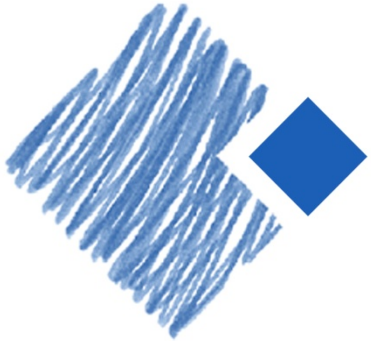

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We make it work

Food effect studies with MR products – when and how?

Dr. Barbara Schug
SocraTec R&D, Oberursel , Germany
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AGAH Workshop, The new European modified Release Guideline-from cook book to interpretation, Bonn, June 15th – 16th, 2015

dies with MR products?

Robust but faster in test

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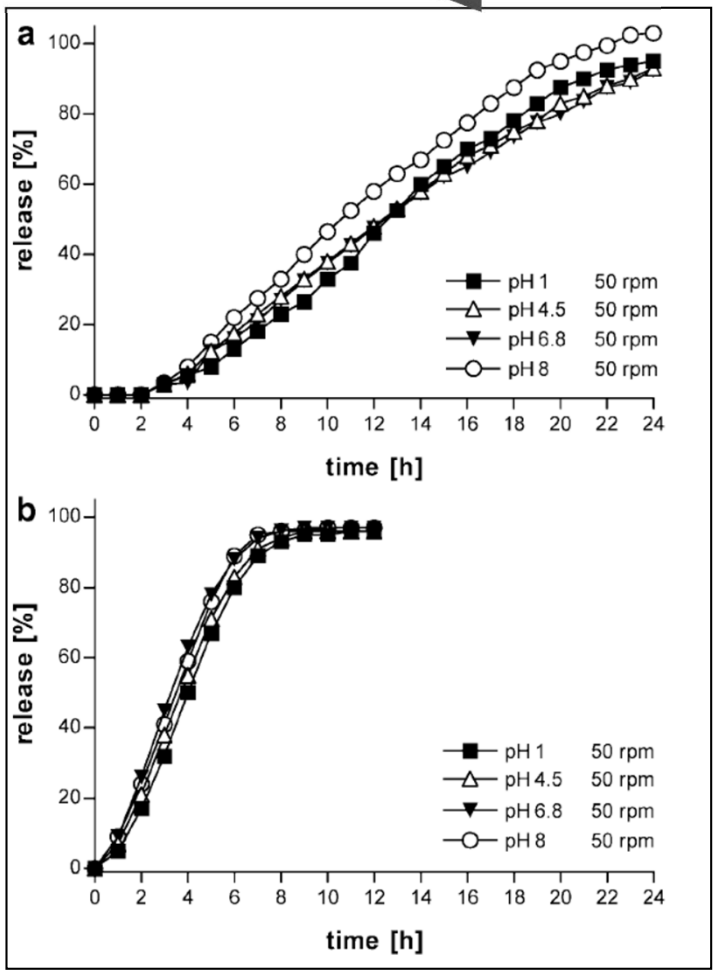
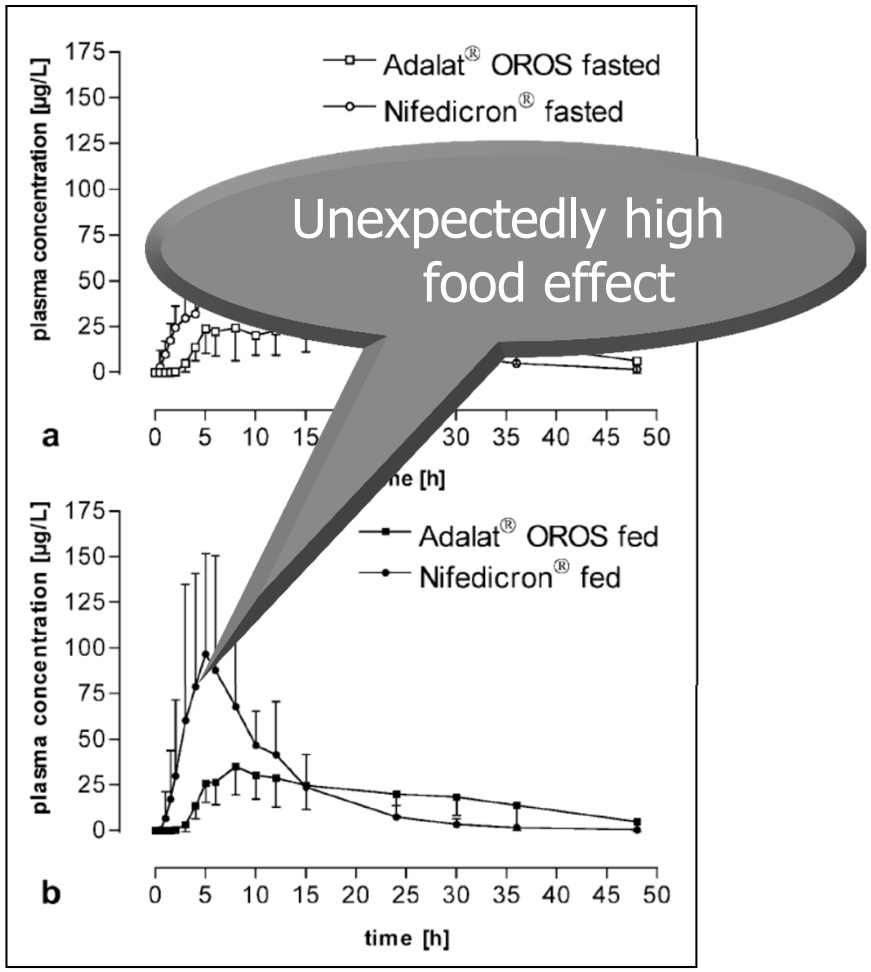


