Role of Analytical Chemistry in Drug Discovery & Development

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AstraZeneca

Analytical Chemistry within AstraZeneca

AZ R&D

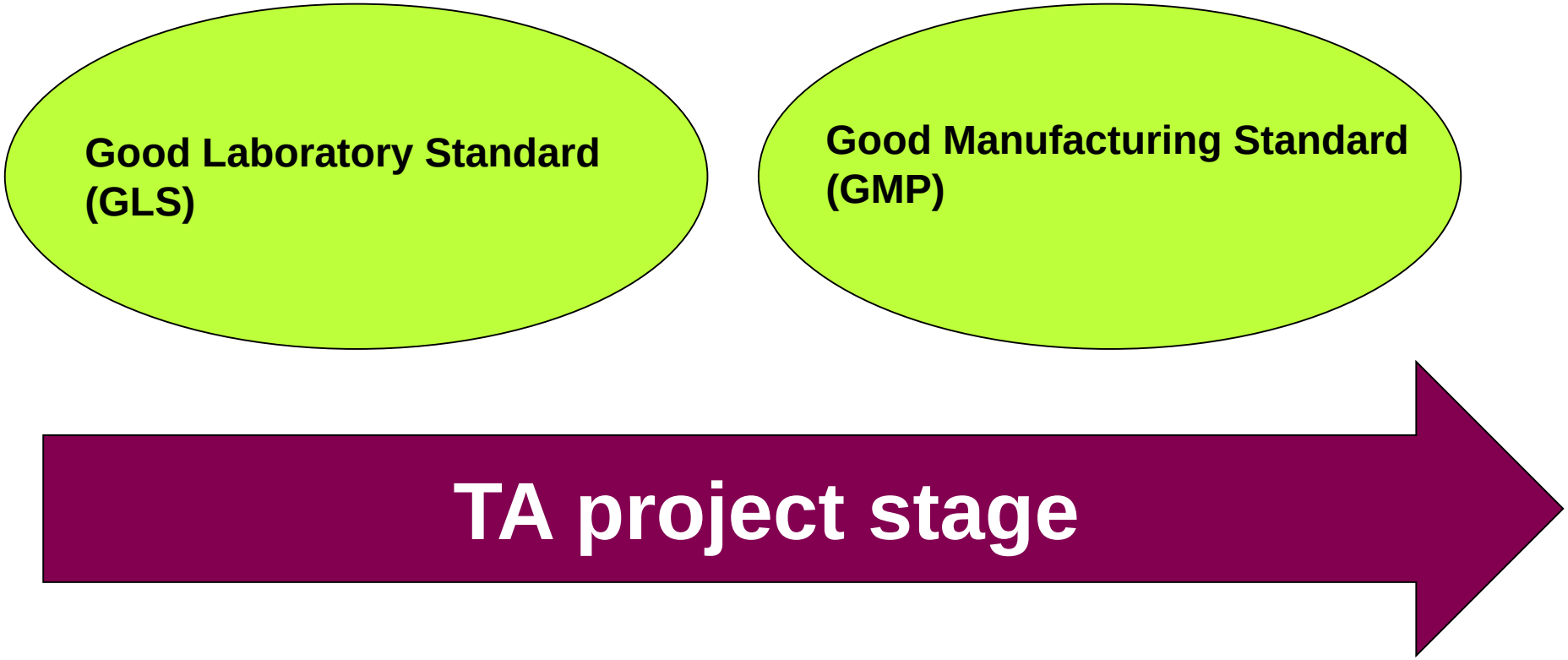
- Discovery
  - Support medicinal chemistry (synthetic route assay and purity)
  - Support preparative chromatography
  - Support toxicological studies
  - Bioanalysis (tissue, animal and human)
  - Stability testing

- 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)

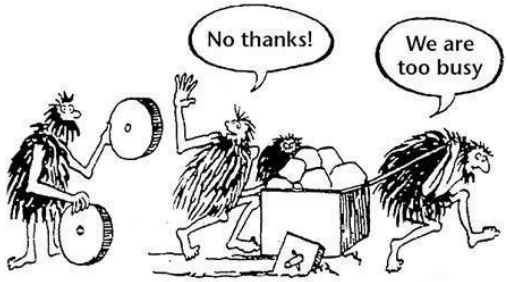
PT&D function contains 1300 individuals – 500 are analytical chemists
Ops Södertälje additional 250 analytical chemists
Total amount of analytical chemists in Gothenburg are about 400

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:

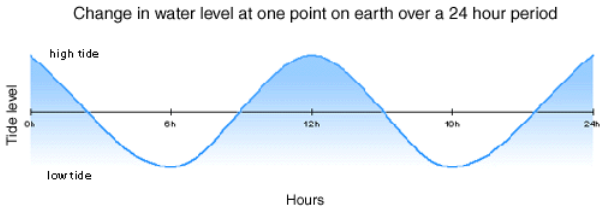
Clarification phase – Risk assessment – Planning – Execute – Evaluation –

Mechanistic understanding – Spread knowledge

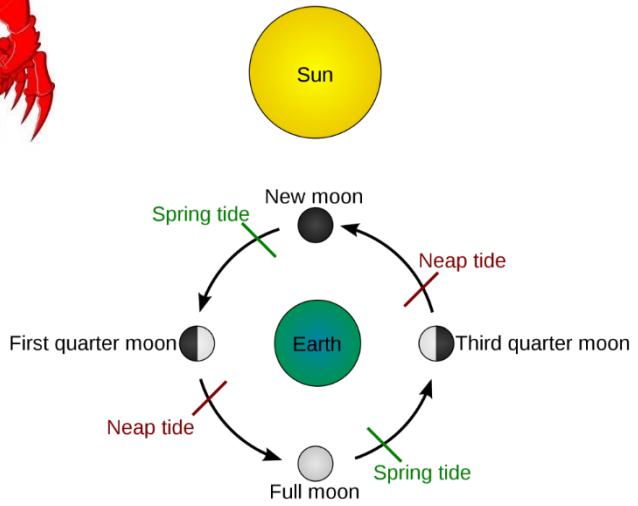
TRAINING TRAINING TRAINING TRAINING!!!!!!!!

