# Role of Analytical Chemistry in Drug Discovery & Development

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AstraZeneca

# Analytical Chemistry within AstraZeneca

## AZ R&D

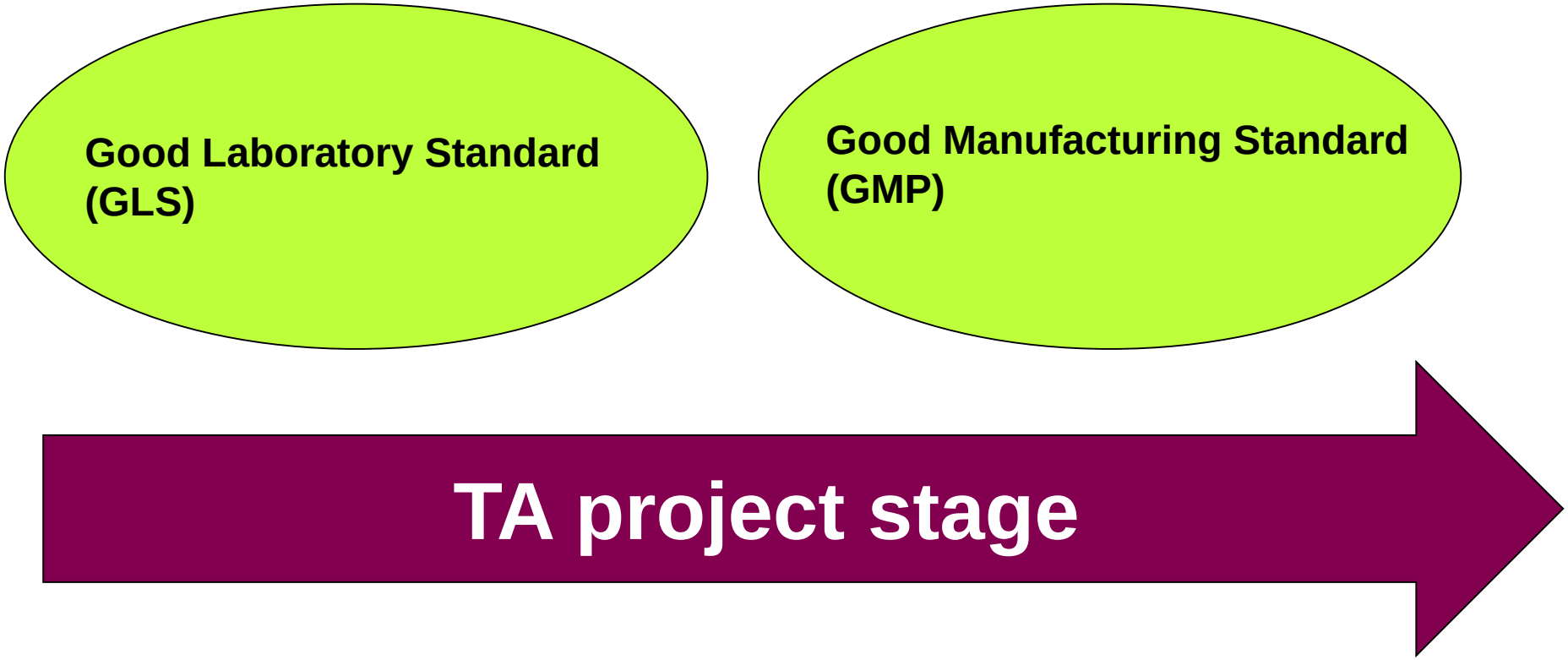
- Discovery
  - Support medicinal chemistry (synthetic route assay and purity)
  - Support preparative chromatography
  - Support toxicological studies
  - Bioanalysis (tissue, animal and human)
  - Stability testing

- Development
  - Analytical support to the development of the final product
  - Release testing of clinical trial material
  - Bioanalysis (support clinical studies)
  - Stability testing
  - Product maintenance

## AstraZeneca Operation

- Release testing of commercial product batches
- Stability testing
  - Annual
  - Changes
- Analytical support when manufacturing issues

# Analytical Chemistry and Quality Standard



# Analytical chemistry – accountability of Chemistry, Manufacturing & Control (CMC) documentation (e.g. NDA and MAA)

## Substance

- S1 (General information)
- S2 (Manufacture)
- S3 (Characterisation)
- S4 (Control of drug substance)
- S5 (Reference standards material
- S6 (Container closure)
- S7 (Stability)

## Product

- P1 (Description and Composition)
- P2 (Pharmaceutical Development)
- P3 (Manufacture)
- P4 (Control of excipients)
- P5 (Control of drug product)
- P6 (Reference standards material
- P7 (Container closure system)
- P8 (Stability)

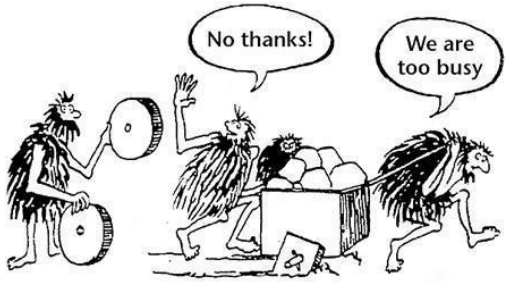
**PT&D function contains 1300 individuals – 500 are analytical chemists**
**Ops Södertälje additional 250 analytical chemists**
**Total amount of analytical chemists in Gothenburg are about 400**

# How to secure Quality Control (QC) and manufacture procedure quality over time

PQS handled as internal changes (GMP)


Variations handled externally

**Continuous Improvement of QC and manufacture procedures after regulatory approval is possible**

# LC Method Development Problem solving and Troubleshooting

**General process:**

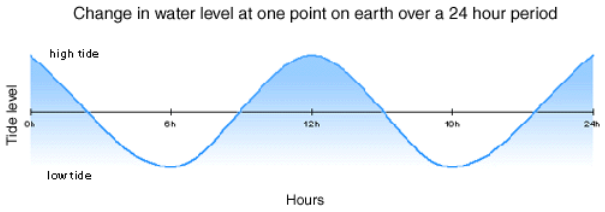
**Clarification phase – Risk assessment – Planning – Execute – Evaluation –**

**Mechanistic understanding – Spread knowledge**

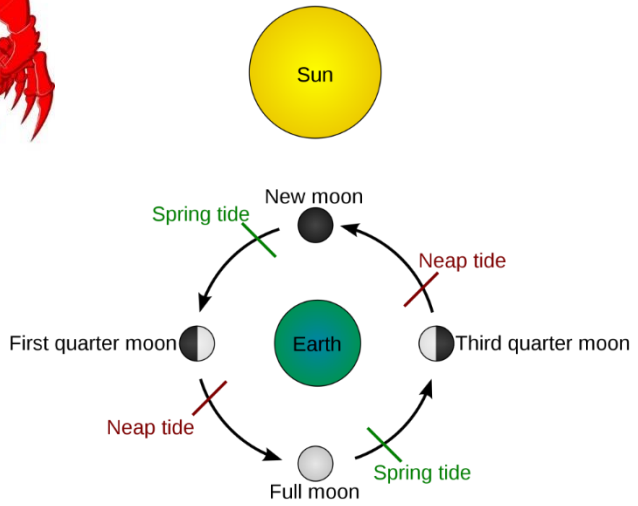
**TRAINING TRAINING TRAINING TRAINING!!!!!!!!**