in vitro dissolution



Unexpectedly high food effect

plasma concentration

Source: B.S. Schug et al.: Eur J Clin Pharmacol, 2002

Why food studies with MR products?

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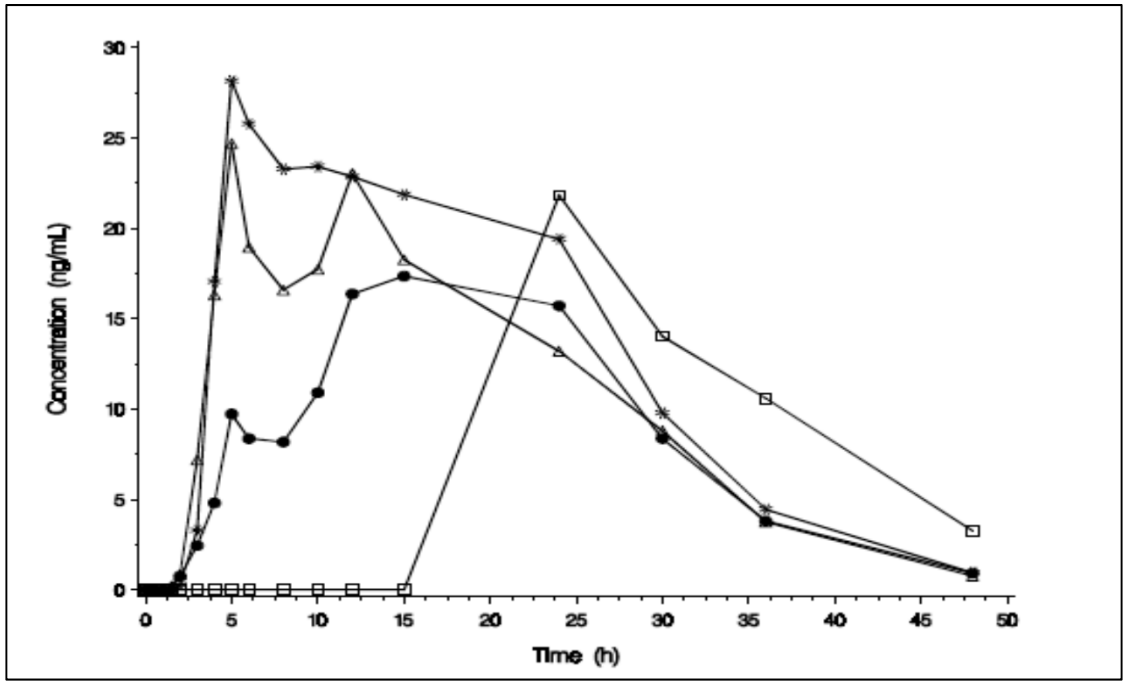
Again ... nifedipine modified – release products



Astonishing lag-time but no dose-dumping!

Source: B.S. Schug et al.: Eur J Clin Pharmacol, 2002

What is the reason?