Empirical versus Mechanistic Model
Example – the Tide

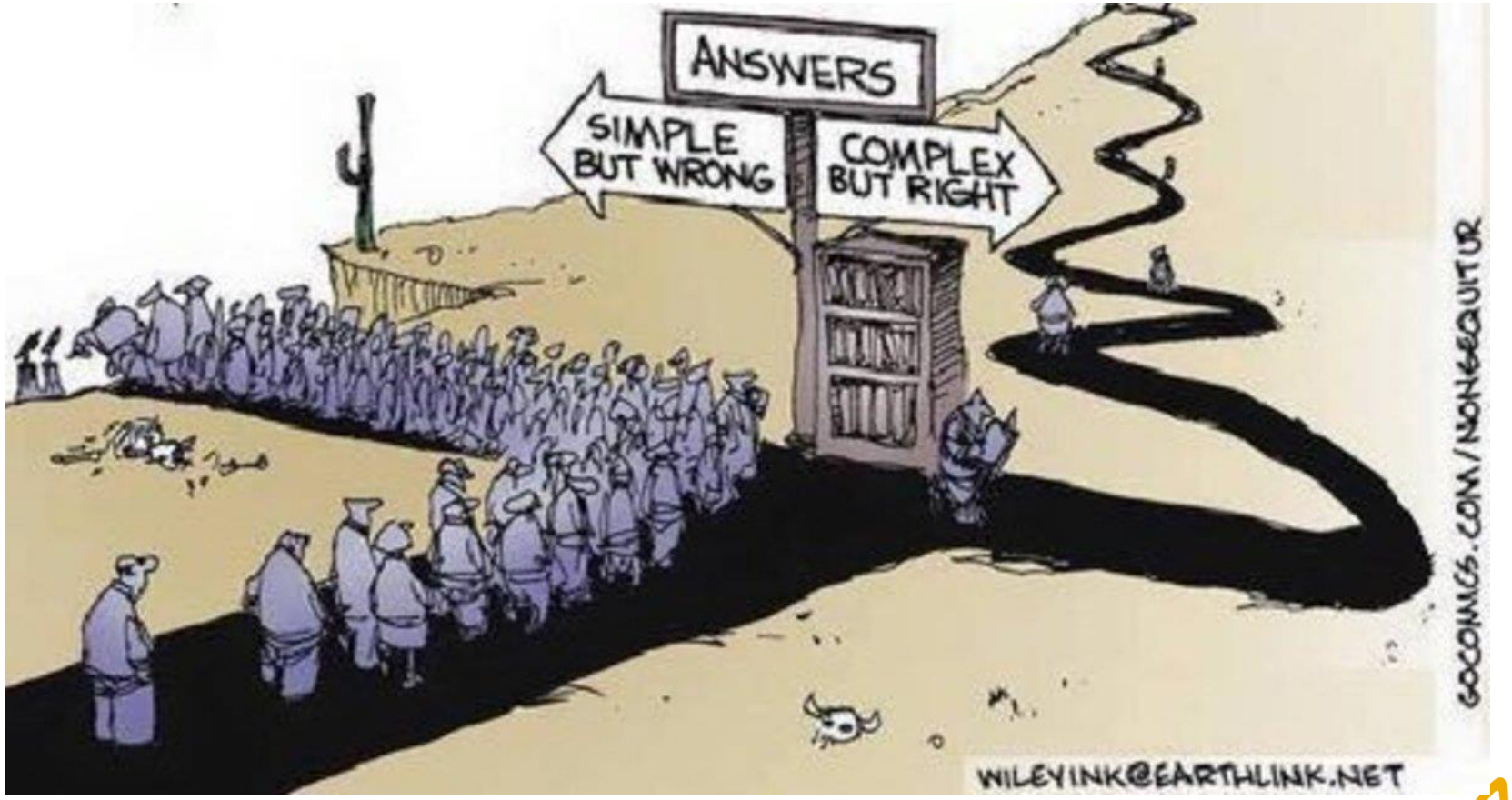
Empirical model based on observations



Mechanistic model based on physical laws



Good/bad Science



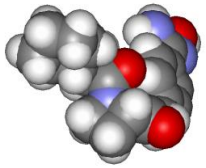
Analytical chemistry in drug discovery & development – examples

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

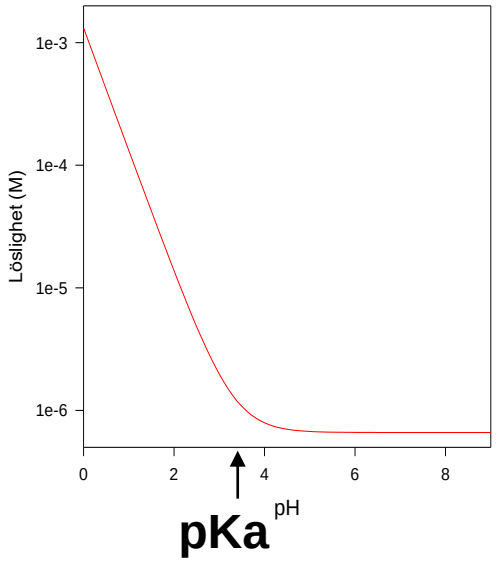


Molecular Properties

Hydrophilic or lipophilic ?