# Empirical versus Mechanistic Model
## *Example – the Tide*

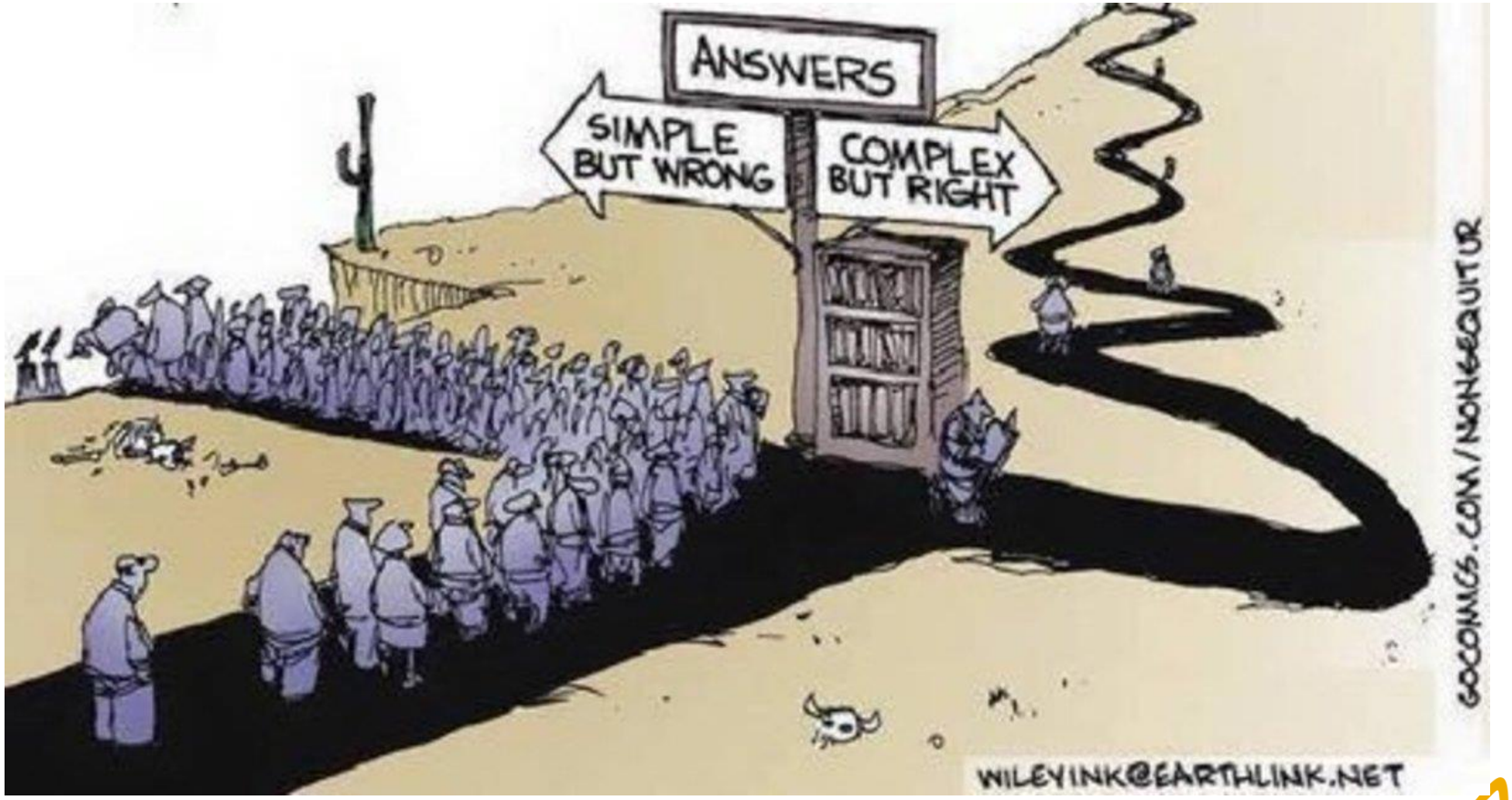
**Empirical model based on observations**




**Mechanistic model based on physical laws**



# Good/bad Science



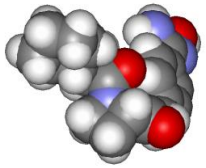
# Analytical chemistry in drug discovery & development – examples

**Low number of samples** **High number of samples**


**Low number of analyses**
**Expensive and specific instruments**
**e.g. NMR**
**GLS**

**High number of analyses**
**Generic instruments**
**e.g. HPLC/UPLC**
**Higher degree of automation**
**GMP**

# Molecular properties of importance

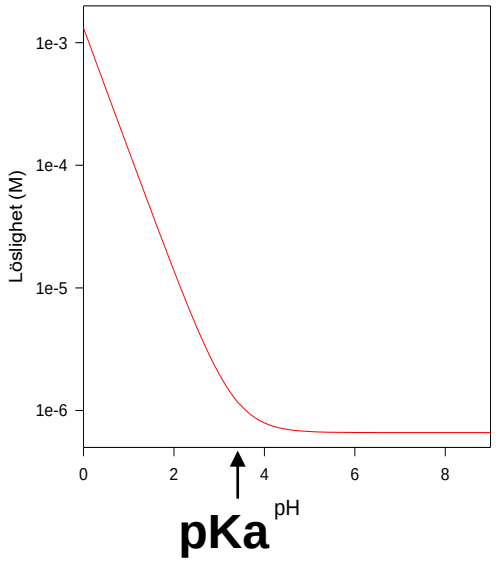


**Molecular Properties**

Hydrophilic or lipophilic ?

Acid, base, or uncharged(vs. pH) ?

Surface active ?

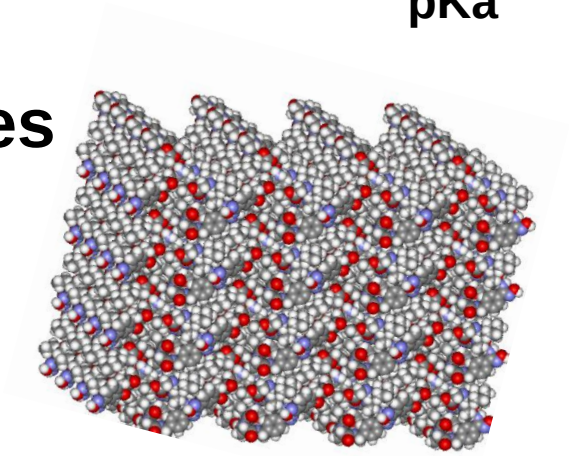



**Solid & liquid state properties**

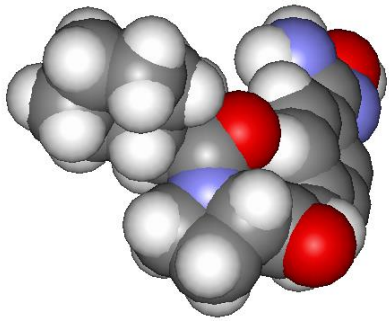
Solubility in water (vs. pH) ?