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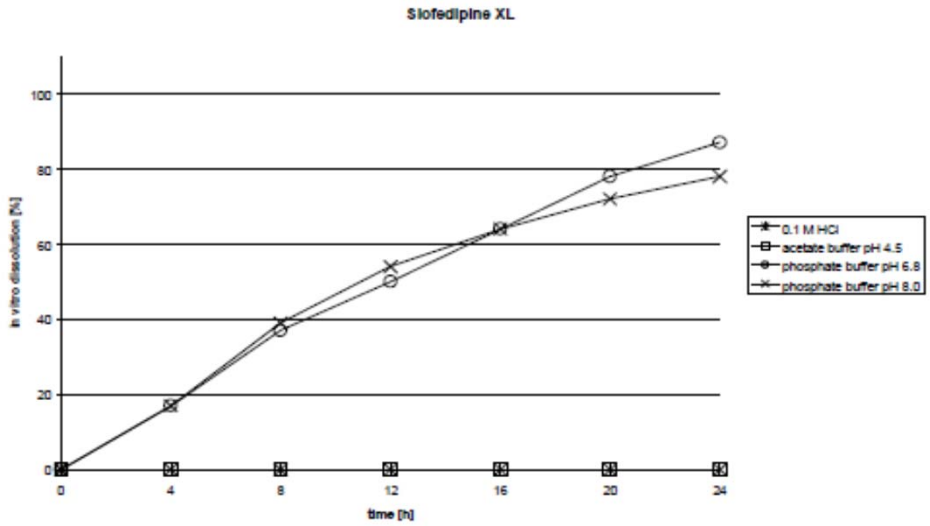
In vitro dissolution results reveal the secret



Slofedipine XL exhibits enteric-coated formulation properties!

Source: B.S. Schug et al.: Eur J Clin Pharmacol, 2002

Guideline criteria

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Guideline differentiates between product's status

- modified release dosage forms of new chemical entities
- modified release formulation of a drug that is already authorised in a formulation with different release rate
- modified release formulation that is intended for abridged application

Differentiation depending on administration condition in the label claim

- to be administered in fasted state
- to be administered independent from food intake
- to be administered with a certain timing in relation to food intake
- other conditions related to food intake (e.g. " light meal")

But ... food interaction studies always needed !

Guideline criteria

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Differentiation with regard to formulation type?

- delayed release formulation
- formulation intended for prolonged residence time
- enteric coated formulations
- prolonged residence time in the stomach

Food interaction studies always needed

Differentiation regarding different product strengths

- composition of the different strengths
- linearity of the pharmacokinetics

Waiver or bracketing possible!

MR: New chemical entity

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Food study – when to be done?

- very early during drug development
- aim ⇨ early recommendation for efficacy and safety studies
- aim ⇨ avoidance of dose dumping!

Food study – how to be done?

- administration conditions should be the same as for JR formulations
- in principal a 2-way-crossover study may suffice (MR-formulation fed vs. fasting)

How to design the food study ?

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EU guideline CPMP/QWP/EWP/1401/98 (since 2010)

- fasting conditions: 10 h fasted state prior to administration followed by further 4 h without food intake
- fed conditions: commonly overnight fasting prior to breakfast with the breakfast being ingested within 30 min followed by administration (commonly within 5 min)
- if no specific food recommendation is planned for the SmPC: high-fat (“American”) breakfast

High fat meal: IR / MR guideline

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EU guideline CPMP/QWP/EWP/1401/98 (since 2010)

"This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively."

"An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity."

A little mathematics…

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Slightly inconsistent requirements in both guidelines (IR and MR)

- 800 – 1000 kcal
- approximately 50 % derived from fat
- 150 kcal from protein, 250 kcal from carbohydrates and 500 – 600 kcal from fat
- 400 – 500 kcal derived from fat

Discrepancy not important but somewhat astonishing for a guideline document

MR – new chemical entity

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Food study – consequences!

- no clinically relevant food effect detected – no further activities needed
- clinically relevant food effect detected – differentiation between drug formulation and drug substance requested!

Consequence – 4-period crossover study

- (MR fed) vs. (MR fasted) vs. (solution fed) vs. (solution fasted)
- solution not feasible? IR tablet requested
- no recommendation for evaluation given (2x2 way ANOVA or 4 way ANOVA)

How to define clinical relevance at this early stage of development?

