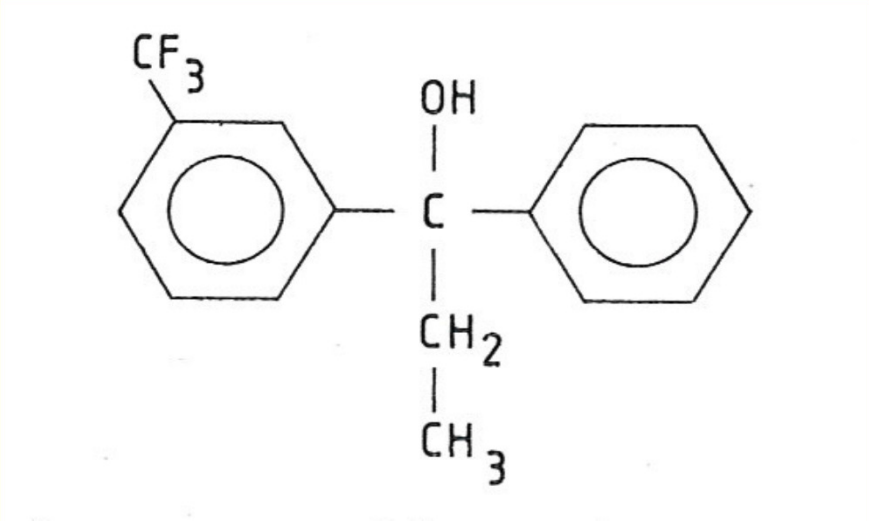
Pleasure-giving materials

- Transporters
- Pharmacogenomics
- Psychoactive drugs
- Antacid and inhibitor of gastric juice secretion

DRUG-FOOD INTERACTION

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

CHEMICAL STRUCTURE OF FLUMECINOL (ZIXORYN^{R})

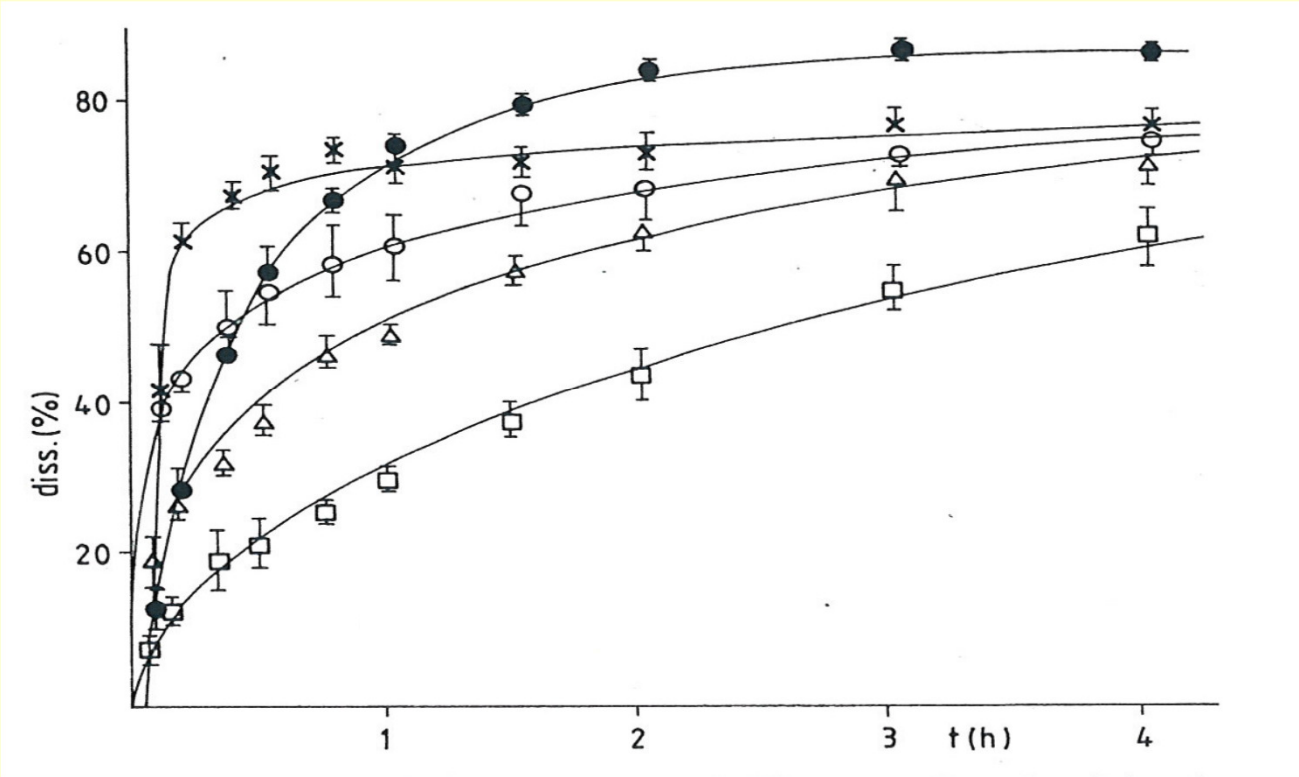


hepatic enzyme inducer (CYP-450 2B1)

METHOD OF FORMULATION OF DIFFERENT ORAL FLUMECINOL PREPARATIONS

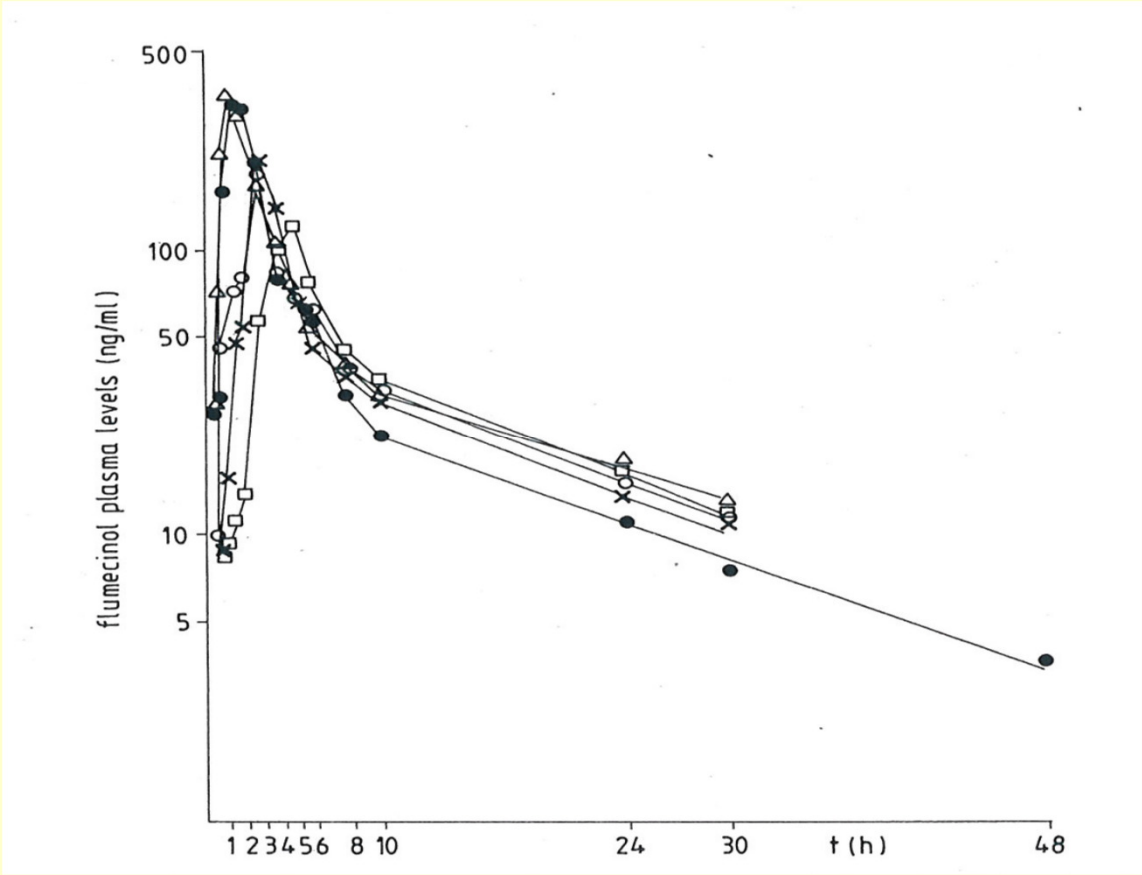
Symbol		Formulation	Method for technology
Adsorbate	o—o	adsorbate in hard gelatine capsule	absorption of flumecinol on the surface of silicium dioxide
Microcapsules	Δ—Δ	microcapsules in hard gelaine capsule	microencapsulation by coacervation technique
ß-cyclodextrine inclusion complex	x—x	tablet	inclusion 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

