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Scientific rationale for development of advanced preparations with known active drug ingredients

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Example: simvastatin

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Drug substance properties

- poor solubility (~5mg/250mL), high permeability ...
- ... thus, BCS Class-II drug ⇨ formulation determined BA
- pharmacokinetic properties
  - pro-drug (first pass effect: 95%); CYP3A4 major metabolic enzyme
  - $t_{1/2}$ 2 h; excretion (parent and metabolites) primarily via bile

Consequences for straight-forward drug development

- intended pharmaceutical form: conventional IR tablet ...
  - excipients needed to increase solubility (e.g. Tween 80) ...
  - ... nonetheless, incomplete dissolution in media without surfactants
- ... proof-of-concept study confirmed PD/clinical efficacy
- entire clinical programme realised with conventional tablet
  - clinical efficacy & safety assessed in Phase-III studies in patients

Problem & intended improvement

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Obvious BA problems

- low BA due to intestinal metabolism (pro-drug)
- however, also hints for incomplete absorption (?)

⇨ initiatives started to improve oral BA (>20 papers since 2002)

Concepts for improving BA and successful projects

- improvement of solubility, e.g.
  - self microemulsifying delivery systems, solid dispersions, ...
- absorption via lymphatic system ⇨ bypassing the liver
  - drug encapsulation, e.g. solid lipid nanoparticles
- absorption from more distal intestine
  - CYP3A4 expression declines from upper to lower intestine

Question: scientifically sound rationale for improvement?

Cerivastatin "case" initiated discussion

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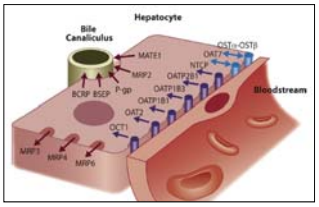
Statins: efficacious, but not without problems

- therapeutic benefit proven in outcome studies
- undesired effects: gastro-intestinal disorders; myopathies

Pharmacodynamic/clinical background

- determinant for efficacy: dose/extent of bioavailability
  ⇨ goal: sufficient exposure at site of action (hepatocytes)
- safety: primarily determined by plasma peak concentrations
  ⇨ goal: reduced maximum exposure (in plasma)

- essential finding: selective uptake into hepatocytes
  - mediated by OATP1B1 transporter ...
  - ... thus, uptake should be saturable



Rationale for product optimisation

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Goal: advanced risk/benefit relationship

- improvement of efficacy not necessary ...
- ... however, reduction of side effects desirable
  ⇨ limitation of peak concentrations in plasma

Clinical concept for drug product development

- pharmacokinetic/biopharmaceutical goals ...
  - sufficiently high "hepatic" bioavailability (site of action)
  - reduced systemic ("peripheral") exposure

... achievable via retarded drug delivery/absorption?

Proof of concept

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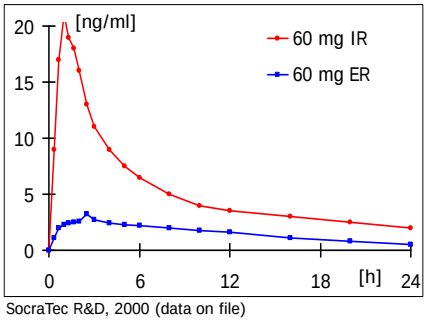
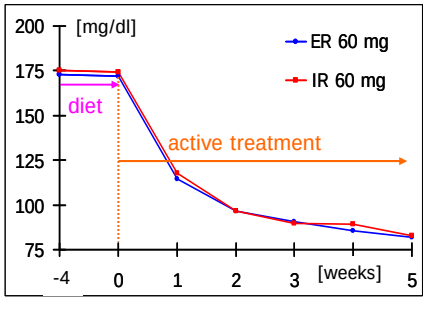
Simvastatin pilot ER preparation *vs.* IR market form

bioavailability [n=36]



SocraTec R&D, 2000 (data on file)

clinical (LDL-cholesterol)



Conclusion: modified release statins

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Clinical/therapeutic benefit(s)

- better safety margin ...
  - trend towards reduced AE, to be confirmed clinically
- ... improved efficacy likely/expected
  - drug targeting (higher hepatic concentrations/exposure)

Perspectives

- dose reduction/clinical improvement should be achievable
- goals for formulation development
  - retardation of intestinal drug absorption ...
  - ... extension/prolongation of profiles not intended ...
  - ... and (most likely) not necessary
  - consistent BA at site of action, not in central circulation