MR – new chemical entity

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Consequence – additional food studies

- investigations of the effect of different kind of food with regard to caloric/ nutritional content
- investigations of the effect of a meal taken at certain time period before and after the drug

Reference on "Guideline on the investigation of Drug Interactions (CPMP/EWP/560/95/Rev.1)

- non-linear PK with less than dose-proportional increase ⇨ highest and lowest strength
- non-linear PK with larger than dose proportional increase ⇨ highest dose

"Regardless of dose-linearity, further strength(s) may need to be investigated in case the strengths deviate markedly in composition, the substance has poor solubility under GI conditions and a food effect has been observed on the strengths."

Source: CPMP/EWP/560/95/Rev .1

MR – new chemical entity

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Further studies may become necessary depending on the clinical relevance of the food interaction

- time before and after meal to be investigated to come to reasonable recommendations in the labelling

Further studies which may become necessary depending on the labelling

- if to be taken with a meal ⇨ moderate meal containing 400-500 kcal (out of which 150 kcal are from fat)
- if to be taken on an empty stomach ⇨ studies to establish the time interval before and after a meal

Source: CPMP/EWP/560/95/Rev.1

MR – new chemical entity

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Further questions to be answered

- complex binding ⇨ calcium-rich meal might need to be tested
- pediatric population planned ⇨ diet relevant for newborns and infants by PopPK approach
- CYP3A4 ⇨ grapefruit juice
- pellet formulation intended to be administrated via gastric tube ⇨ stability and in-vitro testing may suffice but absence of BE-study should be justified

Biphosphonates – a tricky drug class

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Indications

- postmenopausal osteoporosis
- Paget´s disease (osteitis deformans)
- bone metastasis, multiple myeloma and other diseases involving fragile, breakable bones

Particularities

- inflammation / erosion of oesophagus and stomach as common side effect
- very poor systemic availability even more reduced by concomitant food intake

Mode of administration of relevance for efficacy and tolerability

Risedronate – Actonel®

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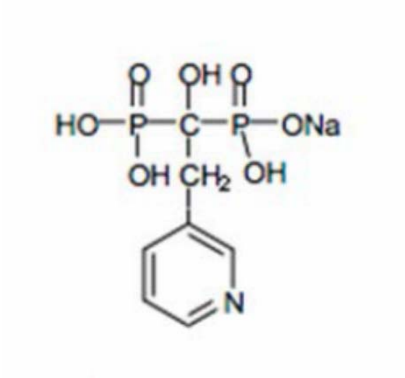
How should I take Actonel®

Take the Actonel tablet first thing in the morning with a full glass (6 to 8 ounces) of water, at least 30 minutes before you eat or drink anything or take any other medicine.



After taking a risedronate tablet, carefully follow these instructions:

- *Do not lie down or recline for at least 30 minutes after taking risedronate.*
- *Do not eat or drink anything other than plain water.*
- *Do not take any other medicines including vitamins, calcium, or antacids for at least 30 minutes after taking risedronate. It may be best to take your other medicines at a different time of the day. Talk with your doctor about the best dosing schedule for your other medicines.*

Residronate – clinical trials

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Phase – II – clinical trials

- recommended dosing scheme was at least 2 hours from any meal
- convenient proposal 2h after dinner

Phase – III – clinical trials

- either 0,5 h before meal
- or 1 h after meal

Source: Mitchell et al; Br. J Clin Pharmacol 48 (536-542), 1999

Results of (late) food interaction study

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Obviously, the SmPC does not reflect the optimum bioavailability conditions but the traditional use from the phase III study !

- ● Group 1: 10h fasted before intake, 4h after followed by lunch
- o Group 2: 1h prior to high fat American Breakfast
- △ Group 3: 0,5h prior to high fat American Breakfast
- ▲ Group 4: 2h after ingestion of a standard dinner

Mitchell et al; Br. J Clin Pharmacol 48 (536-542), 1999

MR – new formulation of "old" drug

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Food study – what needs to be done?

- no clinically relevant food interaction of the IR-form ⇨ 2-way crossover study (MR fed) vs. MR (fasted)
- clinically relevant food interaction of the IR form ⇨ 4-way crossover study (MR fed) vs. (MR fasted) vs. (IR fed) vs. IR (fasted)

Both study approaches intend to quantify the extent of a potential formulation-related interaction

MR – new formulation

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When is a waiver for all lower strengths acceptable?

- proportional composition
- same manufacturing process
- linear pharmacokinetics (even if less than proportional increase?)
- similar dissolution profiles in a range of media (whatever this means)

If these requirements are not met …

- … bracketing approach!