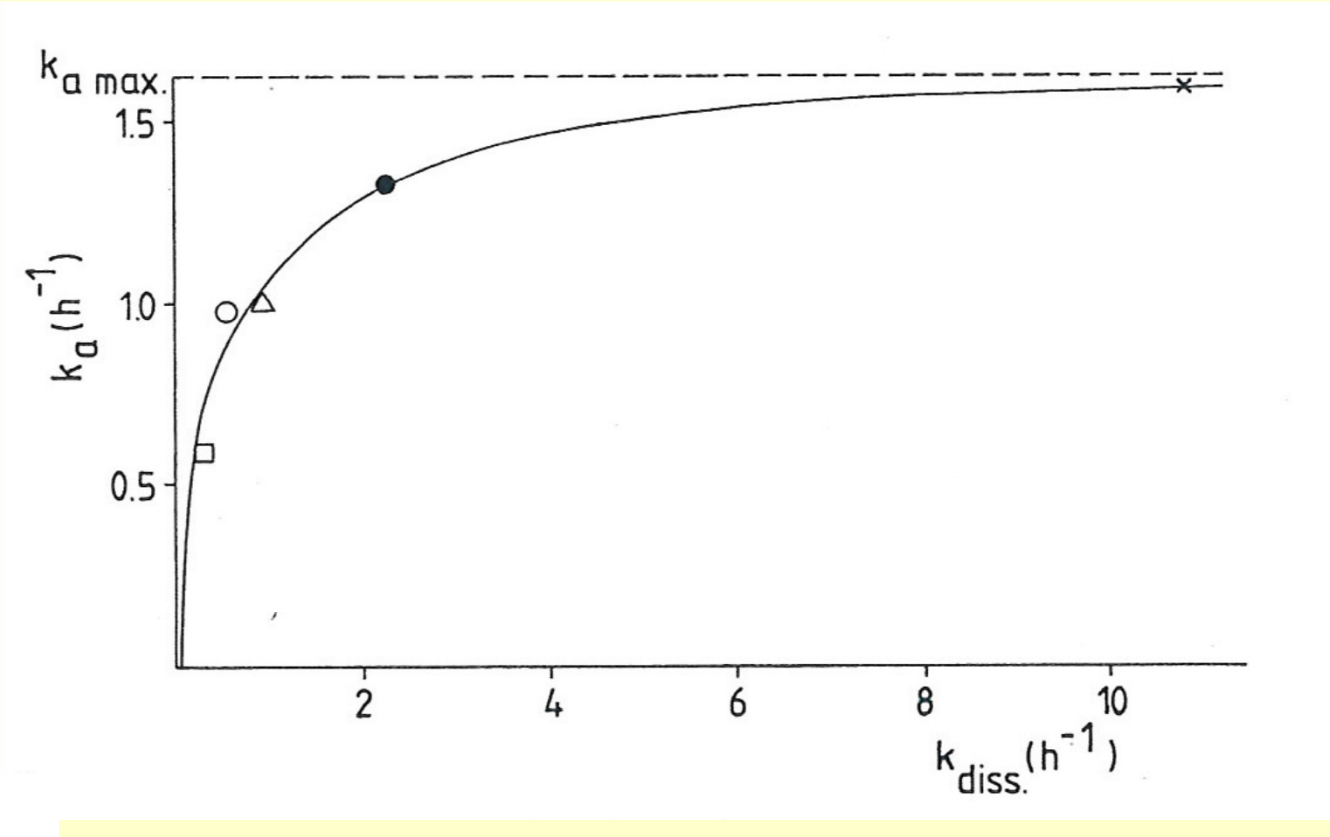


PHARMACOKINETIC CURVES OF FLUMECINOL IN HUMAN

AFTER 100 MG SINGLE ORAL ADMINISTRATION OF 5 DIFFERENT FORMULATIONS

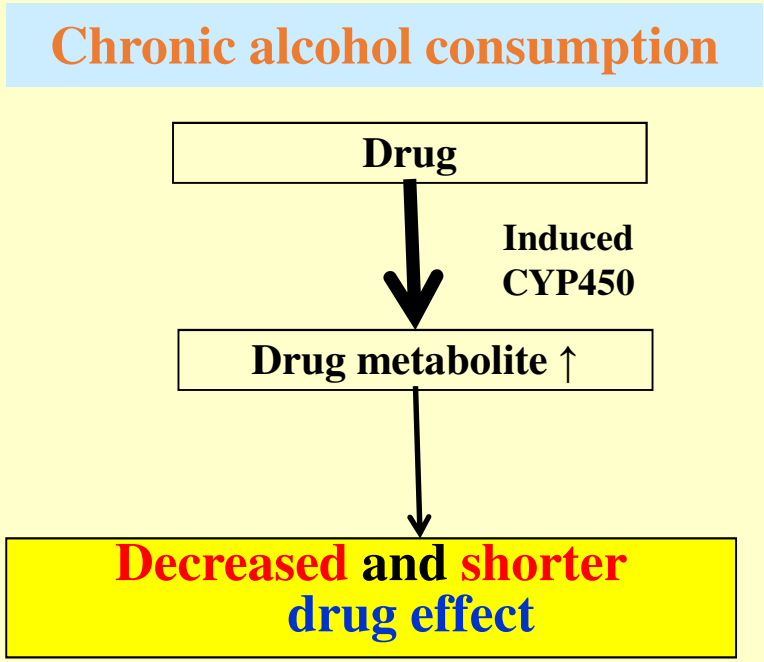


THE RELATIONSHIP OF *IN VIVO* ABSORPTION TO *IN VITRO* DISSOLUTION RATE CONSTANTS



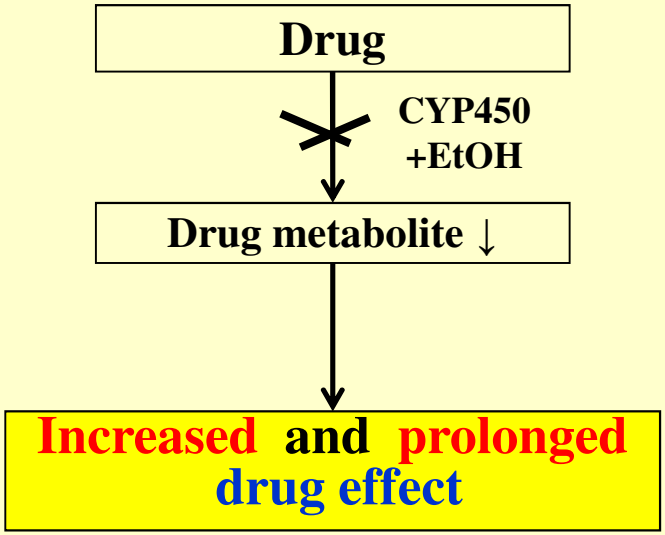
DRUG – ALCOHOL INTERACTION

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

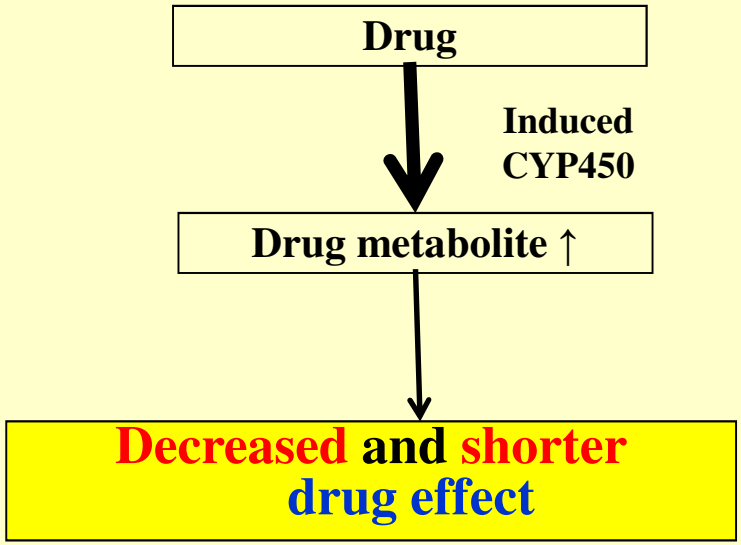


THE INFLUENCE OF *ACUT* AND *CHRONIC* ALCOHOL CONSUMPTION ON THE CYTOCHROM P450 ENZYMES AND ON THE DRUG EFFECT

Acut alcohol consumption



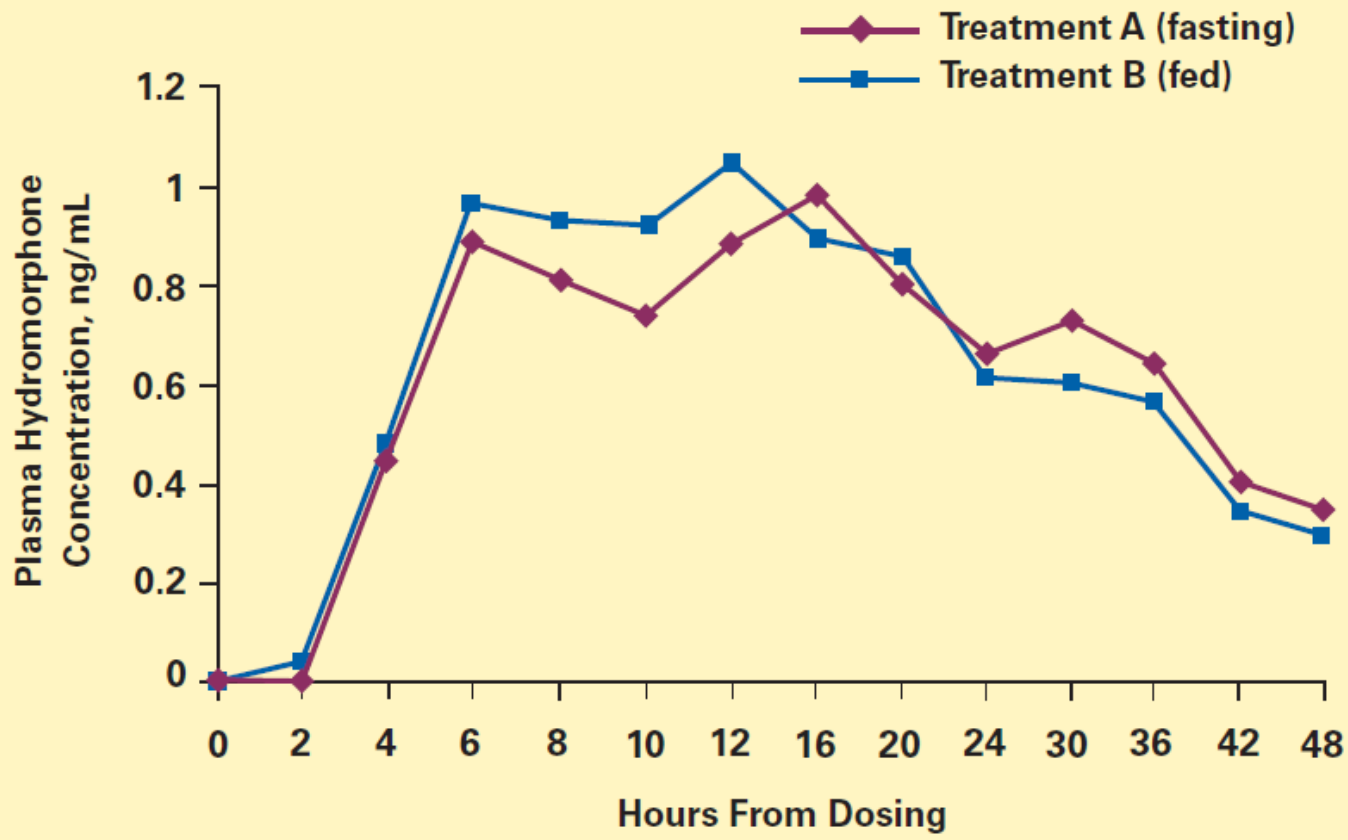