Example: rheumatoid arthritis

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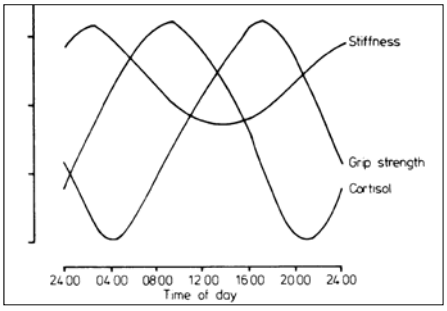
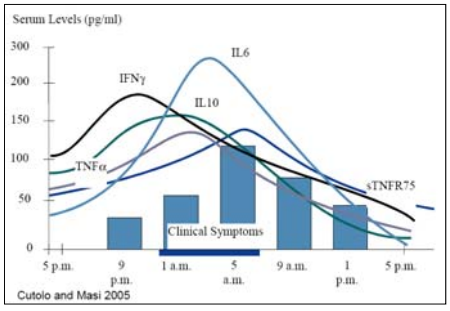
Diurnal pattern of disease symptoms and cytokines





Therapeutic concept

- suppression of cytokines (especially IL6) by glucocorticoids
- improved efficacy and tolerability expected ...
- ... when administered during early morning hours

Proof-of-concept

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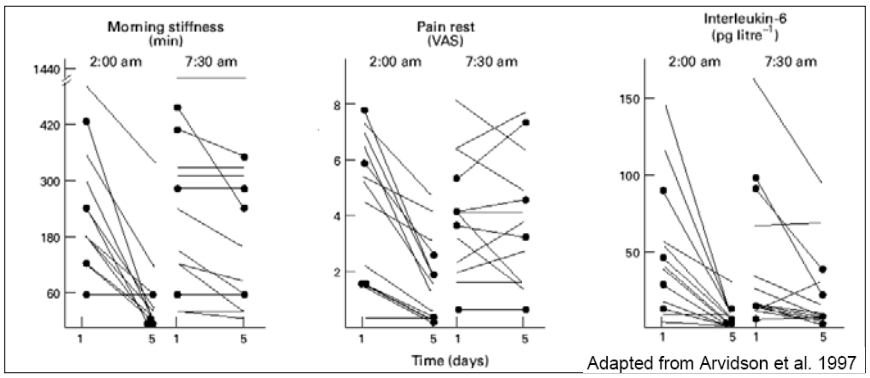
Effects of time of oral cortisone administration



Adapted from Arvidson et al. 1997

Observation

- drug intake at 2:00 a.m. superior to 7:30 a.m. for all effects

Treatment of rheumatoid arthritis

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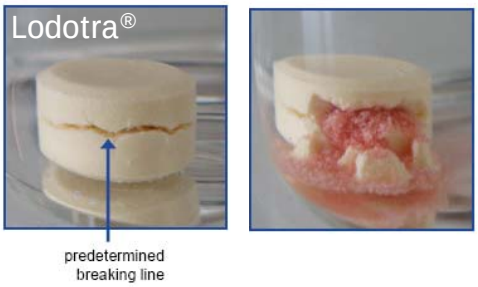
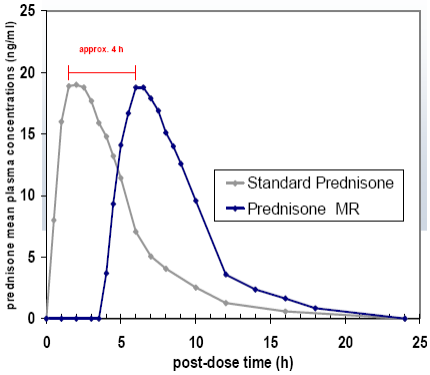
Lodotra®: "in-time" prednisone





- goal: sufficient concentrations in early morning hours
- concept: release 4 hours after evening, fed administration

Lodotra®: development process

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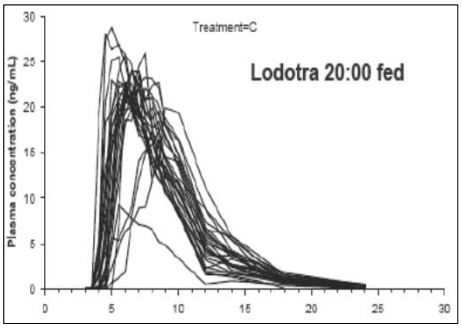
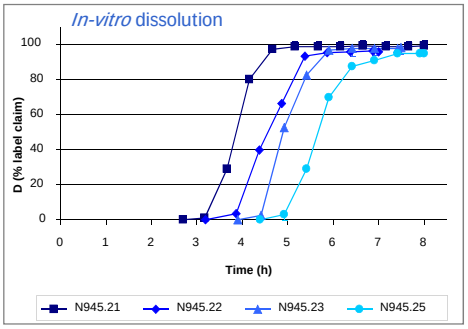
In-vivo proof of concept



Batch selection/verification



- authorities: *in-vivo* verification of specifications requested
- suggested design: single-dose comparison in fasted state

... however, suggested design scientifically appropriate?