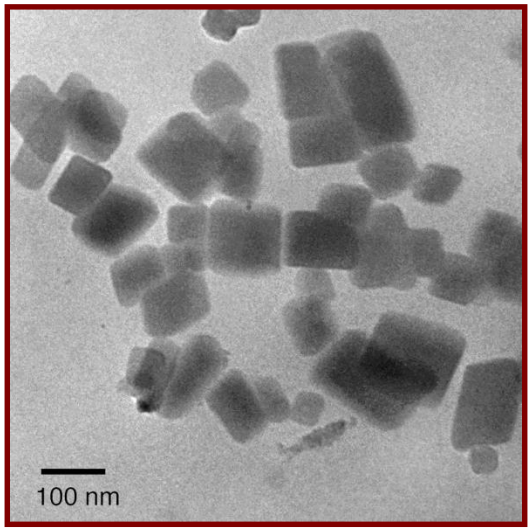
Crystalline or Amorphous ?

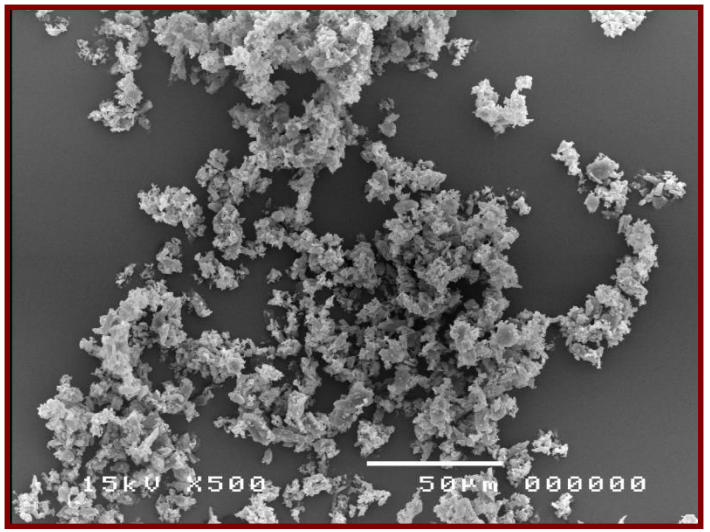
Salt form or parent form?

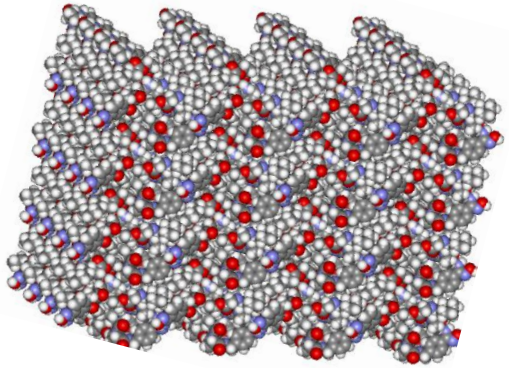


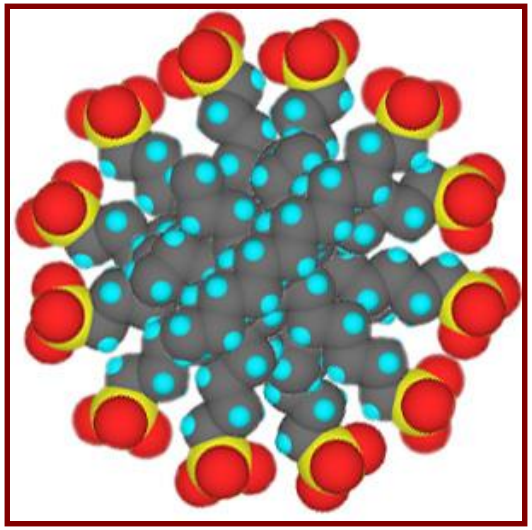
# How does the molecule crystallize or aggregate?