Chronic alcohol consumption



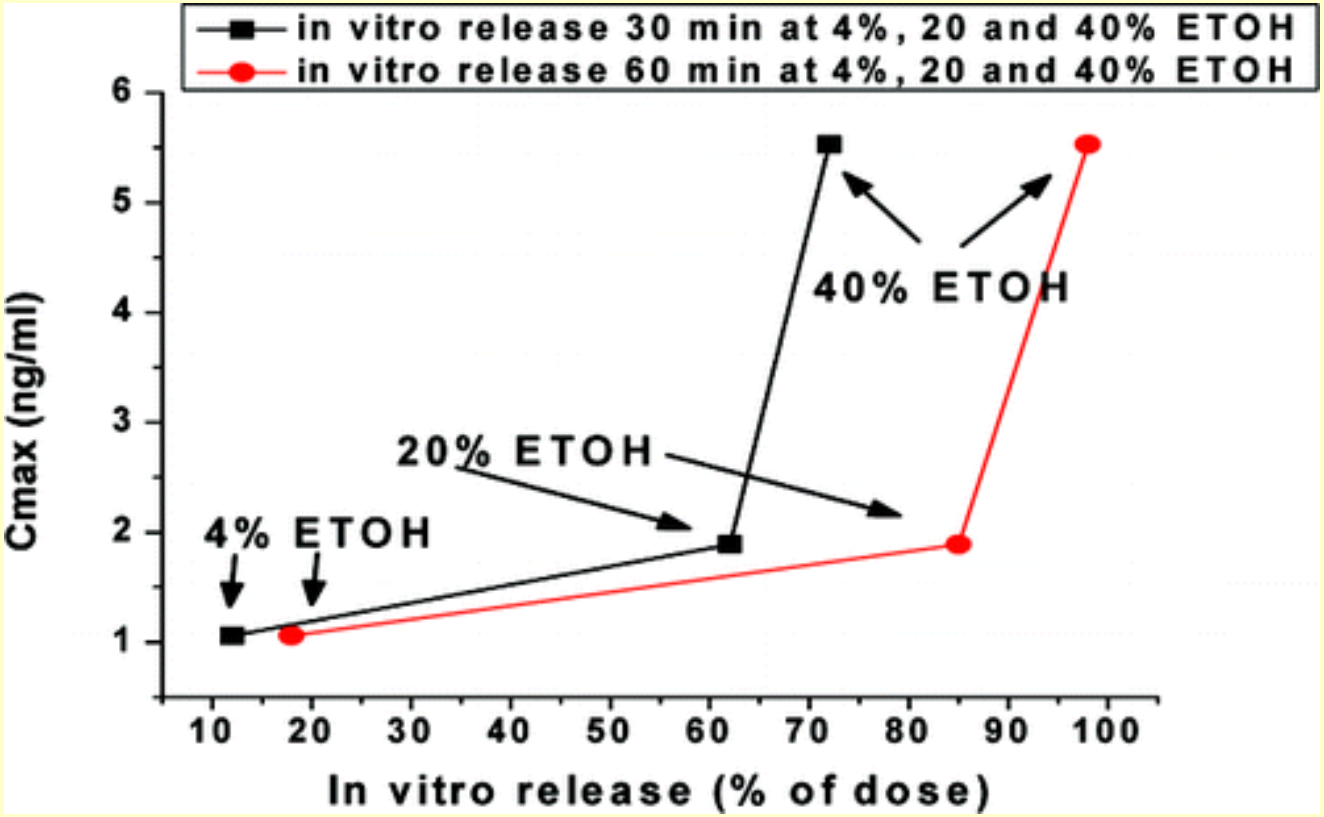
PHARMACOKINETICS OF HYDROMORPHONE (JURNISTA^{R}) IN HUMAN BEFORE AND AFTER THE MEAL

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



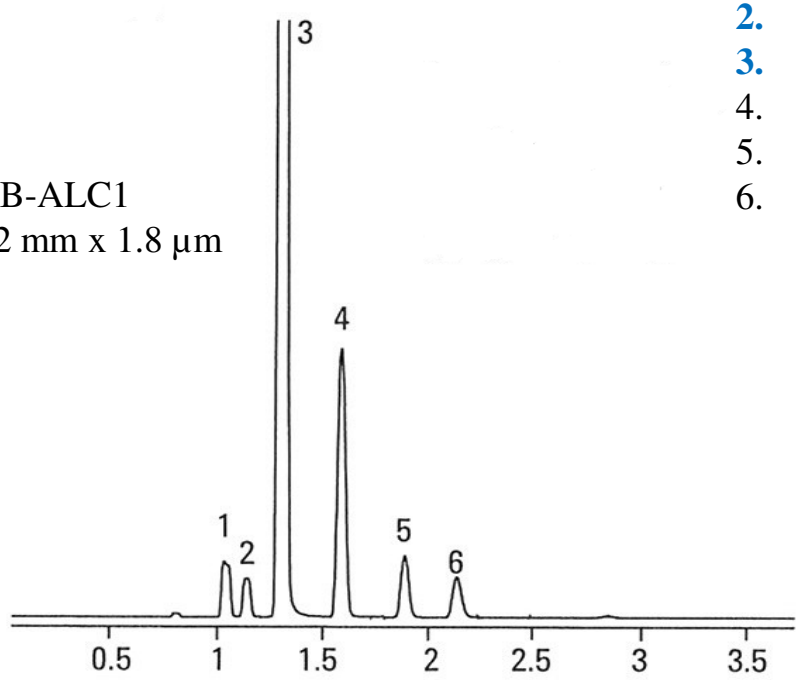
IN VITRO DISSOLUTION PROFILE OF A CONTROLLED RELEASE HYDROMORPHONE IN ETHANOL CONCENTRATIONS OF UP TO 40%



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.

DETERMINATION OF BLOOD ALCOHOL LEVEL WITH GC-HEADSPACE TECHNIQUE

Colomn: DB-ALC1
30 m x 0.32 mm x 1.8 µm



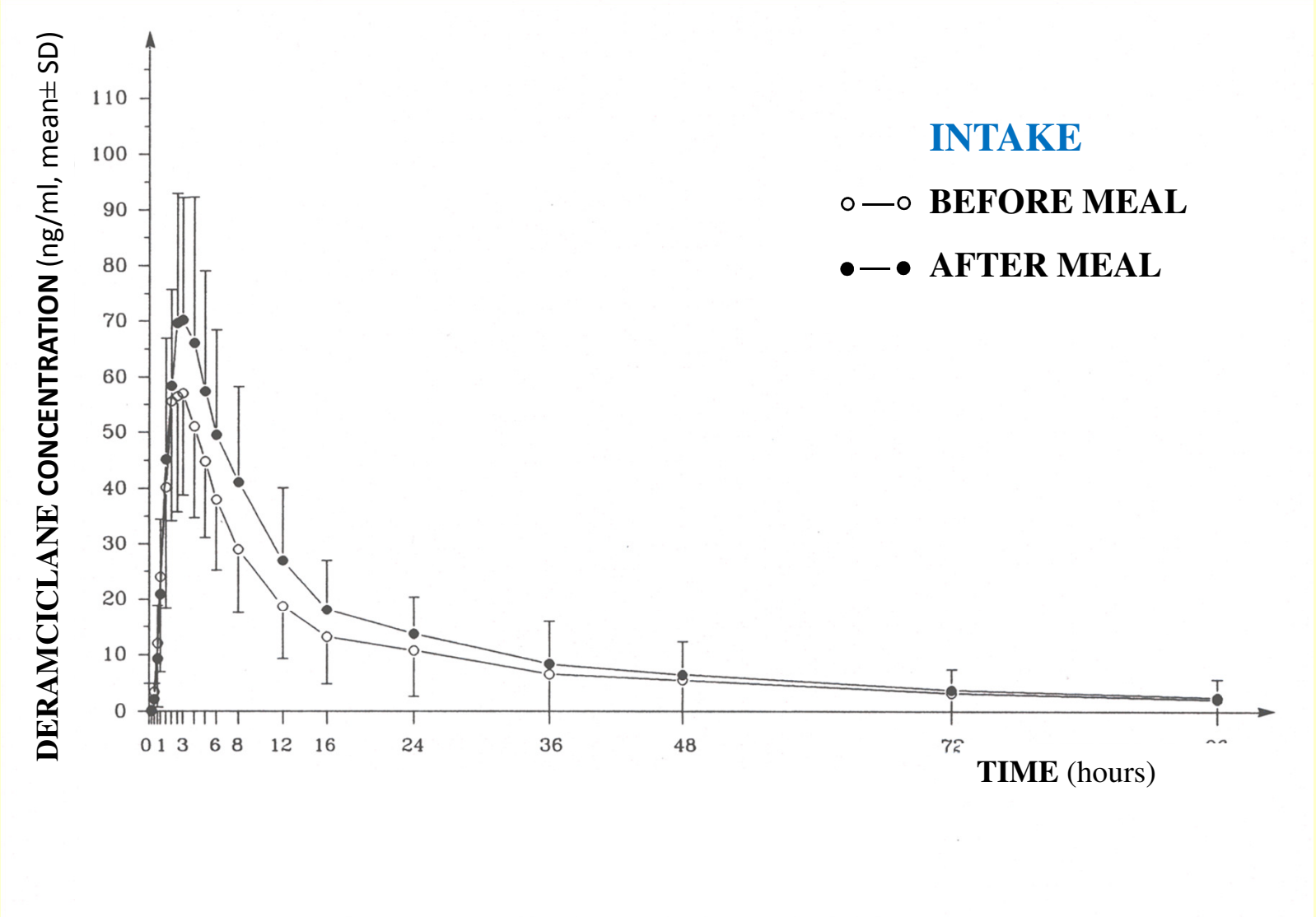
1. methanol
2. **acetaldehyde**
3. **ethanol**
4. Iso-propanol
5. acetone
6. 1-propanol