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

Surface active ?

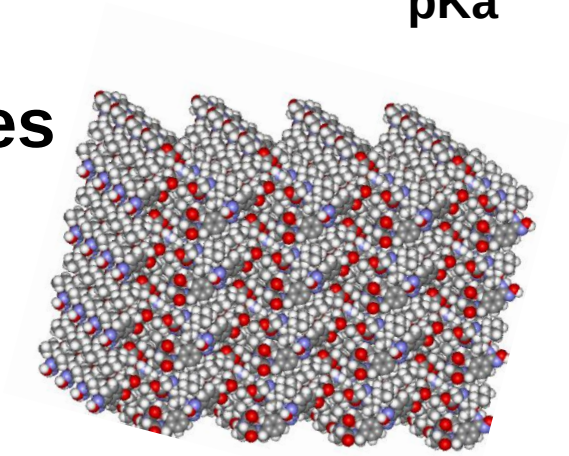


Solid & liquid state properties

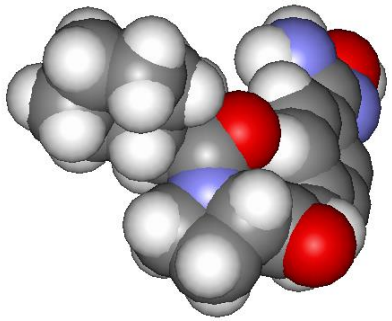
Solubility in water (vs. pH) ?

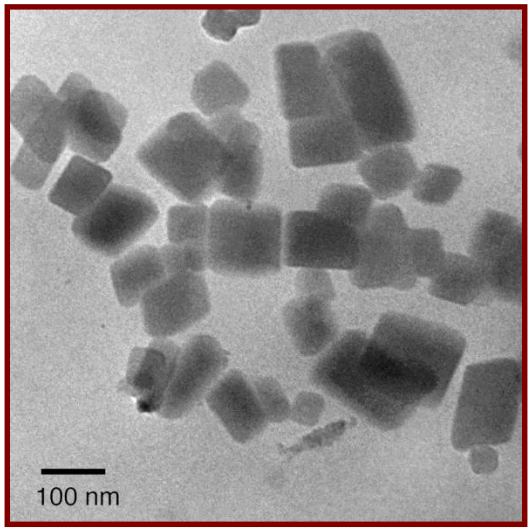
Crystalline or Amorphous ?

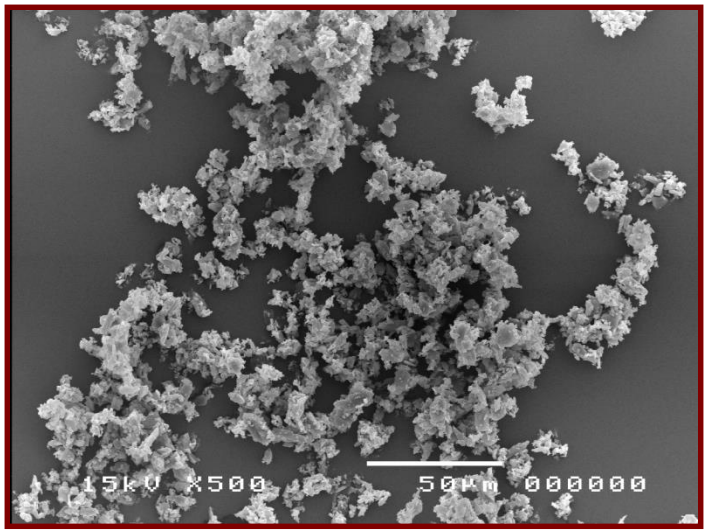
Salt form or parent form?

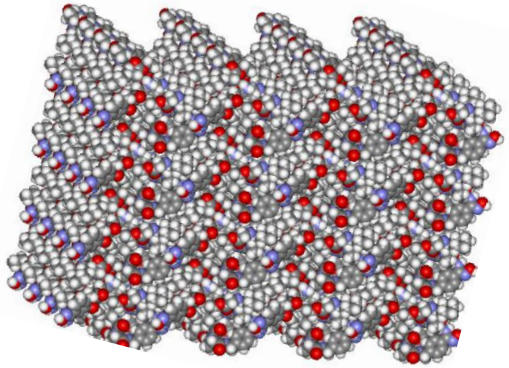


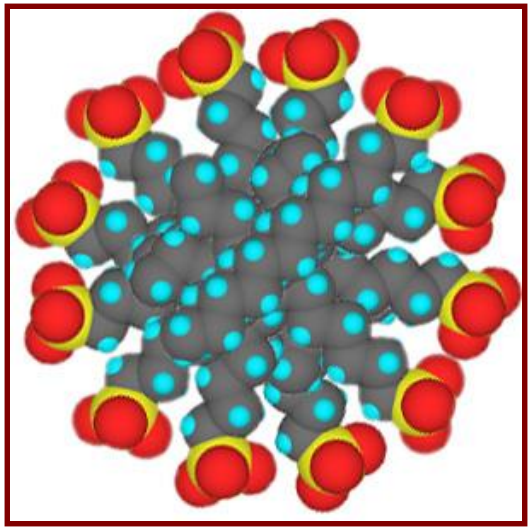
How does the molecule crystallize or aggregate?