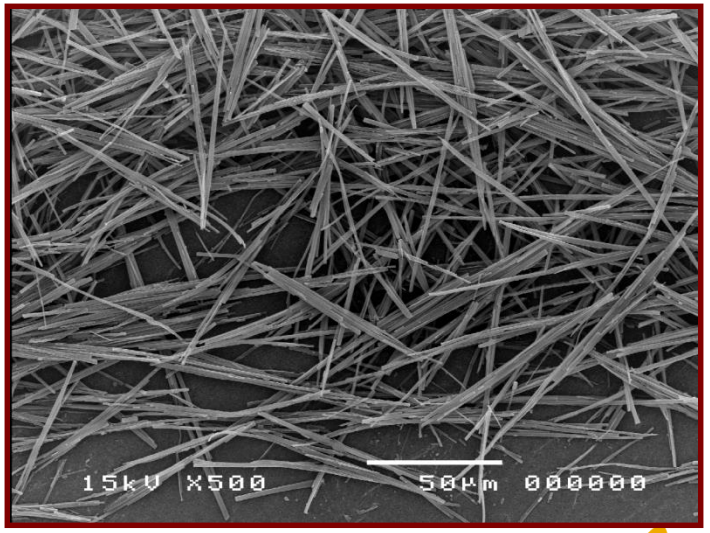




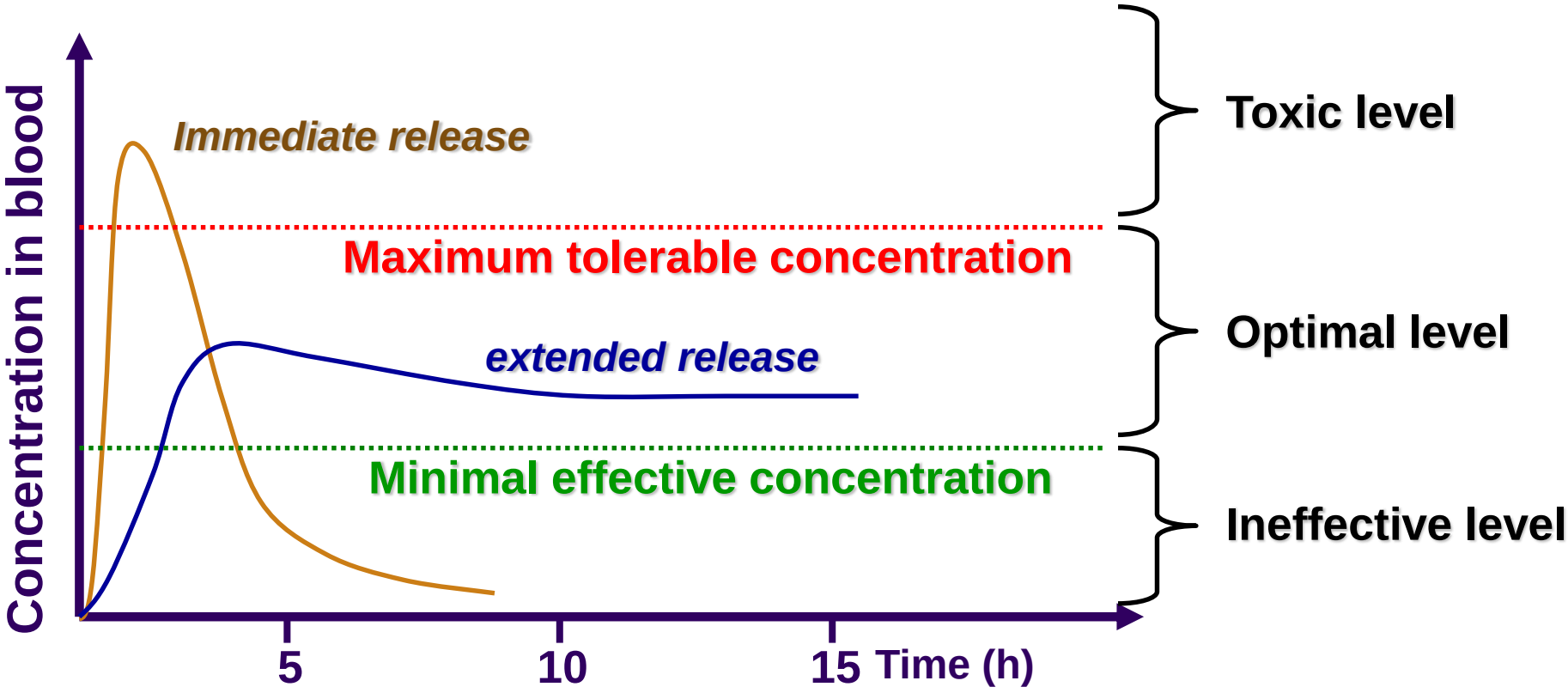








**All affect the bioavailability of the drug substance**

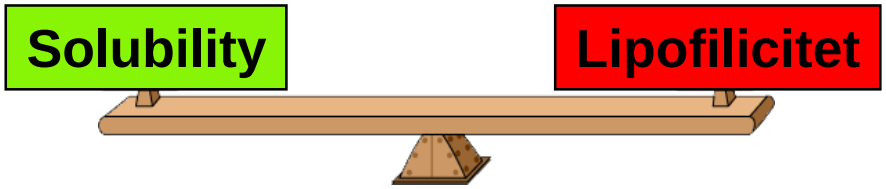
# What action is desired in the body?

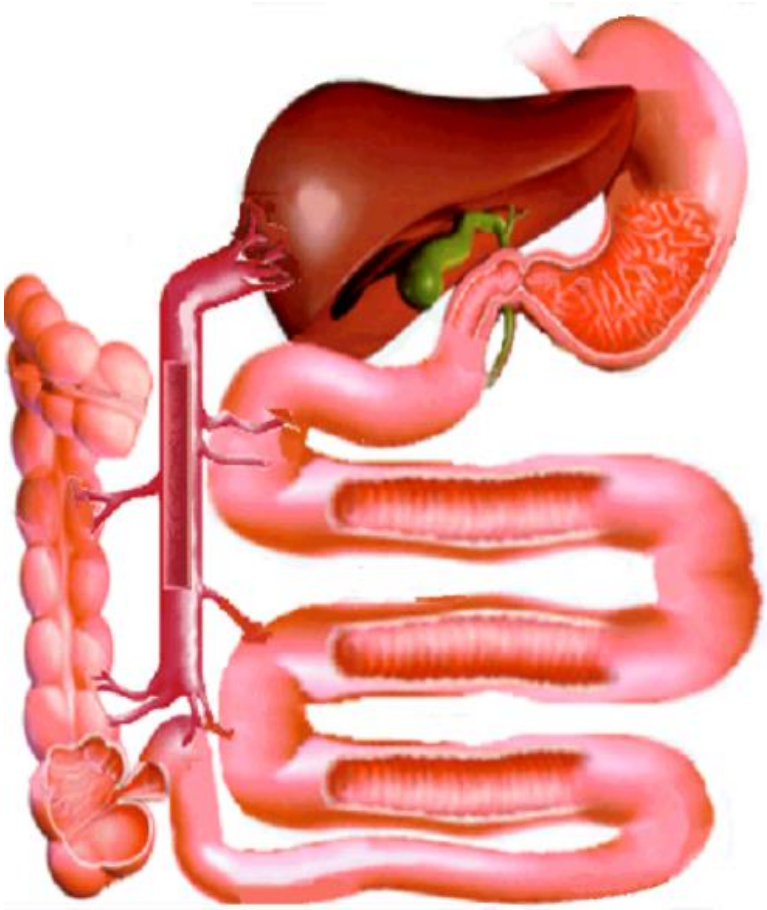



**Ex: Oral tablet**

# Absorption in small and large intestine

## God absorption if:



# Structure Elucidation – Safety Aspects

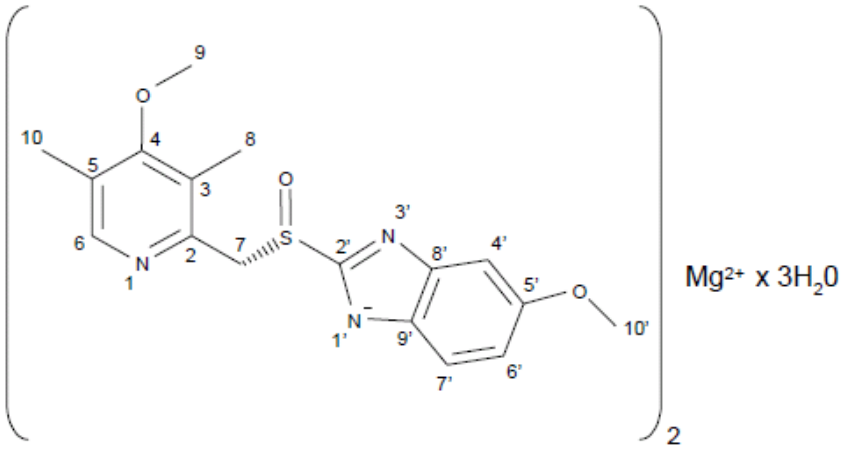
## Toxicological studies to support clinical studies

- Identity
- Assay
- Homogeneity
- Important to know amount of  degradents in tested batches