Pharmacokinetic evaluation

- AUC and c_{max}
- parameter to verify the shape of concentration (early and terminal partial AUC)

MR – new formulation

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Consequence – additional food studies

- investigations of the effected different kind of food with regard to caloric/ nutritional content
- investigations of the effect of a meal taken at certain time period before and after the drug

Reference on "Guideline on the investigation of Drug Interactions (CPMP/EWP/560/95/Rev.1)

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"Regardless of dose-linearity, further strength(s) may need to be investigated in case the strengths deviate markedly in composition, the substance has poor solubility under GI conditions and a food effect has been observed on the strengths."

Analogous to new chemical entity

MR – new formulation

SocraTec R&D

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Analogous to new chemical entity

MR – new formulations

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Food effect – consequences of consequences

- If as a consequence of a clinically relevant food interaction or for other reasons a recommendation is given in the labelling regarding fed intake, the multiple dose study needs to be performed under the SmPC labelled conditions
- The same applies to recommendation regarding timing of food intake

To be observed on all study days!

MR – abridged application

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Fed study – which design?

- single dose BE study under fed conditions using a high-fat meal
- 4-way crossover study possible
- 2 crossover studies with (Test fasted) vs. (Ref. fasted) and (Test fed) vs. (Ref. fed) vs. (Test fasted)

Generation of intra-individual food effect data

Dose dumping

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Unexpected release resulting in unforeseen exposure

- observed, i.e. high peak exposure with inadequate modified release profile
- suspected, i.e. absence of levels of a labile active substance in gastro resistant formulation

Consequence: reformulation

But …

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"Much higher peak exposure might also be observed in prolonged release products due to active substance release in the stomach for an extended period of time (i.e. at delayed gastric emptying) with a subsequent absorption of the released dose once the gastric content is emptied. As this unintended increased exposure is not related to a particular product failure causing uncontrolled release, dosing recommendations with regard to e.g. concomitant food intake should be implemented to avoid a prolonged residence in the stomach."

Learnings from real life!

Gastric emptying in healthy subjects

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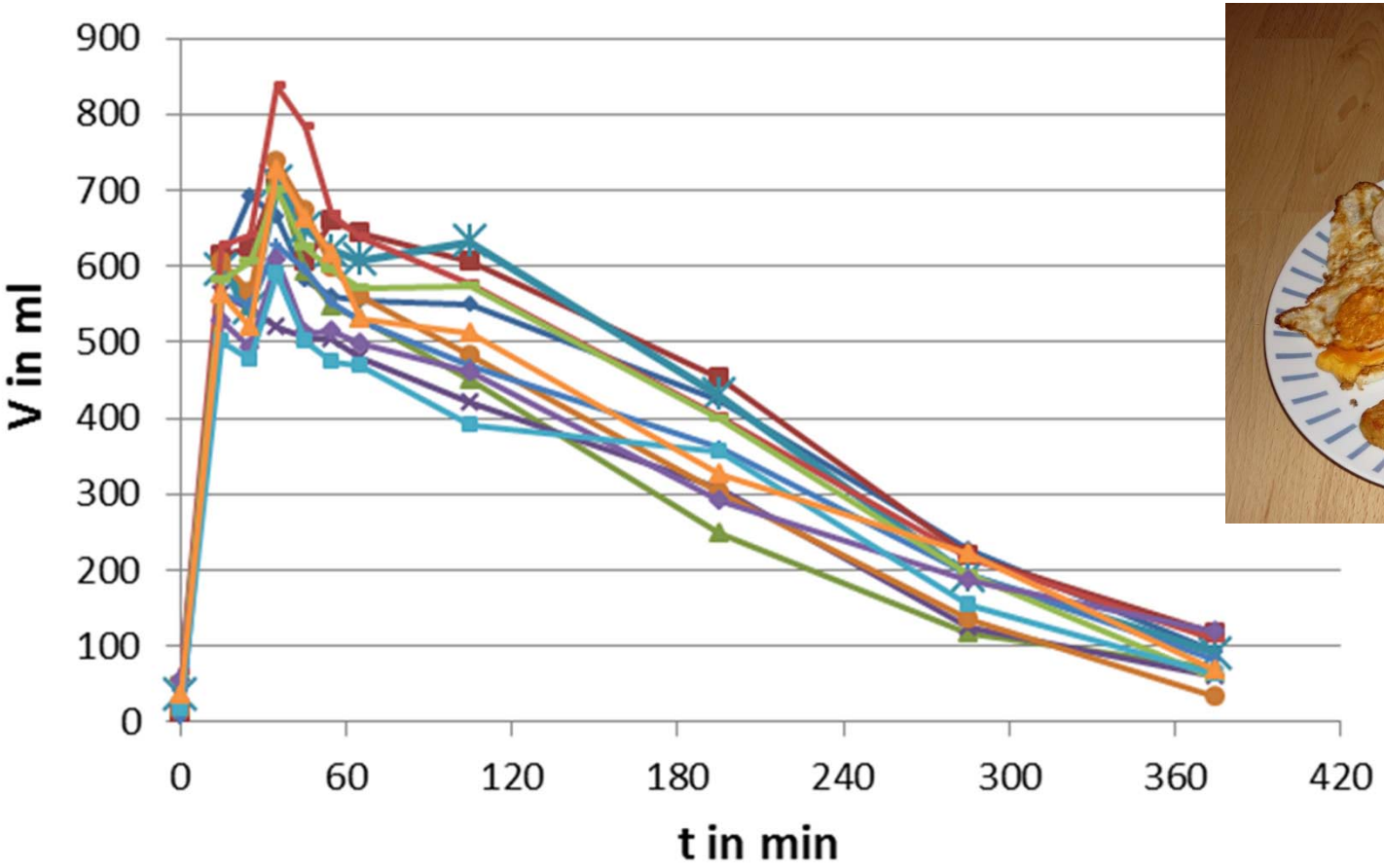