FOOD INTERACTION OF DERAMCICLANE

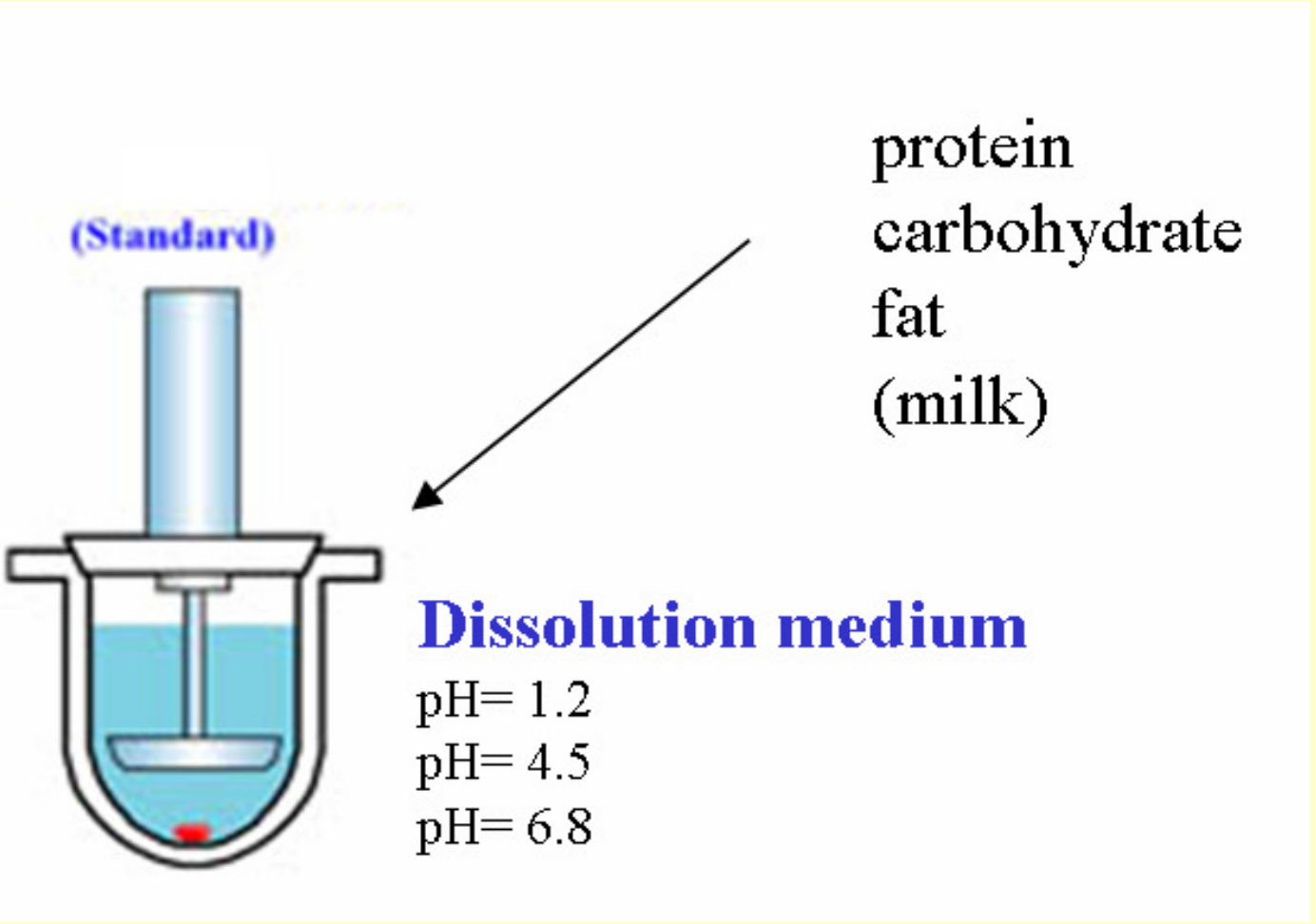
ACID-LABILE DRUGS

- 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



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**

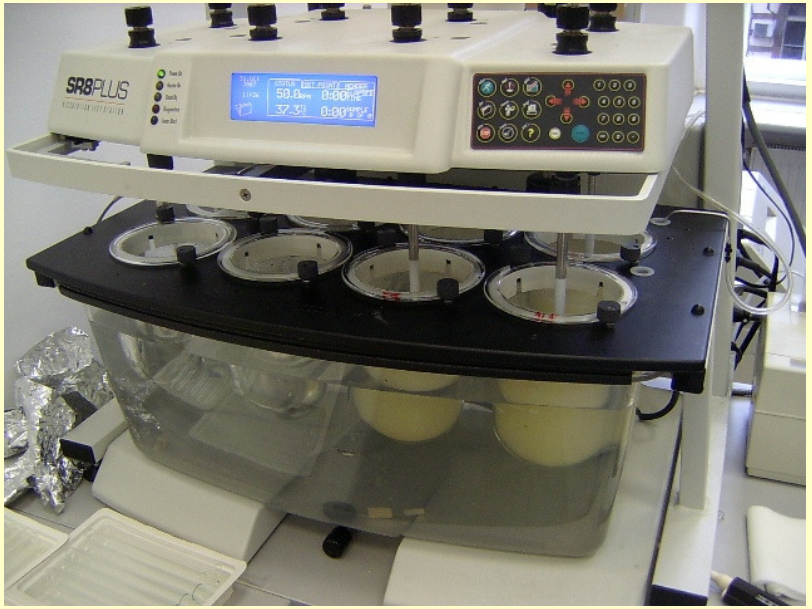
IN-VITRO FOOD EFFECT
SIMULATED 'STANDARD BREAKFAST'

High calorie 'BREAKFAST' 250 ml:

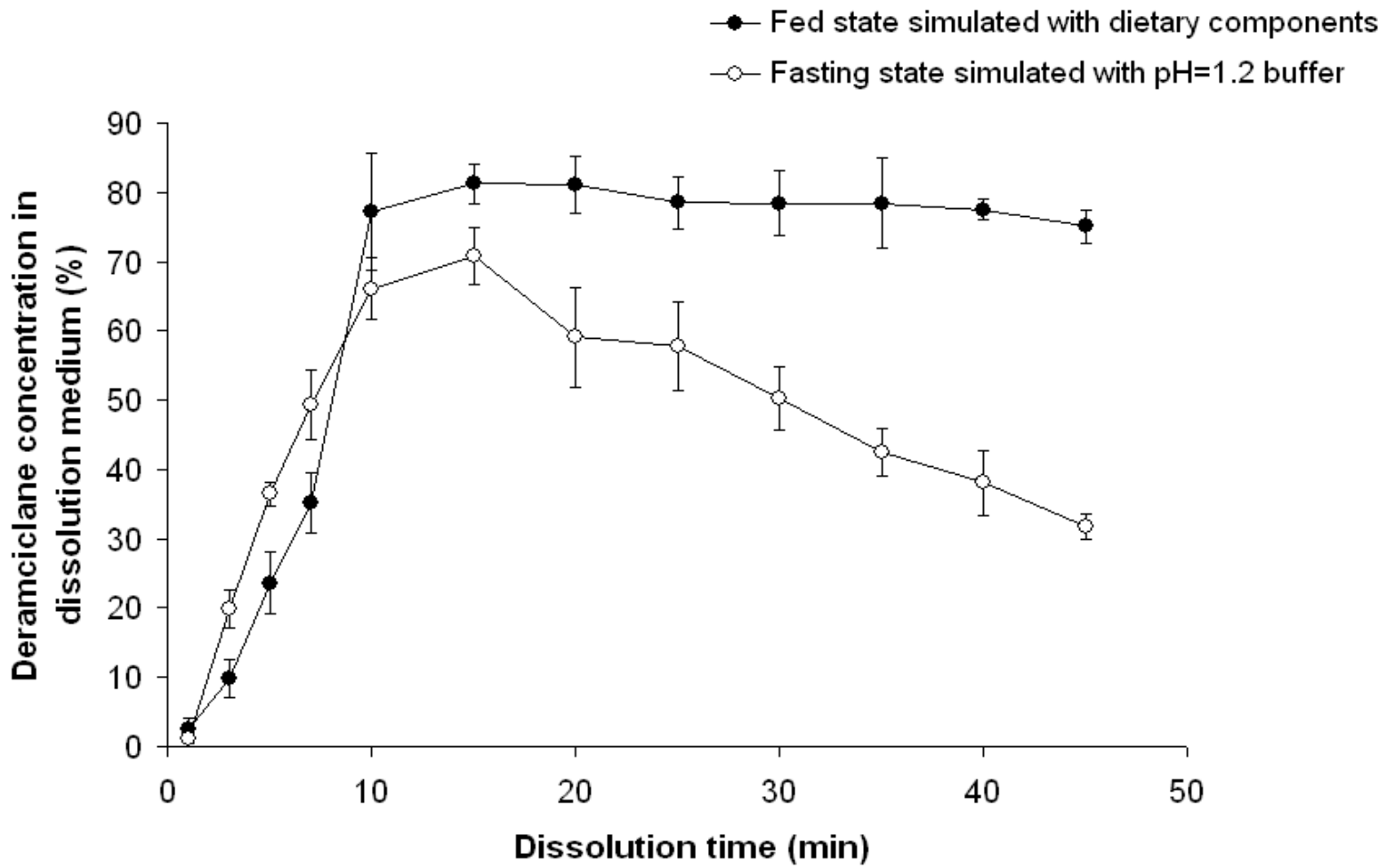
53.8 g oil

31.6 g protein

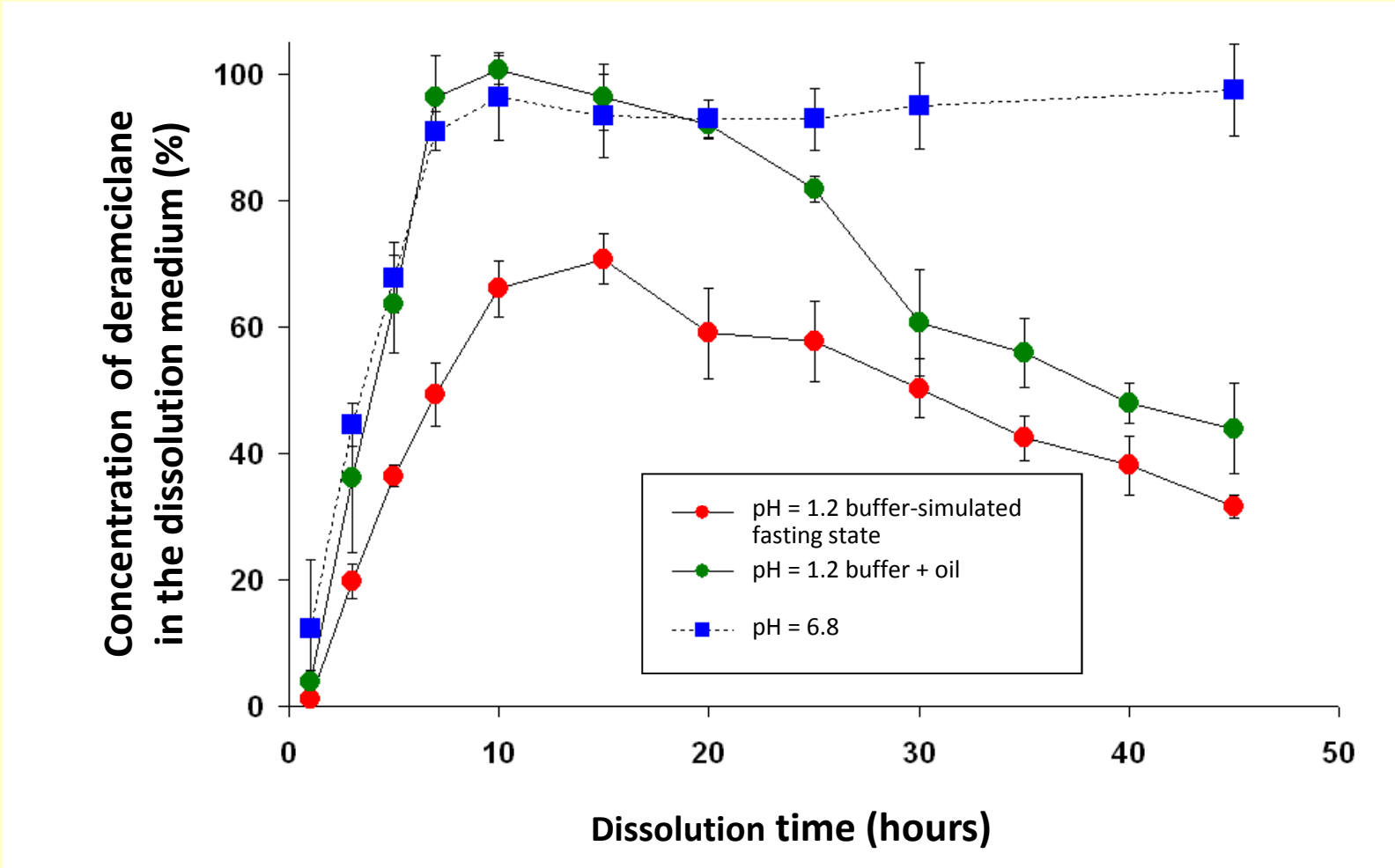
57.4 g carbohydrate



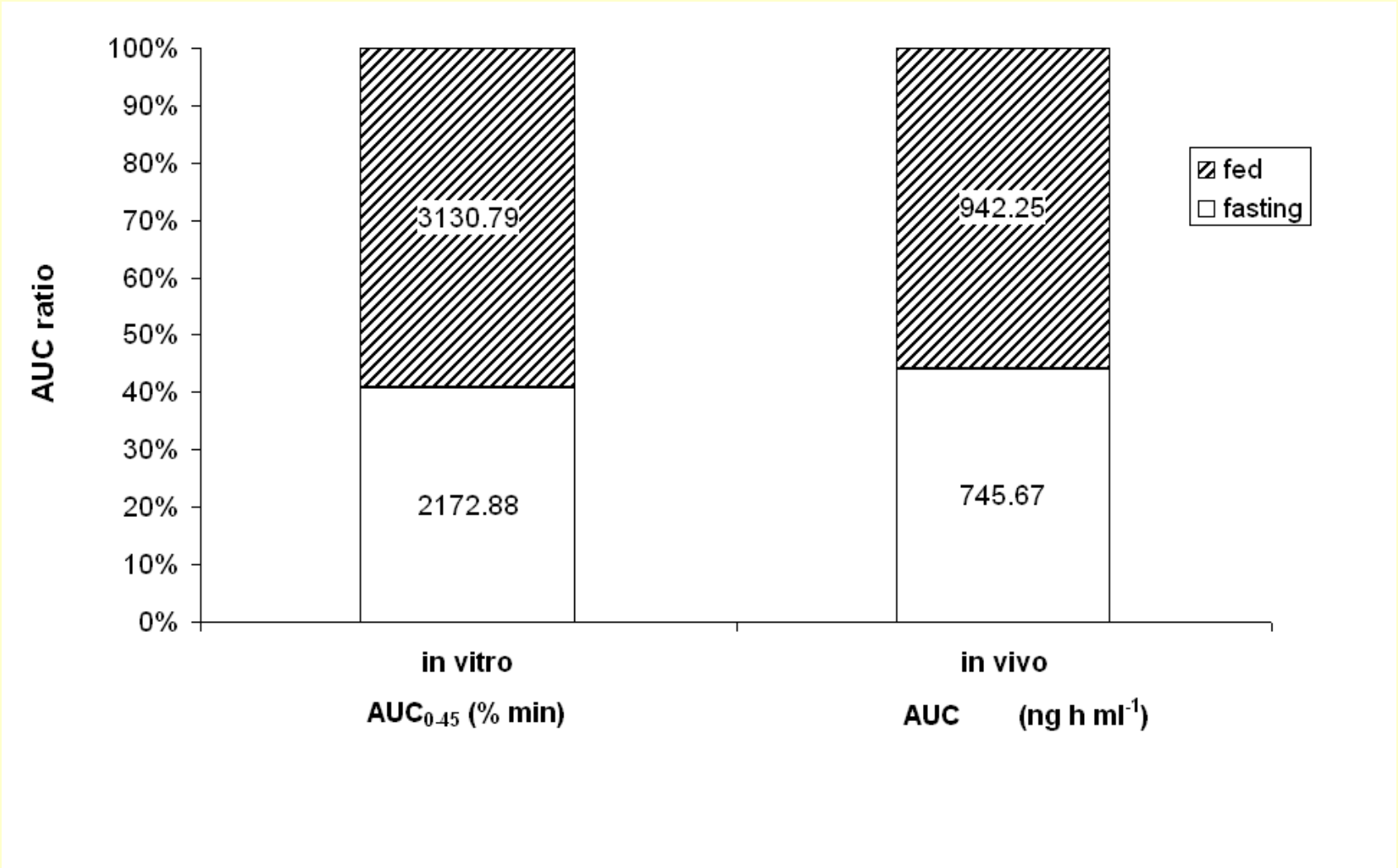
IN -VITRO DISSOLUTION OF DERAMCICLANE (100 mg tabl.)



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



IVIVC CORRELATION OF AUC RATIO AFTER FED AND FASTING STUDY



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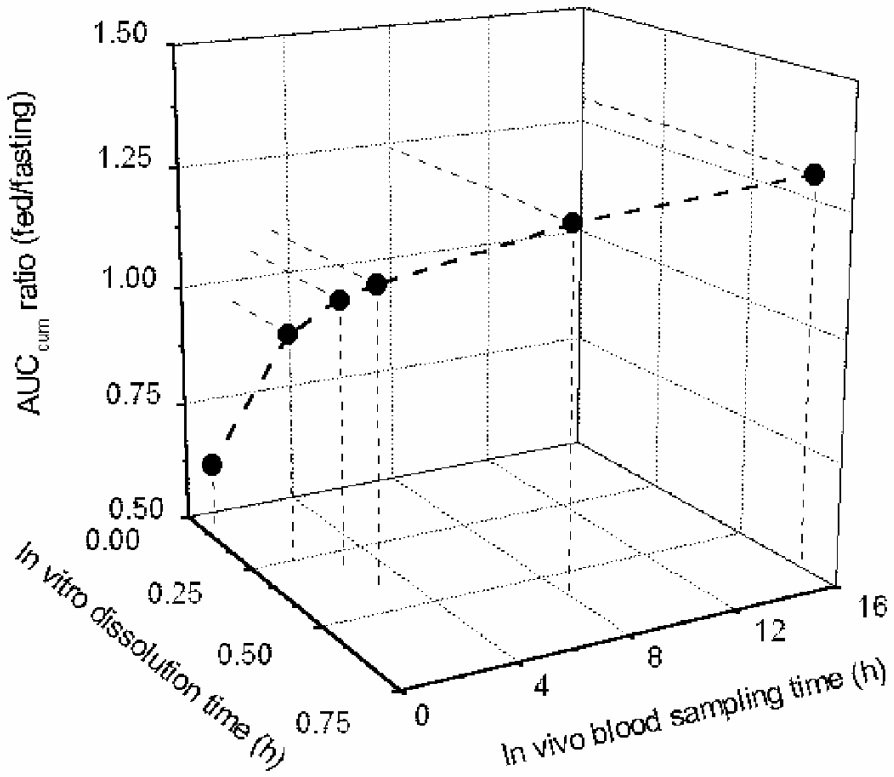


ELSEVIER

European Journal of Pharmaceutical Sciences 15 (2002) 157–162

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

www.elsevier.nl/locate/ejps

In vitro simulation of food effect on dissolution of deramciclane film-coated tablets and correlation with in vivo data in healthy volunteers