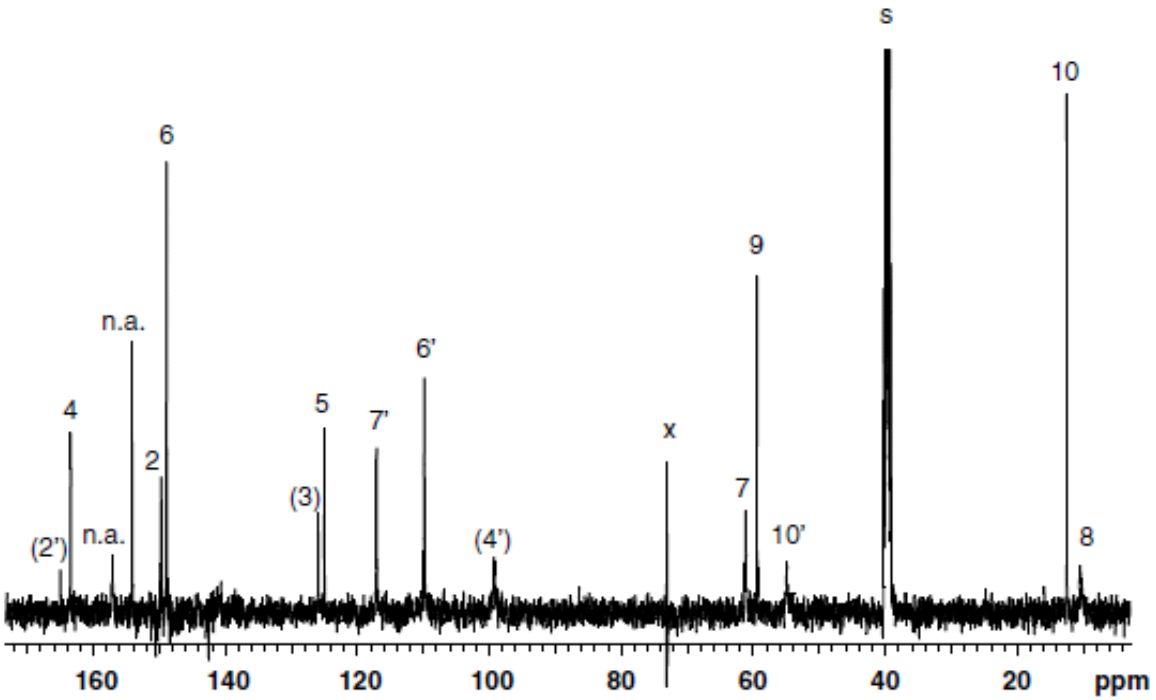
## Development of substance and product manufacturing

- New degradents may be formed
  - Can result in additional toxicological studies
  - Even after launch of product

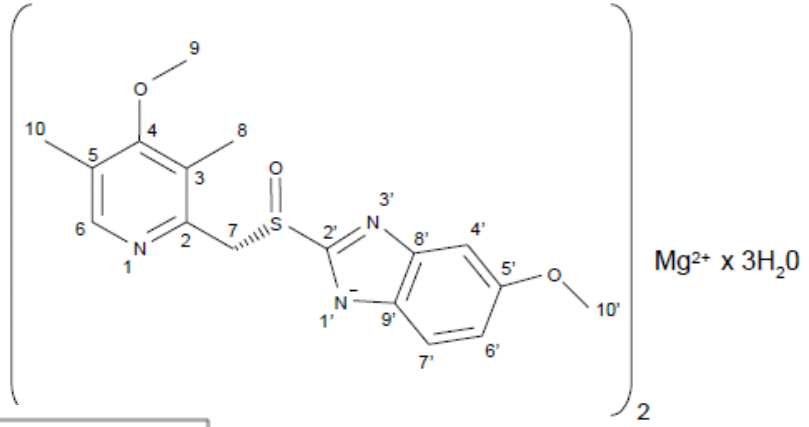
# Nuclear Magnetic Resonance (absorption and re-emit of electromagnetic radiation in a magnetic field)

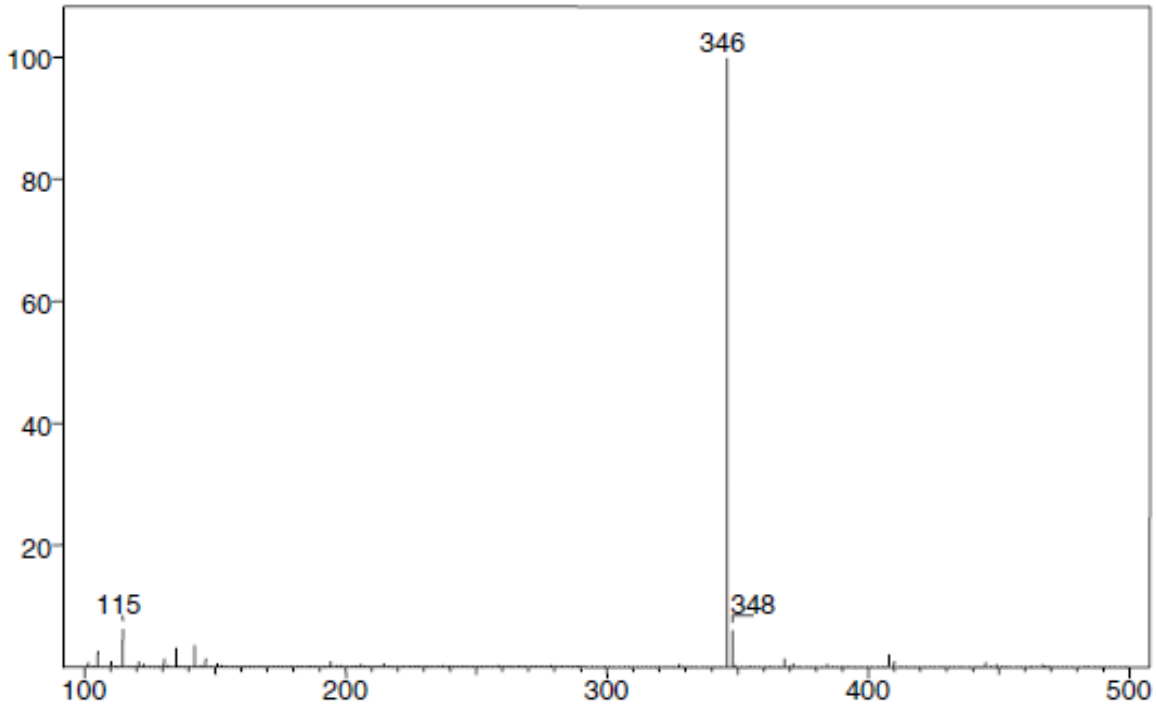


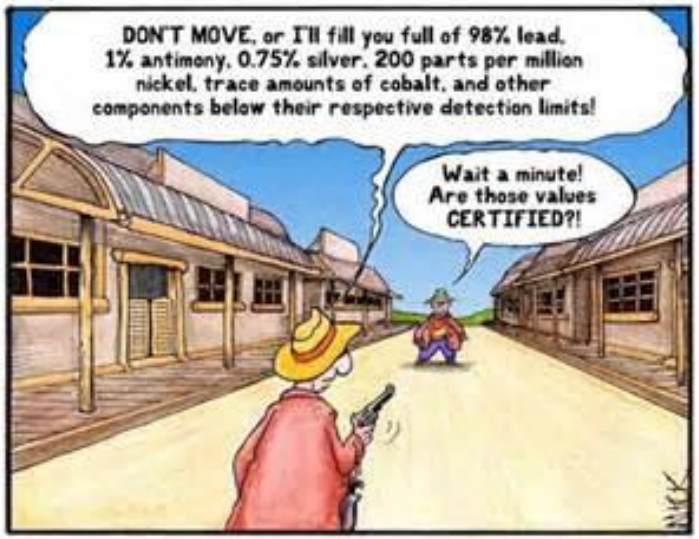

## C13-NMR



# Mass Spectrometry (MS) – measure molecular weight of mother compound or fragment




Analytical Chemists in the Wild West

# Major degradation pathways (predictive science)

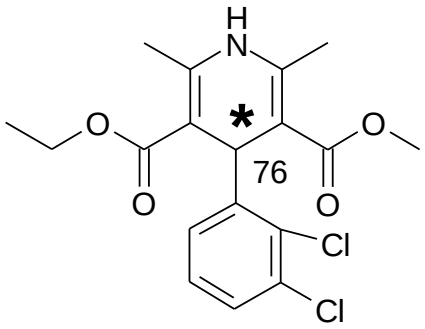
- Oxidation
  - Peroxides
  - Autoxidation
- Hydrolysis
- Thermal
- Photolysis