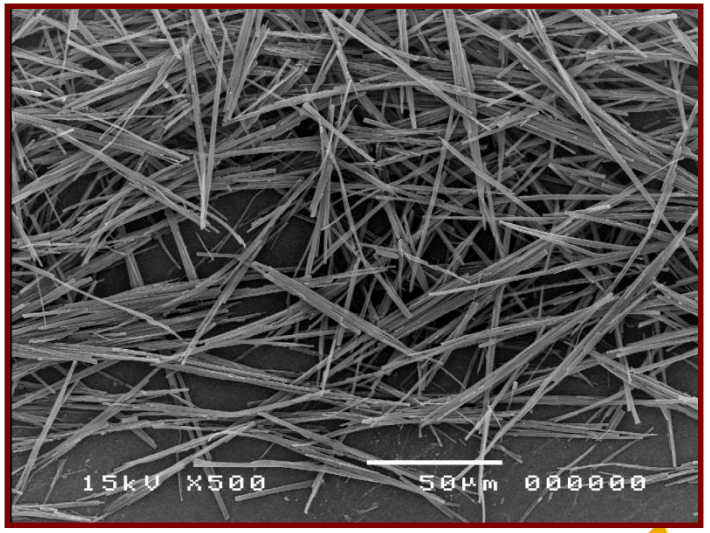






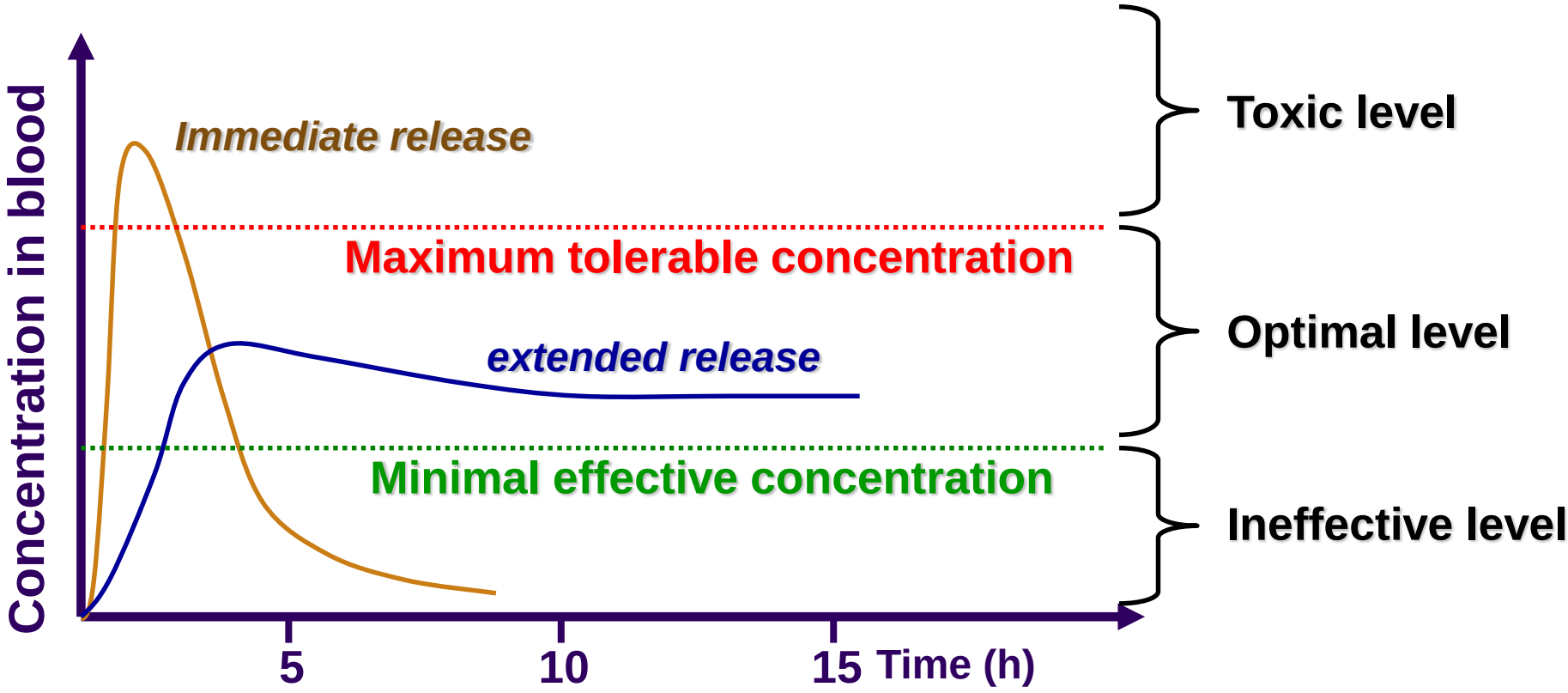






All affect the bioavailability of the drug substance

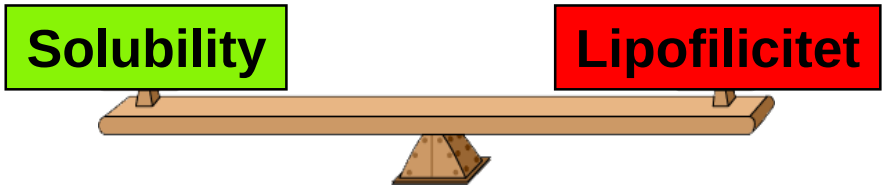
What action is desired in the body?