In the patient population it may even be longer !

With permission from W. Weitschies derived from Koziolek et al, Mol Pharm 2014

Effect of alcohol

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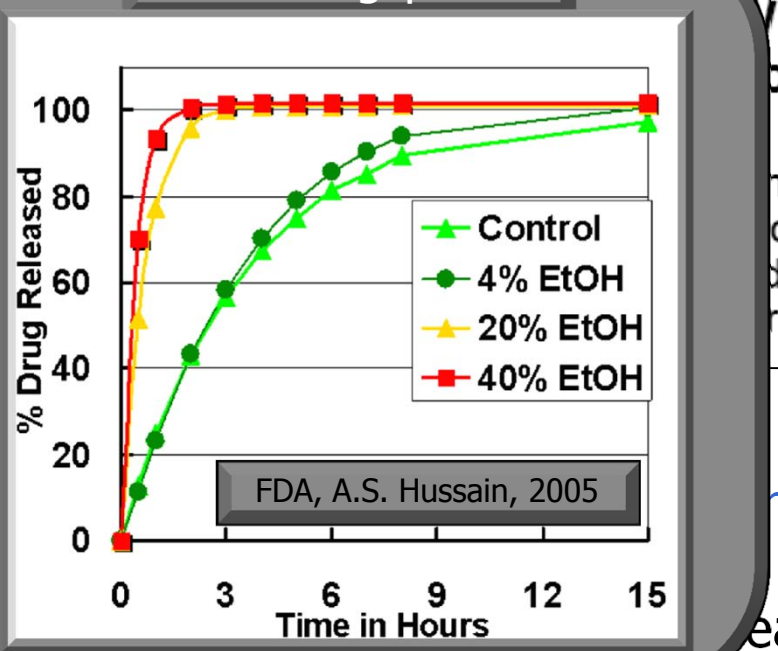
Freisetzungsprofile



Withdraw Palladone for Safety
ons (July 13, 2005)

nd potentially fatal adverse reactions can
chloride) extended release capsules are
d Drug Administration has asked Purdue
raw it from the market.

Out … $_{max}$ significantly increased

- fa…
  - …ease (one subject: 16fold!)
  - 4 % Ethanol: in few su… 2fold increase
- background: alcohol fastens release

Effect product-dependent …

Many thanks to ...

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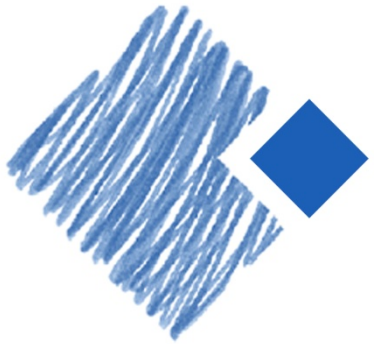
Prof. Dr. Henning Blume for allocating some important slides,

Marina Breit for excellent technical assistance

... and to all who contributed to the trials presented !



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We make it work

Concepts in Drug Research and Development

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