Major degradation pathways

- Autoxidation
  - Hard to predict theoretically
  - Difficult to verify experimentally
  - Autoxidation is probably the degradation pathway that is easiest pursue by QM

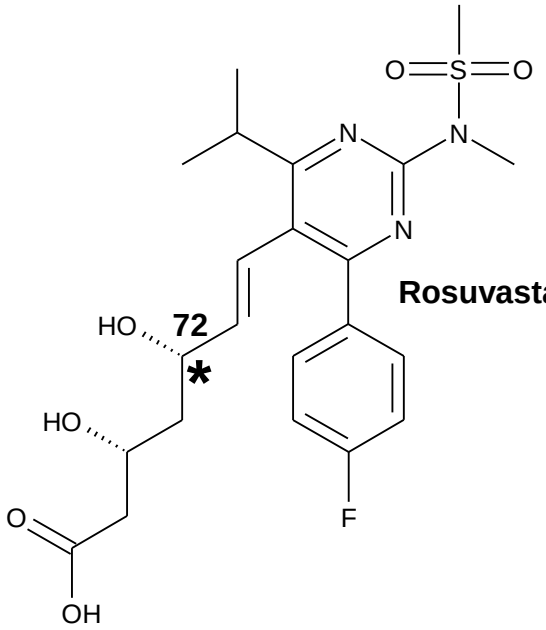
# Examples, Bond Dissociation Energy (BDE) calculations

**Molecule A (78, 84, 93 and 104)**



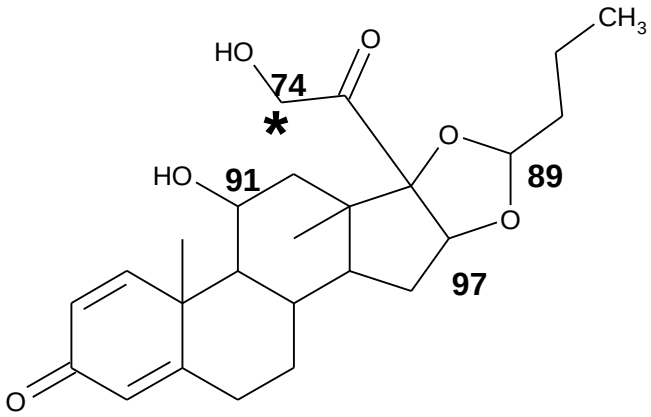

Felodipine

**Molecule C (63, 82, 86, 91 and 92)**




**Rosuvastatine - Crestor**

**Molecule B (75, 80, 87, 88, 89, 95 and 101)**



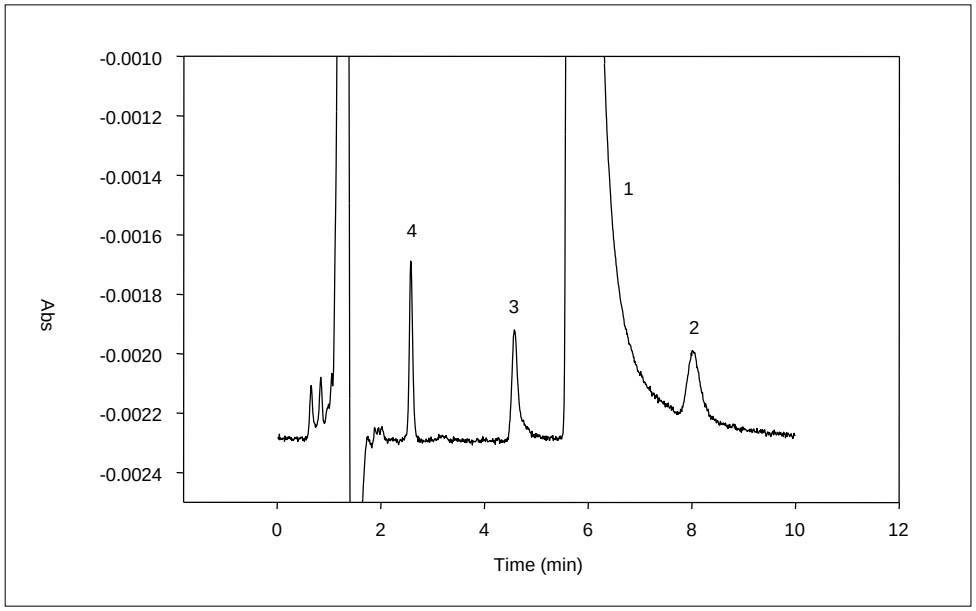

**Budesonide - Pulmicort**

*** Position with known autoxidation sensitivity**

# Separation of alprenolol and organic impurities at the 0.1% level

Stationary phase: Hypercarb (graphitized carbon)