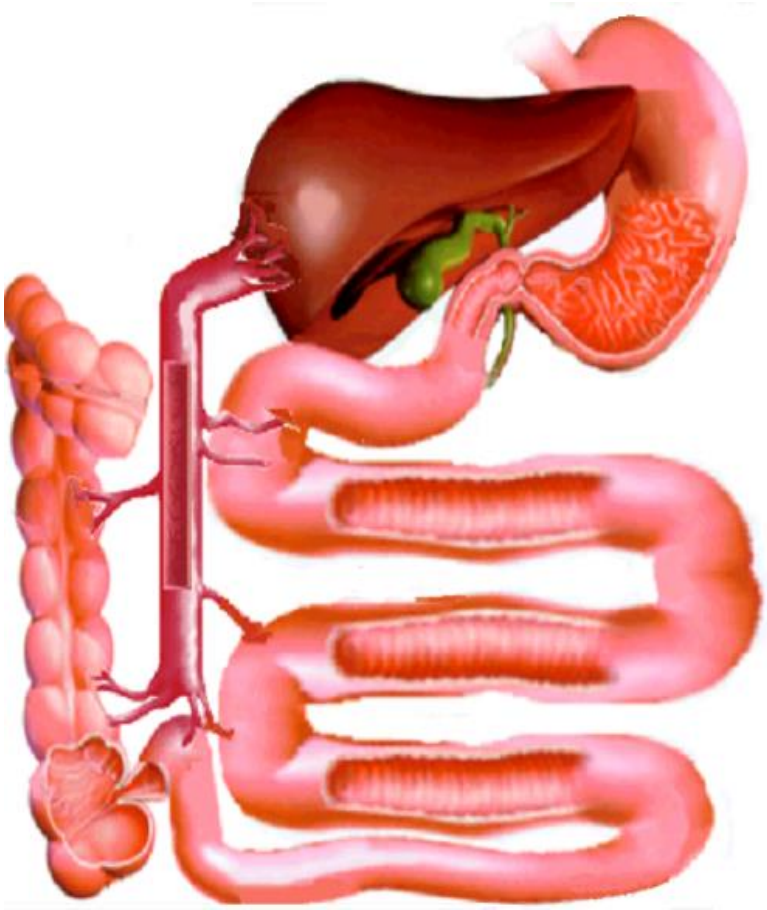


Ex: Oral tablet

Absorption in small and large intestine

God absorption if:





Structure Elucidation – Safety Aspects

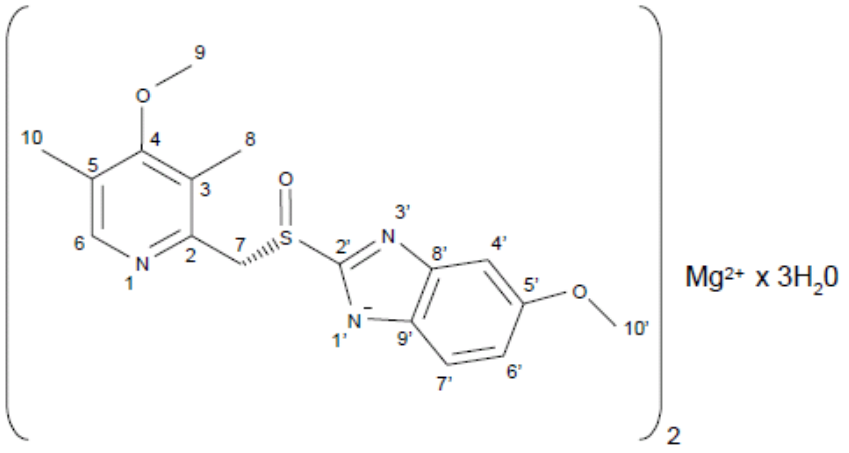
Toxicological studies to support clinical studies

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

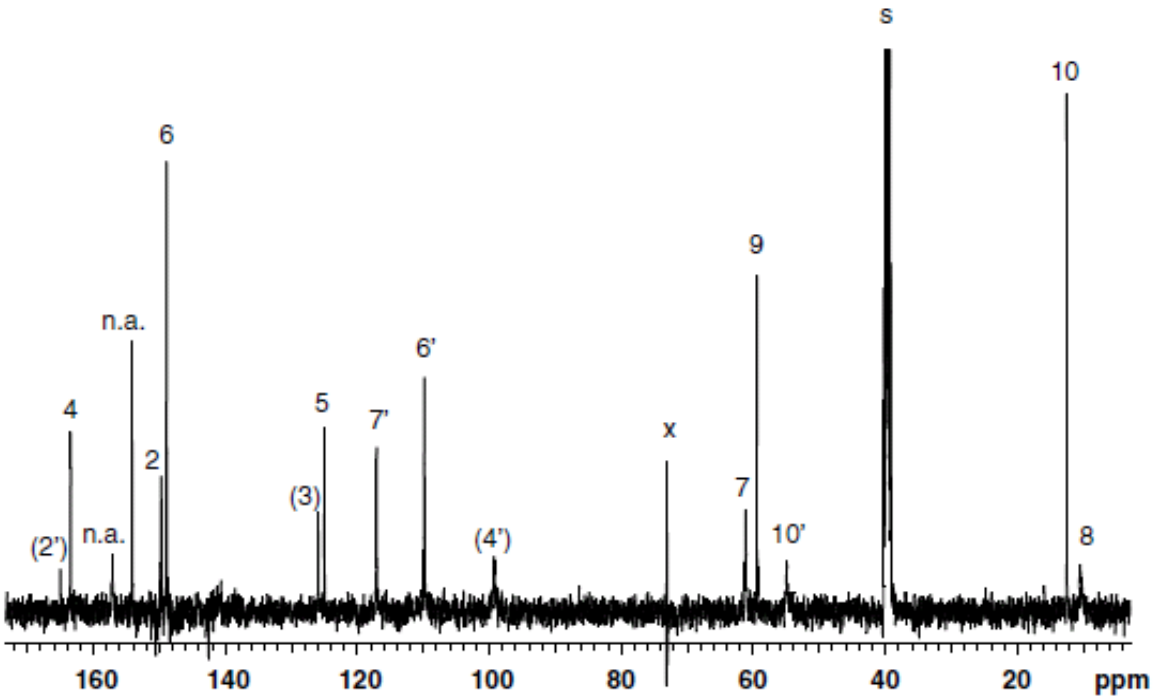
Development of substance and product manufacturing