Samar Al-Behaisi[a,*], István Antal[b], György Morovján[a], József Szúnyog[a], Sándor Drabant[a], Sylvia Marton[b], Imre Klebovich[a]

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

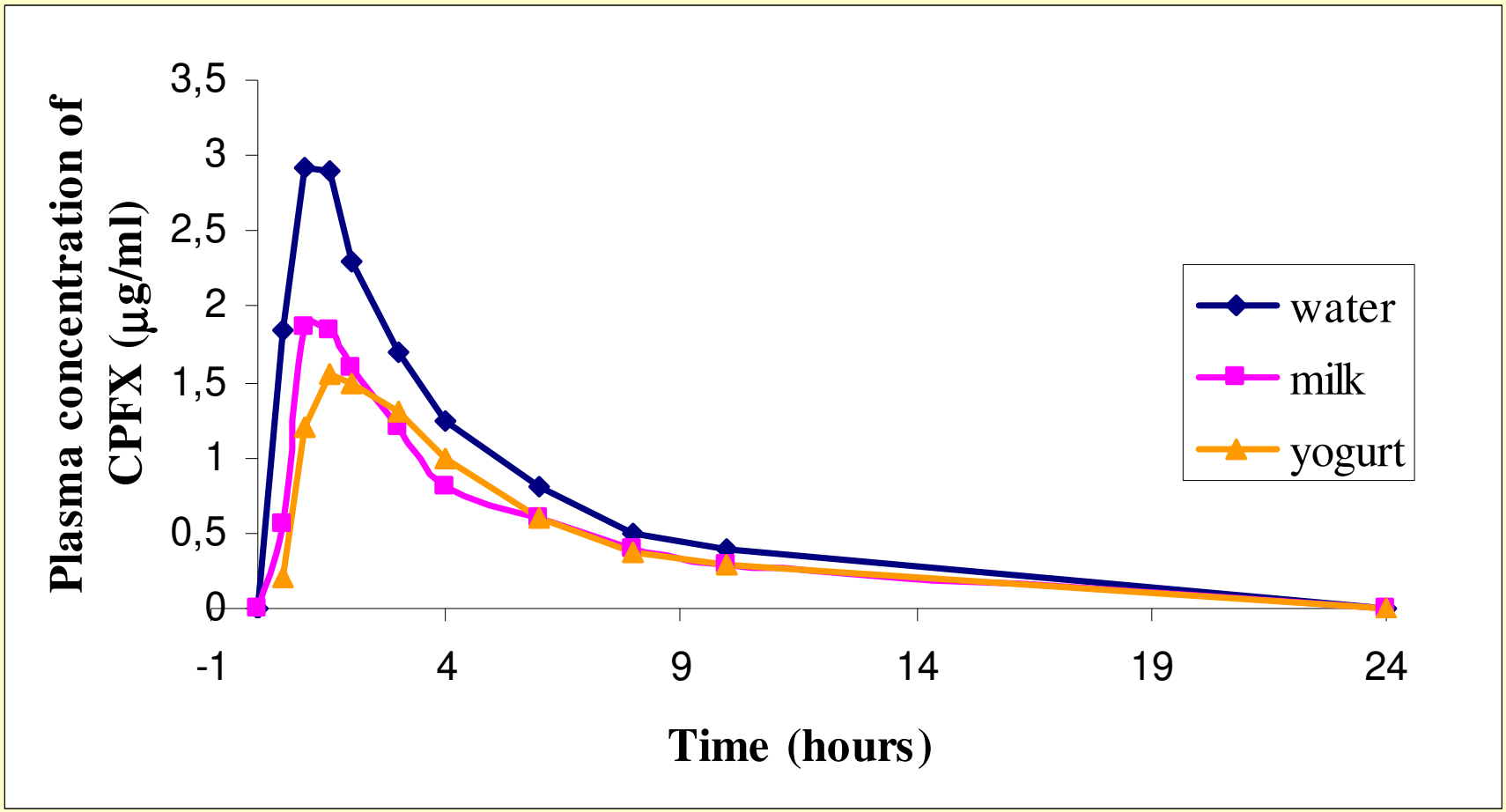
Bioavailability (%):

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

Clodronate ↓ 90 % (with meal)

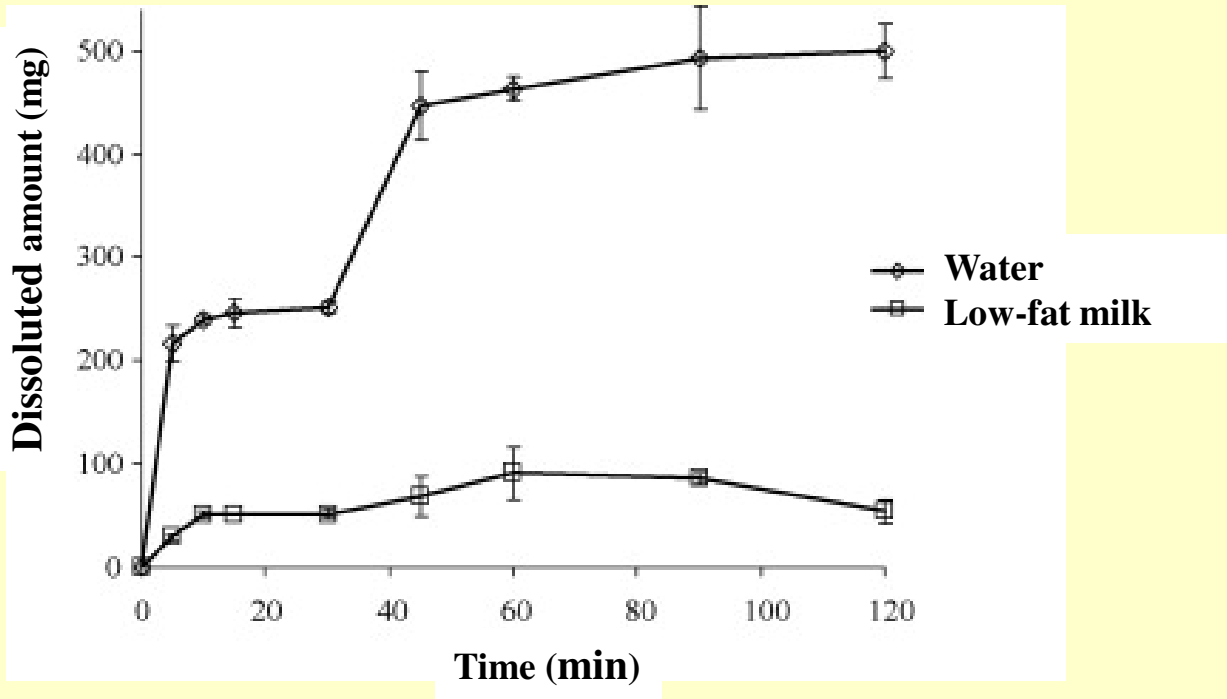
Clodronate ↓ 66 % (2 hours after meal)

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



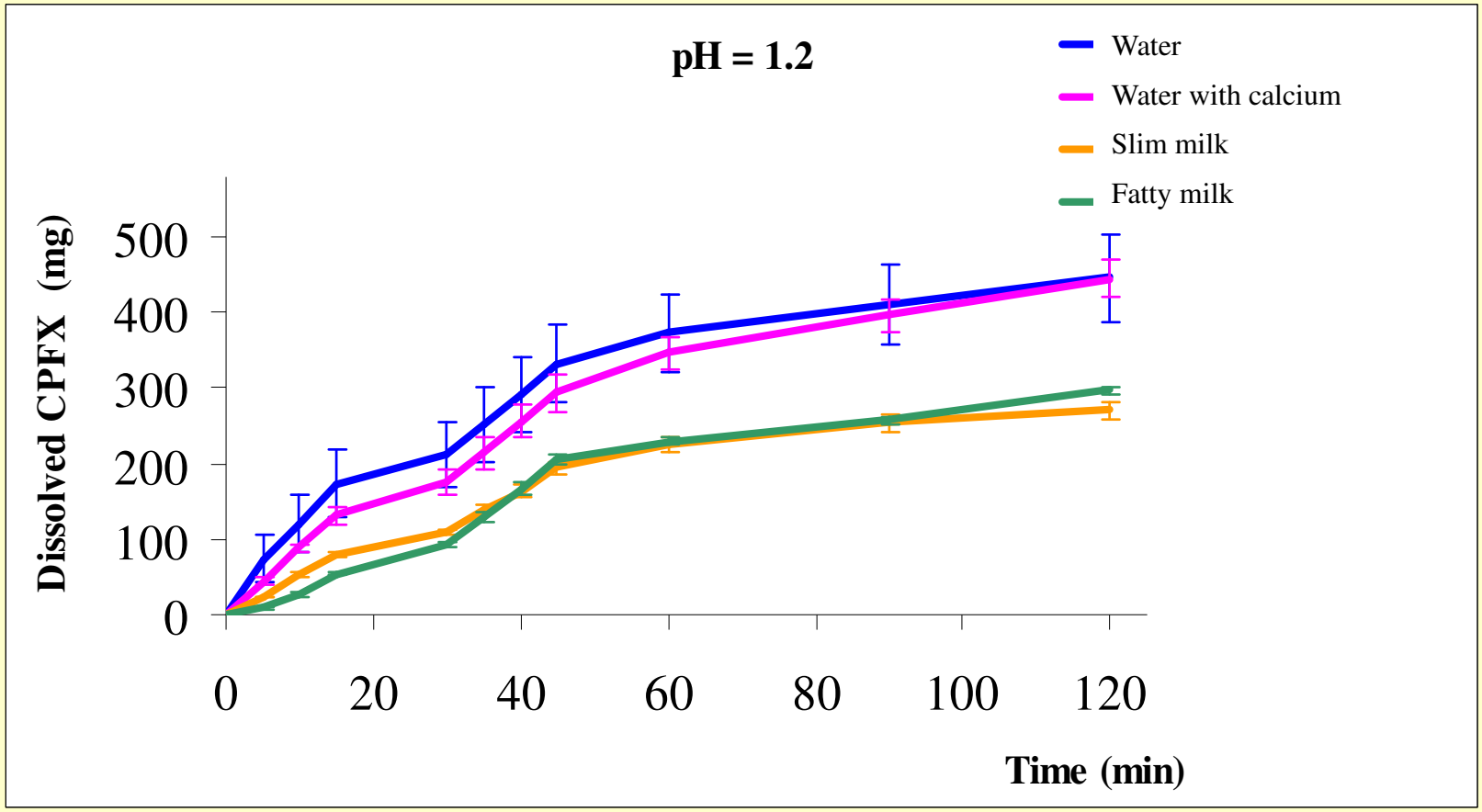
Neuvonen et al. Clin. Pharmacol. Ther., 50, 498-502 (1991).