Mobile phase: 1-methylpiperidine (pH=11) with 50% (v/v) of acetonitrile



# Efficacy (Animal (early) & Human (late))

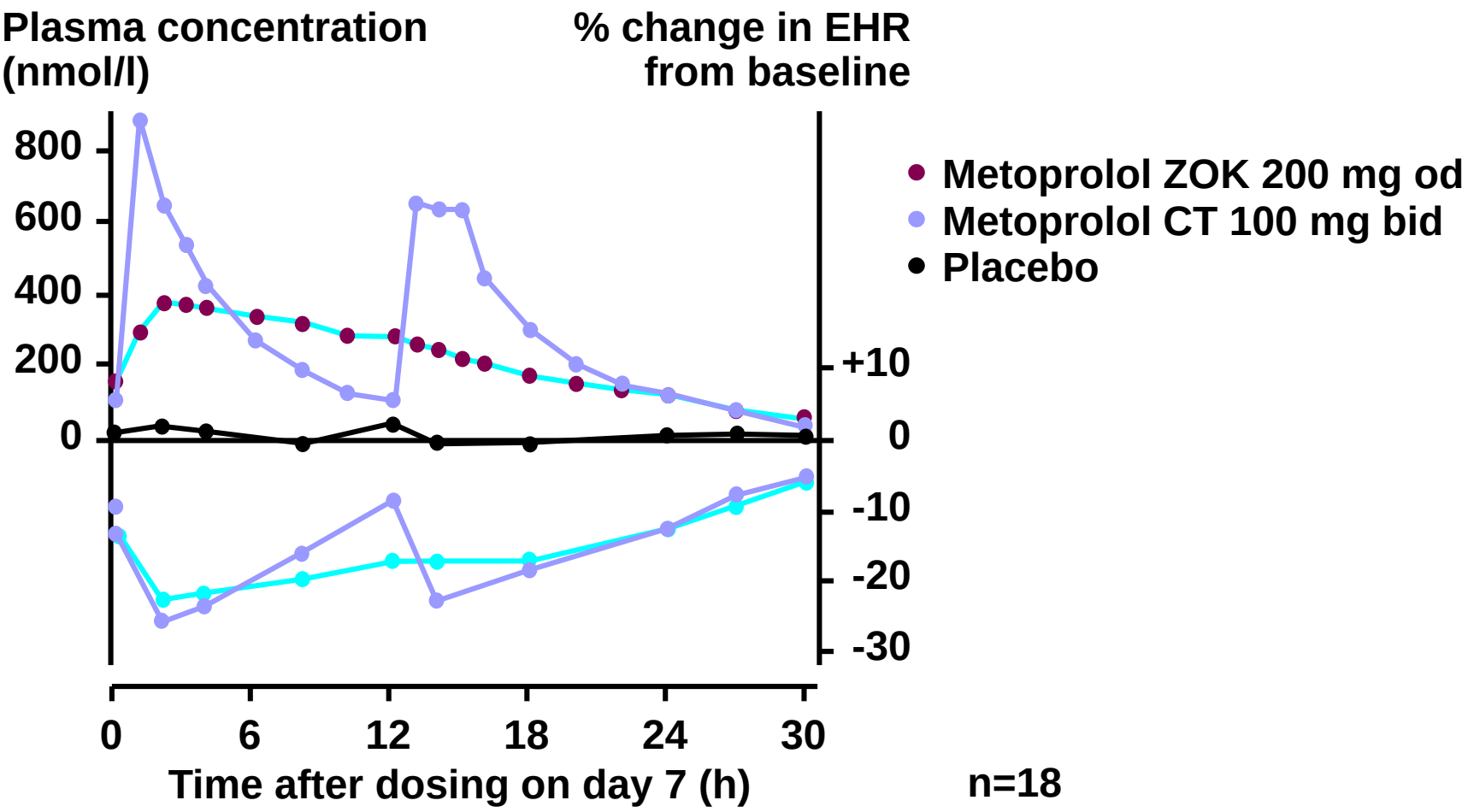
## Assay

- Right dose

## Dissolution

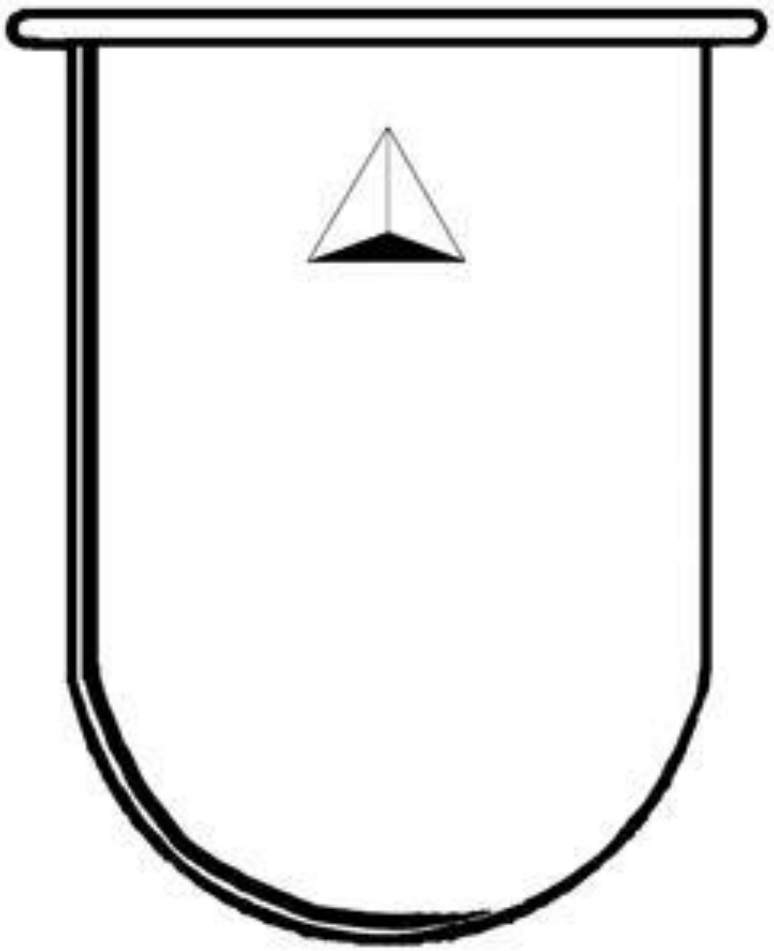
- Immediate release
- Modified release

# Plasma metoprolol concentration and ß1-blockade – Betaloc® ZOK od vs conventional tablets (CT) bid

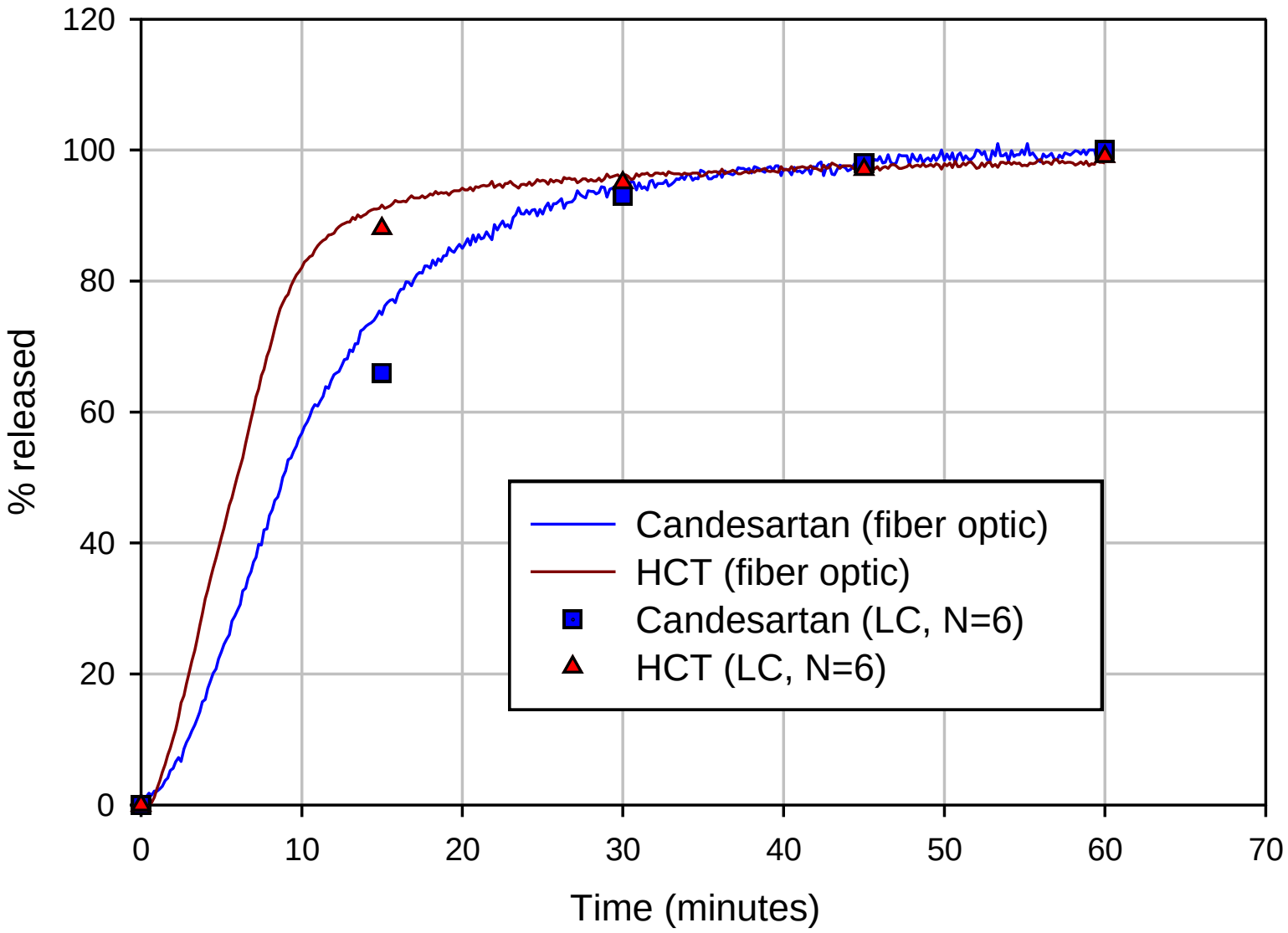



Lücker P et al, J Clin Pharmacol 1990;30:S28-S32

# Dissolution vessel

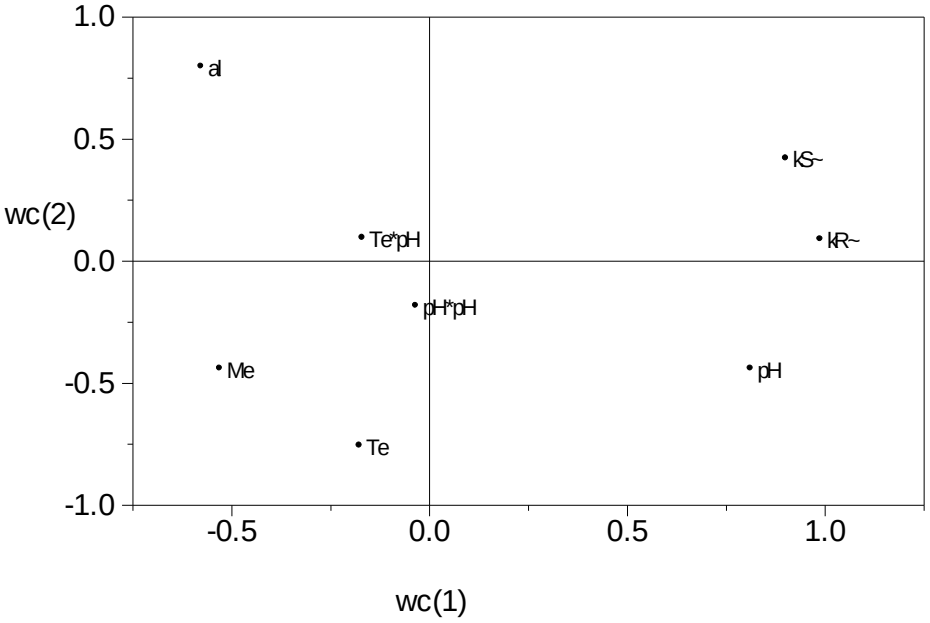


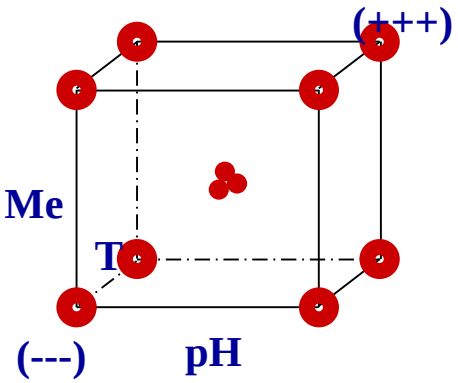
# Fiber optic measurement

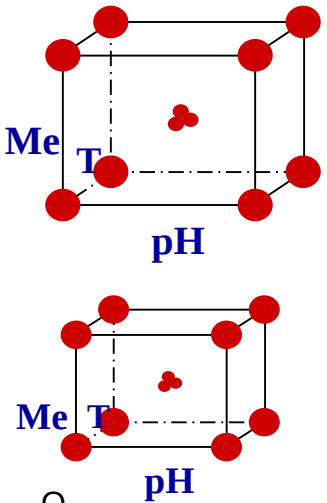


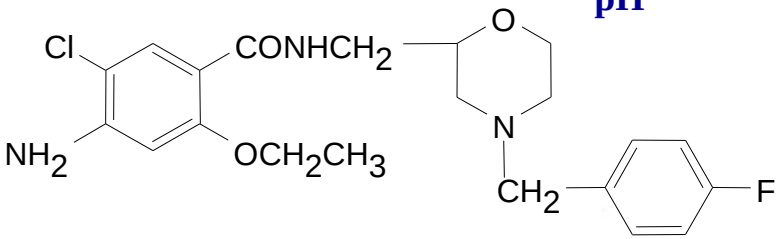
# Chemometrics – Design of Experiments (DoE)

## Loading Scatter




Mosapride

**Table II.** The experimental design including descriptors and responses.

| Exp No | Exp Name | Run Order | In Out | Temp | pH | MeOH | $k_R$ | $k_S$ | α |
|---|---|---|---|---|---|---|---|---|---|