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

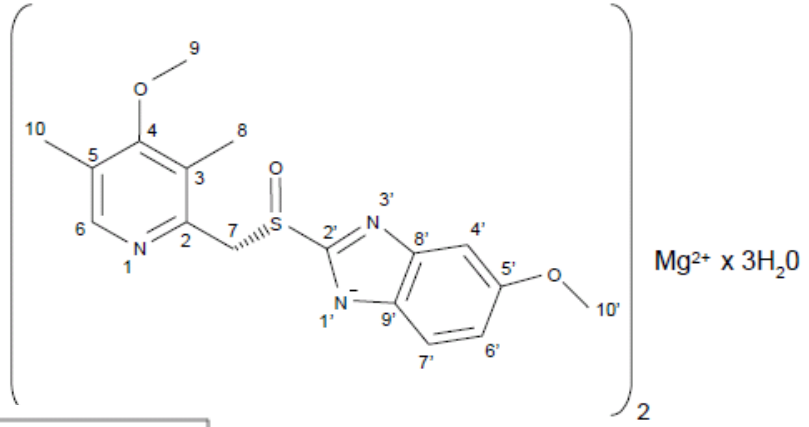
Nuclear Magnetic Resonance (absorption and re-emit of electromagnetic radiation in a magnetic field)

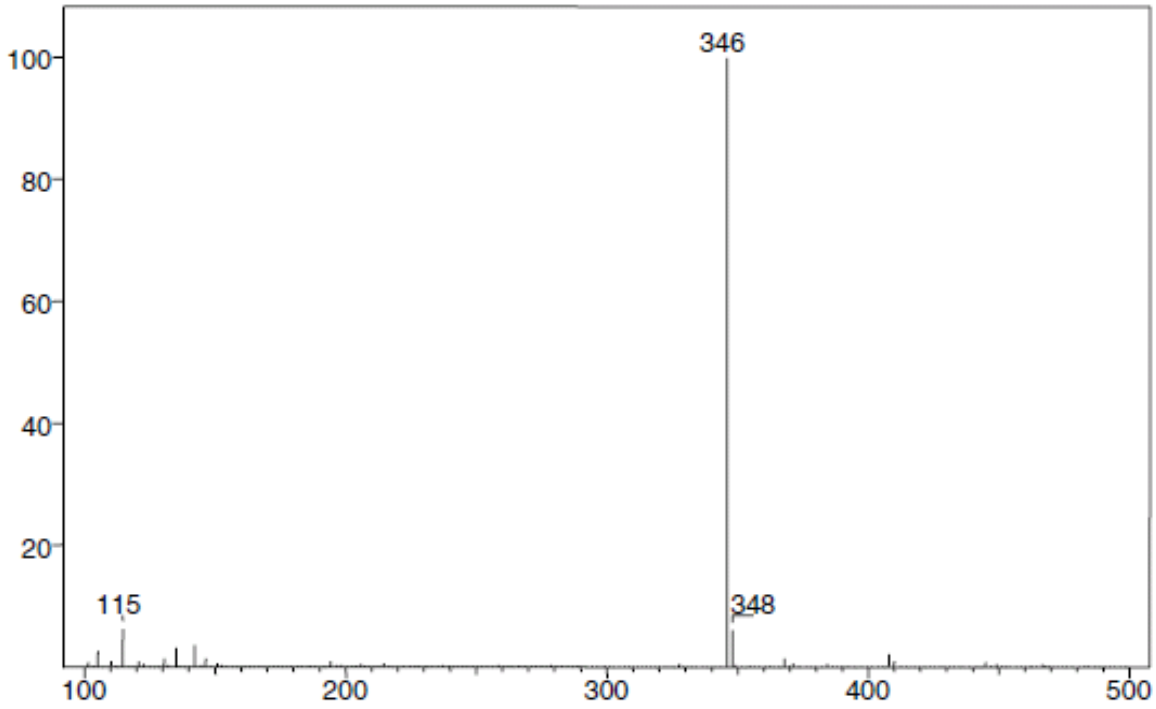


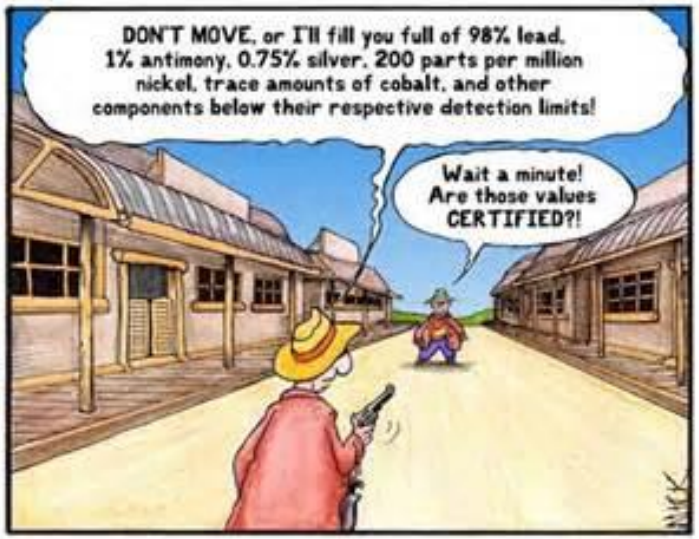
C13-NMR



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







Analytical Chemists in the Wild West

Major degradation pathways (predictive science)