EFFECT OF MILK ON THE DISSOLUTION OF CIPROFLOXACIN

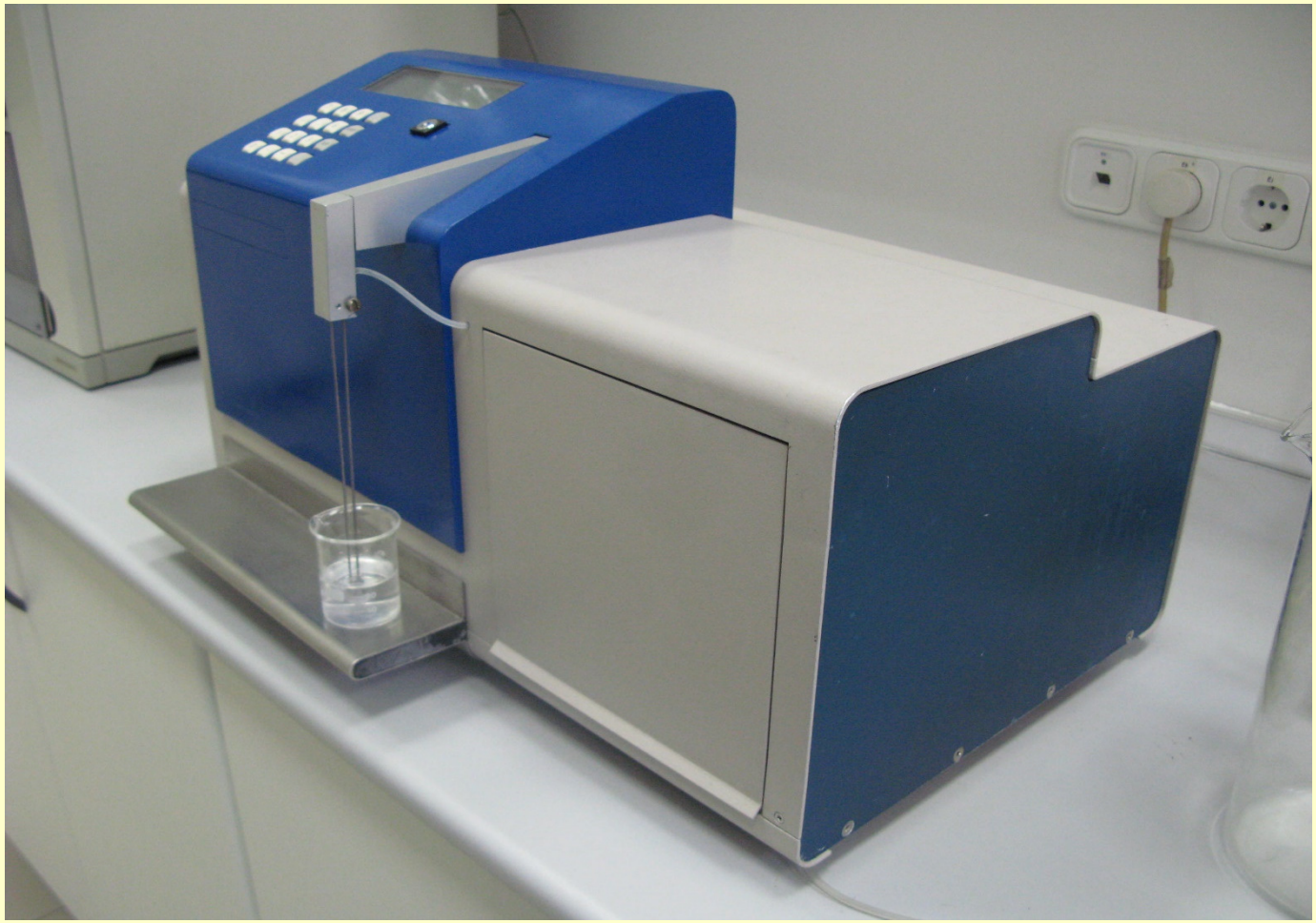


K. Pápai, M. Budai, K. Ludányi, I. Antal, I. Klebovich: In vitro food–drug interaction study: Which milk component has a decreasing effect on the bioavailability of ciprofloxacin?
J. Pharm. Biomed. Anal., 52, 37-42 (2010).

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



MILKO-SCAN 130 MILK ANALYSER



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
$\frac{\textbf{skimmed}}{\textbf{fat}}$ = **ratio**	**0.05 X**	**1.5 X**	**1.8 X**

DIFFERENT TYPES OF MILKS AVAILABLE IN MARKET

Packed milk (fat %)	Fat (g/100g)	Proteins (g/100g)	Carbohydrates (g/100g)
0.3 %	0.4 ± 0.00	4.14 ± 0.01	4.95 ± 0.01
1.5 %	1.49 ± 0.01	3.26 ± 0.01	4.86 ± 0.01
2.8 %	2.82 ± 0.01	3.11 ± 0.01	4.79 ± 0.01
3.6 %	3.63 ± 0.01	2.95 ± 0.01	4.74 ± 0.01

MODERN BIOANALYTICS IN DRUG INTERACTIONS

MODERN BIOANALYTICAL METHODS FOR DETERMINATION OF DRUG-ALCOHOL-FOOD INTERACTIONS

I. Determination of drug level

GC

HPLC

CE

II. Determination of serum (dissolution media) alcohol level

Dynamic - Headspace- **GC**

III. Milk analysis

Milko-Scan 130 (method based on infrared spectroscopy)

IV. Analysis of food products

GC, HPLC and **coupled** technics (**LC-MS, GC-MS, OPLC-MS**)

BIOANALYTICAL TECHNIQUES AND DETECTION MODES

2015

Separation methods:

- **GC** FID, NPD, ECD, RD, MS, MS/MS (+/- EI, +/-CI), Triple Quad, Q-TOF, Ion Trap-MS, ICP-MS

BIOANALYTICAL TECHNIQUES AND DETECTION MODES

2015

Separation methods:

- **GC** FID, NPD, ECD, RD, MS, MS/MS (+/- EI, +/-CI), Triple Quad, Q-TOF, Ion Trap-MS, ICP-MS
- **HPLC** UV, DAD, FLD, EC, RD, MS, MS/MS, Jet Streem-ESI, APCI, APPI, Triple Quad, Q-TOF, Ion Trap-MS

BIOANALYTICAL TECHNIQUES AND DETECTION MODES

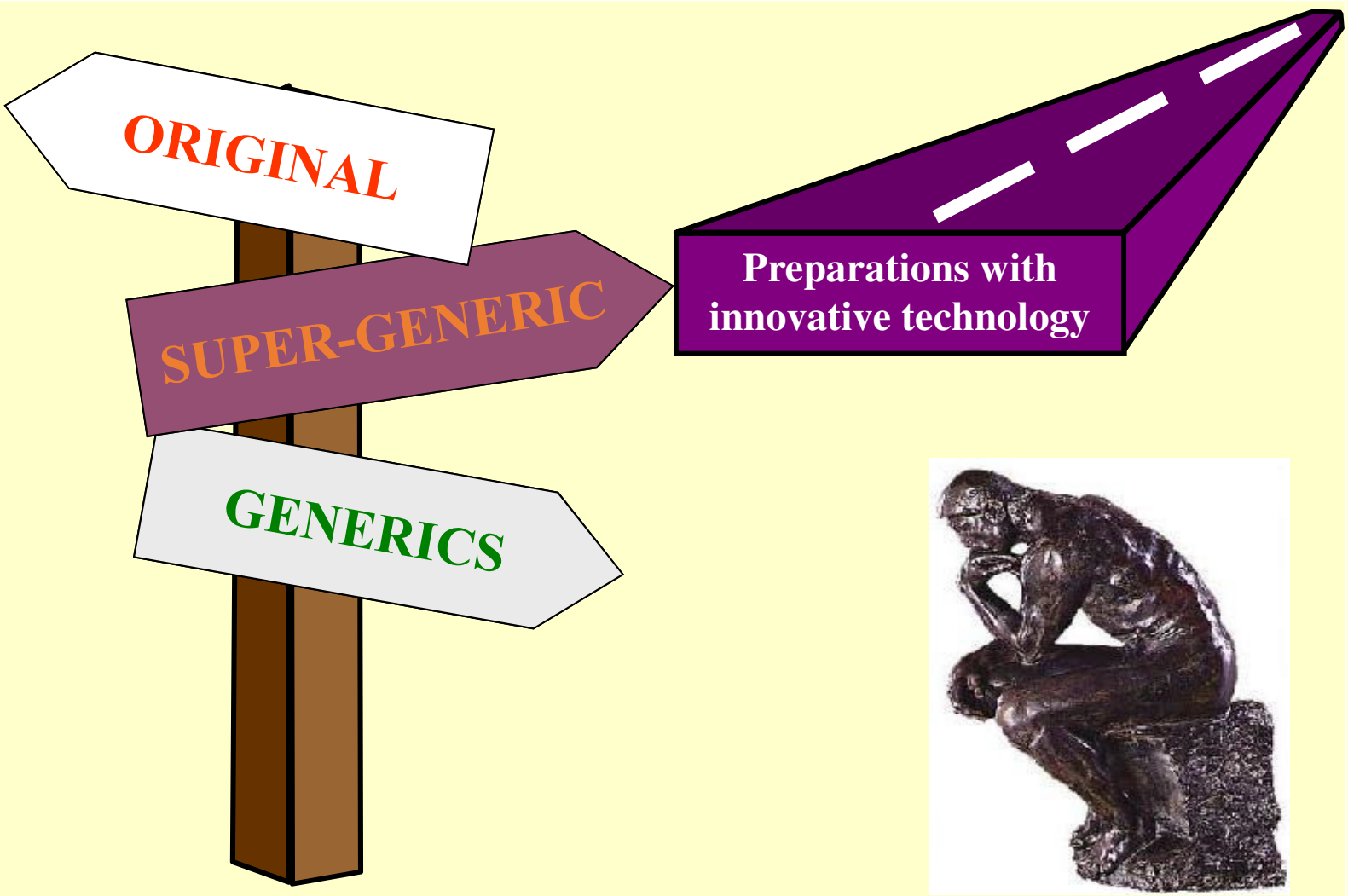
2015

Separation methods:

- **GC** FID, NPD, ECD, RD, MS, MS/MS (+/- EI, +/-CI), Triple Quad, Q-TOF, Ion Trap-MS, ICP-MS
- **HPLC** UV, DAD, FLD, EC, RD, MS, MS/MS, Jet Streem-ESI, APCI, APPI, Triple Quad, Q-TOF, Ion Trap-MS
- **CE** UV, DAD, FLD, MS/MS, Jet-Streem-ESI, Triple Quad

SUMMARY….