Prednisone BA: fasted *vs.* fed state

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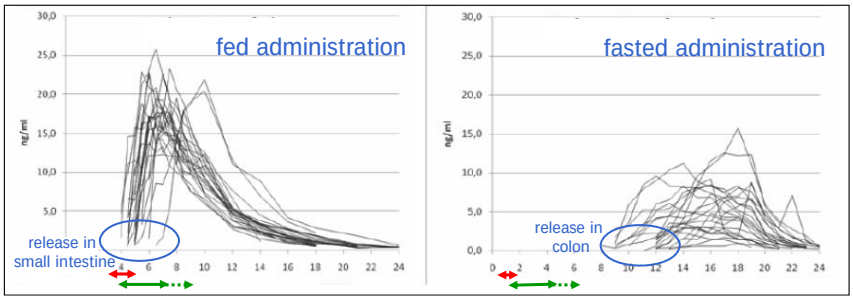
Individual plasma profiles



Interpretation of *in-vivo* results

- fasted: earlier gastric emptying, intestinal transit ...
- ... (very) limited absorption in colon ⇨ reduced BA

Lodotra®: clinical confirmation

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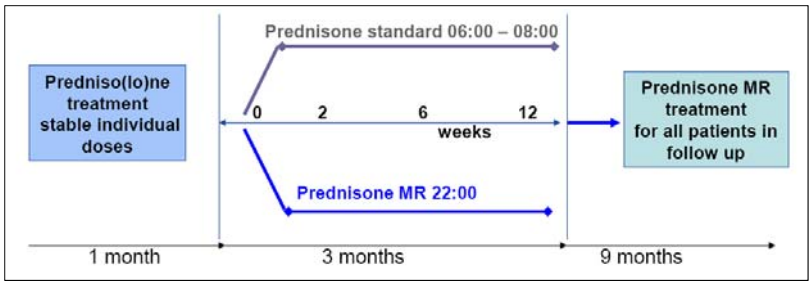
Assessment of therapeutic efficacy

- CAPRA*)-1 and -2 studies (12w; mc; db; pc; N=300)
- study objectives/goals
  - E.U.: significant reduction of IL-6 and morning stiffness
  - USA: 20 % improvement of symptoms ...
  - ... also in comparison to IR prednisone tablets

*) Circadian Administration of Prednisone in Rheumatoid Arthritis



Clinical comparison with standard

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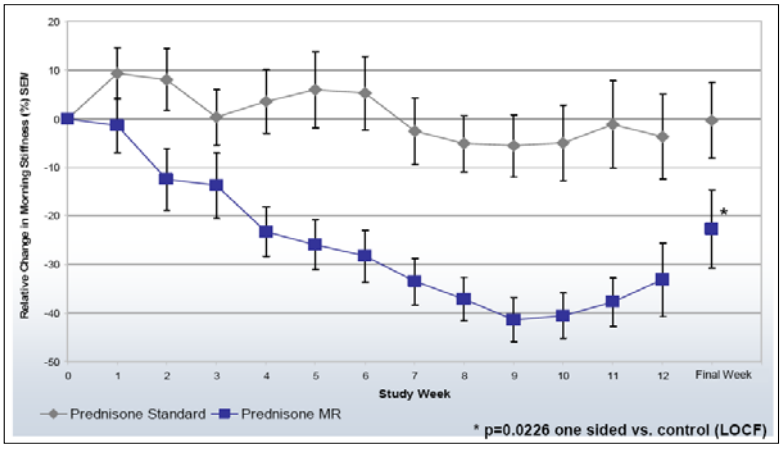
Effect on morning stiffness



Rational development of NTE

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Clinical/pharmacological/mechanistic approach

- from therapeutic need ... towards clinical rationale

Development concepts

- oral preparations with modified release characteristics ...
- ... in order to achieve "target profile"
- gastric retention form (in case of absorption window)
- other routes of administration (transdermal, nasal, ...)

Challenging alternative: "on-demand" drug delivery

- optimum "timing" of administration/absorption ...
- ... "adjusted" to gastrointestinal physiology

Nota bene: superiority does not comply with BE

What did we learn ...?

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Beyond the Guidelines ...???

Bioequivalence concept not applicable for statins!

- pre-systemic site of action (hepatocytes) ...
- ... not "in exchange" with plasma concentrations
- conclusion from plasma profiles on efficacy inappropriate

Fasted administration not (always) "gold standard"

- study design to be defined based on scientific rationale
- fasted state most discriminative, but sometimes unsuitable
- CHMP approach appropriate: follow SmPC conditions