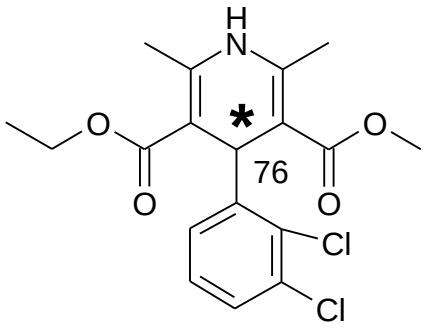
- Oxidation
  - Peroxides
  - Autoxidation
- Hydrolysis
- Thermal
- Photolysis

Major degradation pathways

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

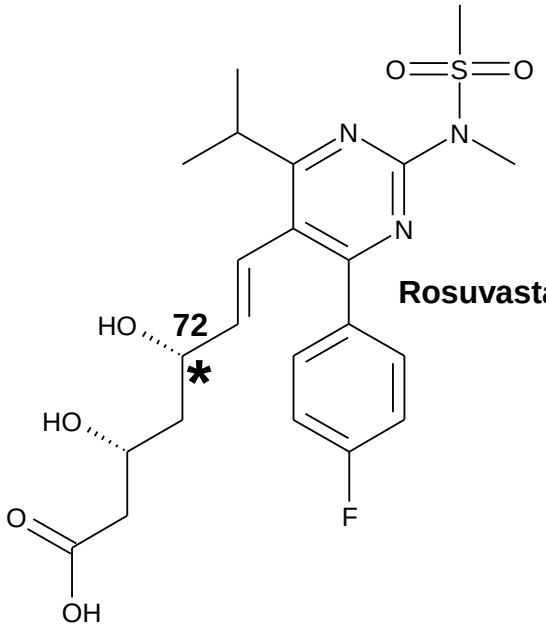
Examples, Bond Dissociation Energy (BDE) calculations

Molecule A (78, 84, 93 and 104)