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



QUIDELINES ON THE INVESTIGATION OF DRUG INTERACTIONS

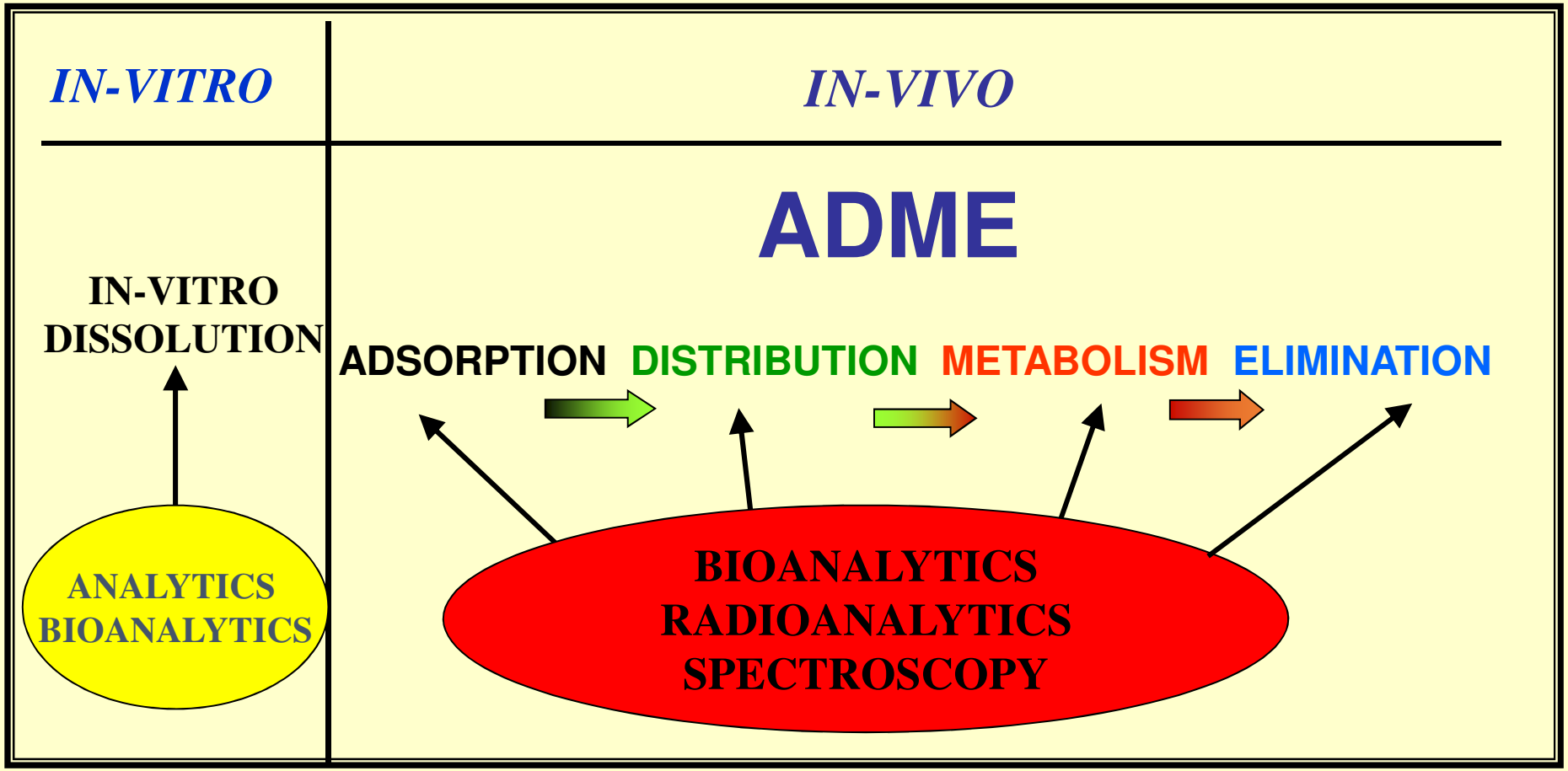
2012 FDA

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

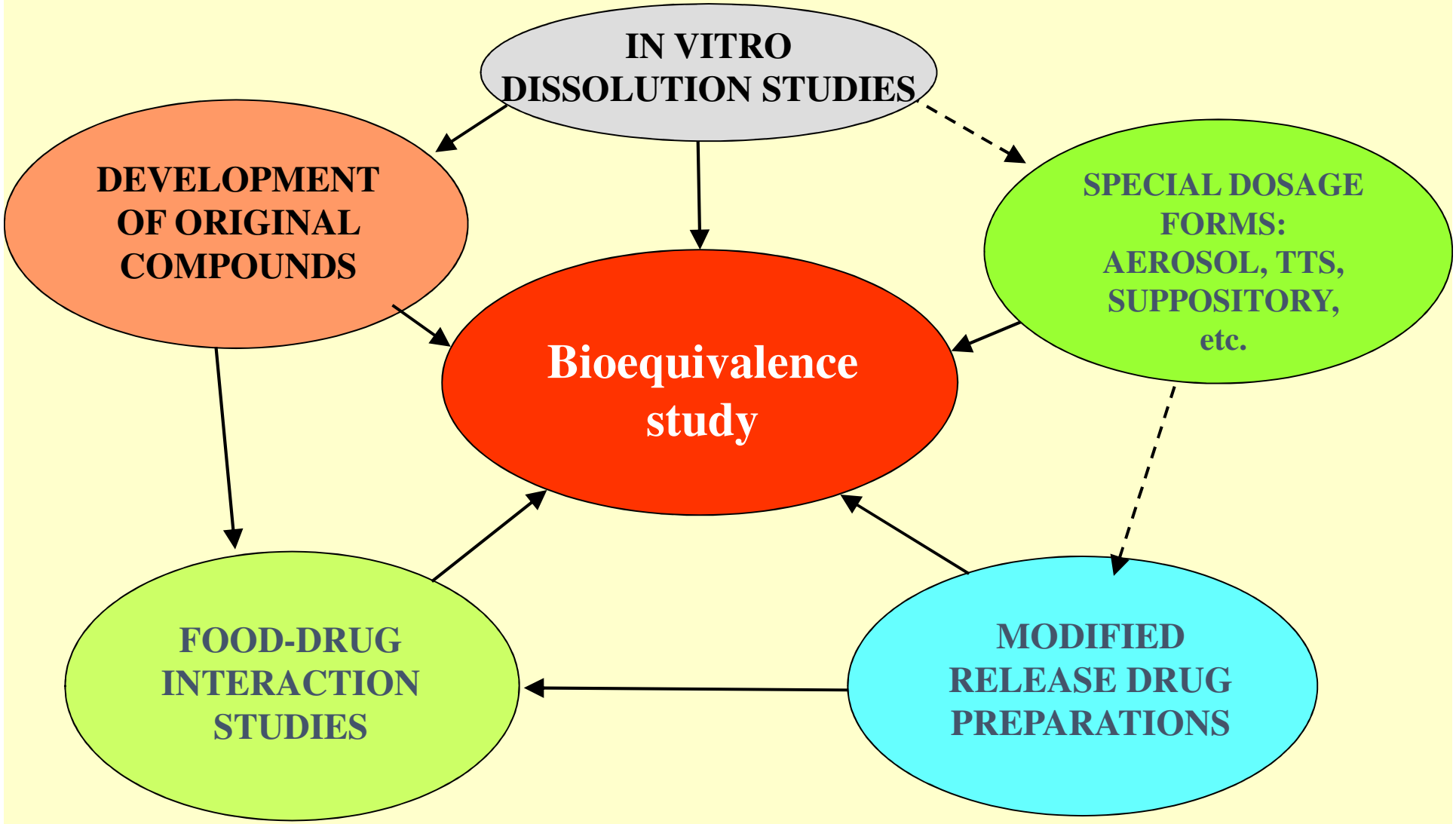
2013 EMA

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

SUMMARY OF ANALYTICAL/BIOANALYTICAL METHODS IN *IN-VITRO* DISSOLUTION AND *IN-VIVO ADME* EXAMINATIONS



RELATIONS BETWEEN DRUG FORMULATION AND THE FOOD-DRUG INTERACTION STUDIES OF BIOEQUIVALENCE



MOST LIKELY FOOD EFFECTS ON BIOAVAILABILITY FOR BCS CLASS I-IV DRUGS

BCS class	Absorption effect by food	Possible mechanism
I. High S/High P	Reduced rate but same extent	Slower gastric emptying
II. Low S/High P	Increased extent	Increased solubility and first-pass metabolism
III. High S/Low P	Reduced extent	Reduced intestinal drug concentration
IV. Low S/Low P	Increased extent	Increased solubility and first-pass metabolism

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
- **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**

„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