| 1 | N1 | 3 | In | 20 | 4.2 | 25 | 1.86 | 4.84 | 2.6 |
| 2 | N2 | 11 | In | 40 | 4.2 | 25 | 1.84 | 3.04 | 1.65 |
| 3 | N3 | 10 | In | 20 | 5.94 | 25 | 21.7 | 24.4 | 1.13 |
| 4 | N4 | 9 | In | 40 | 5.94 | 25 | 9.21 | 6.84 | 0.74 |
| 5 | N5 | 8 | In | 20 | 4.2 | 35 | 0.8 | 1.8 | 2.25 |
| 6 | N6 | 4 | In | 40 | 4.2 | 35 | 0.48 | 0.72 | 1.5 |
| 7 | N7 | 6 | In | 20 | 5.94 | 35 | 4.51 | 5.64 | 1.25 |
| 8 | N8 | 1 | In | 40 | 5.94 | 35 | 1.92 | 1.67 | 0.87 |
| 9 | N9 | 7 | In | 30 | 5.05 | 30 | 2.87 | 4.63 | 1.61 |
| 10 | N10 | 2 | In | 30 | 5.05 | 30 | 2.94 | 4.87 | 1.66 |
| 11 | N11 | 5 | In | 30 | 5.05 | 30 | 2.99 | 4.71 | 1.58 |

# Career ladder for analyst within Product Development

**Scientific manager**

- Lead science activities and strategy
- Genertate excellent science

**Line manager**

- Development of team and individuals
- Support medicine development

**Project manager**

- Lead medicine development project(s)
- Handle budget

# Thank you for your attention!