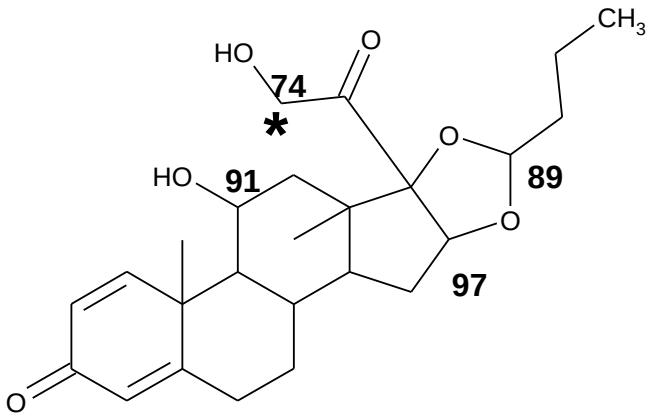
Felodipine

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



Rosuvastatine - Crestor

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



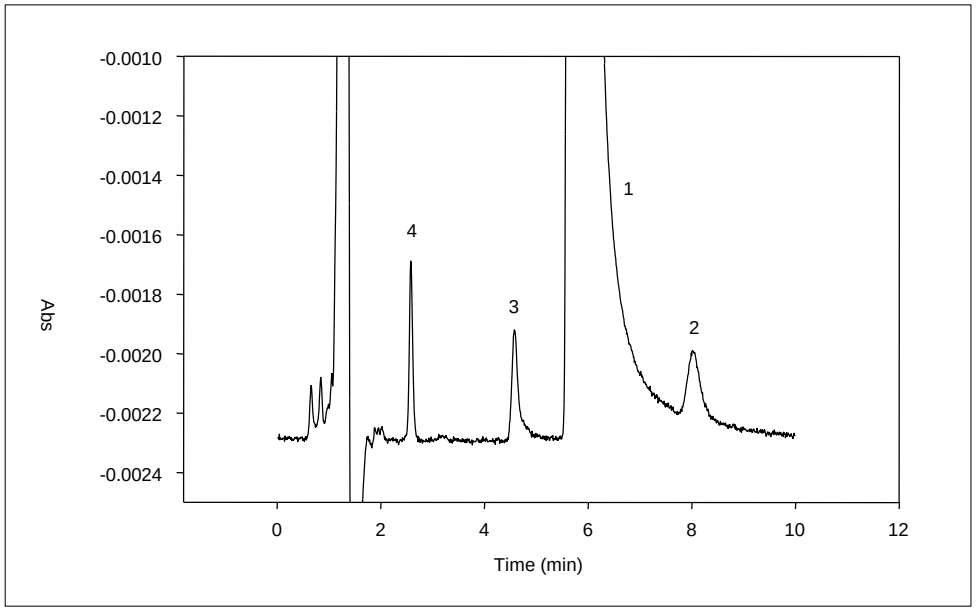
Budesonide - Pulmicort

*** 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))

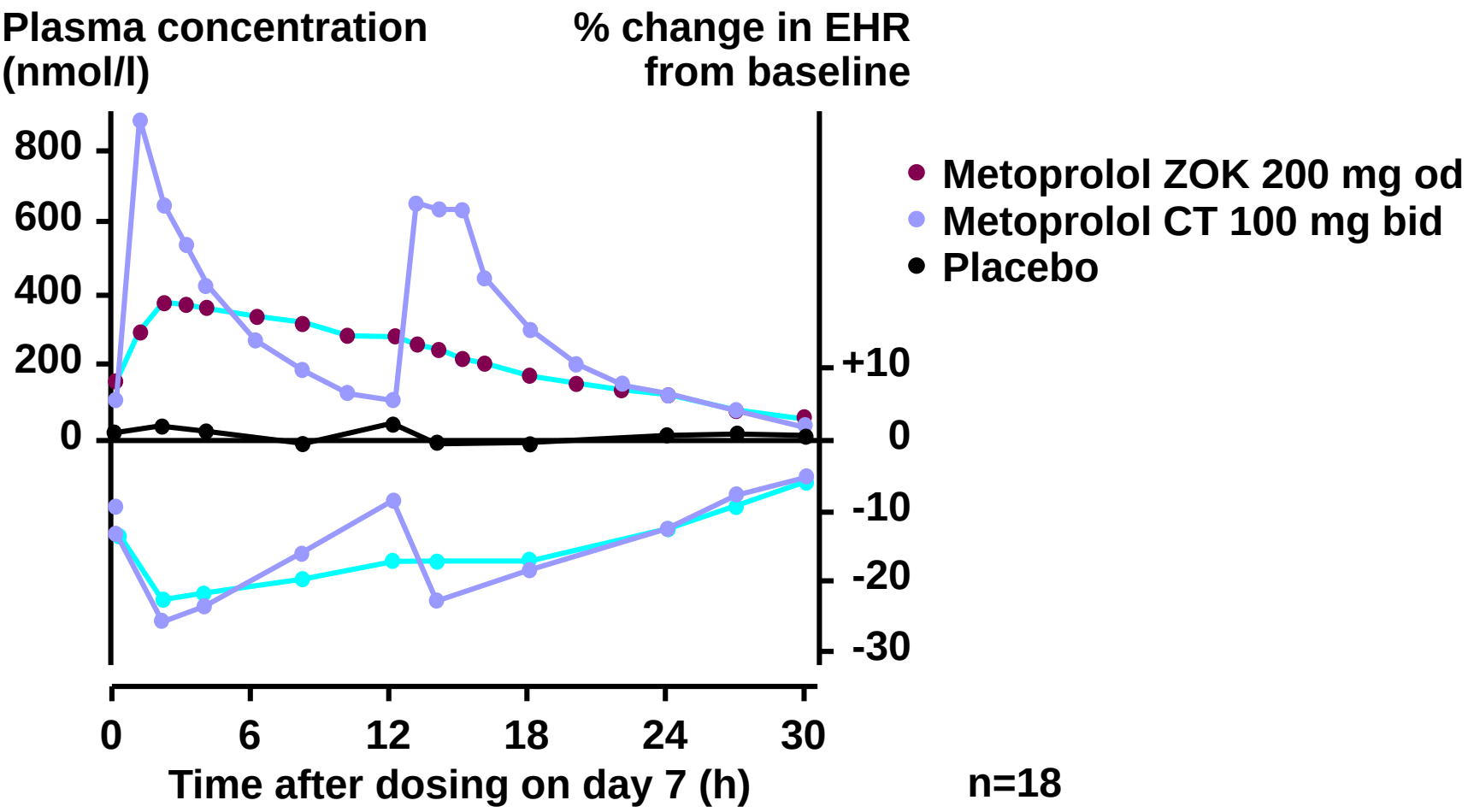
Assay

- Right dose

Dissolution

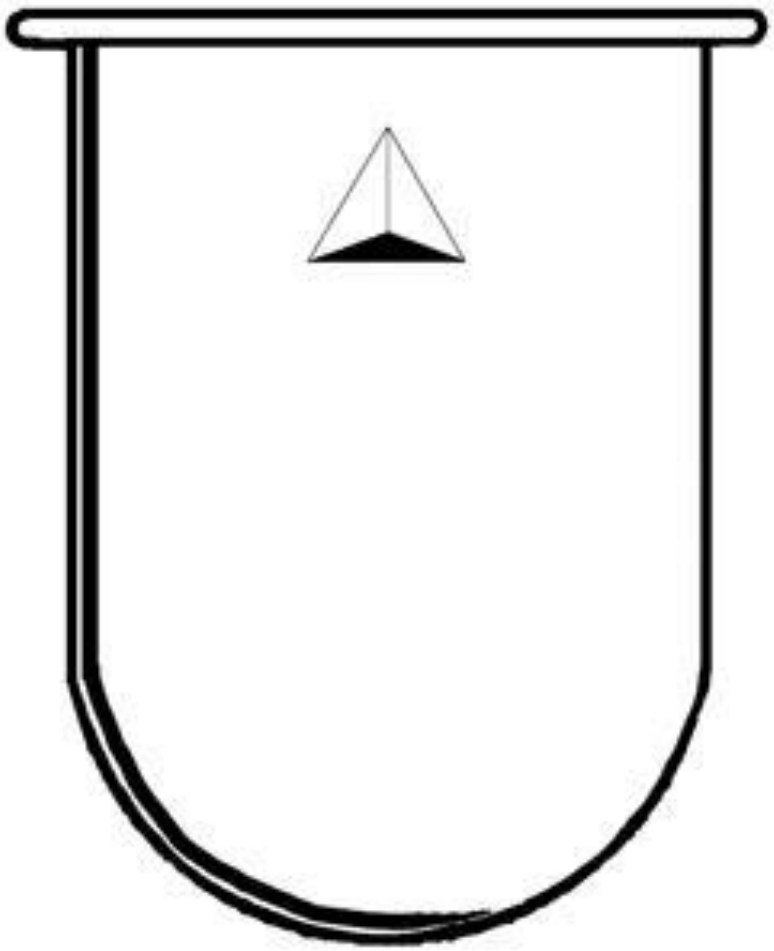
- Immediate release
- Modified release

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

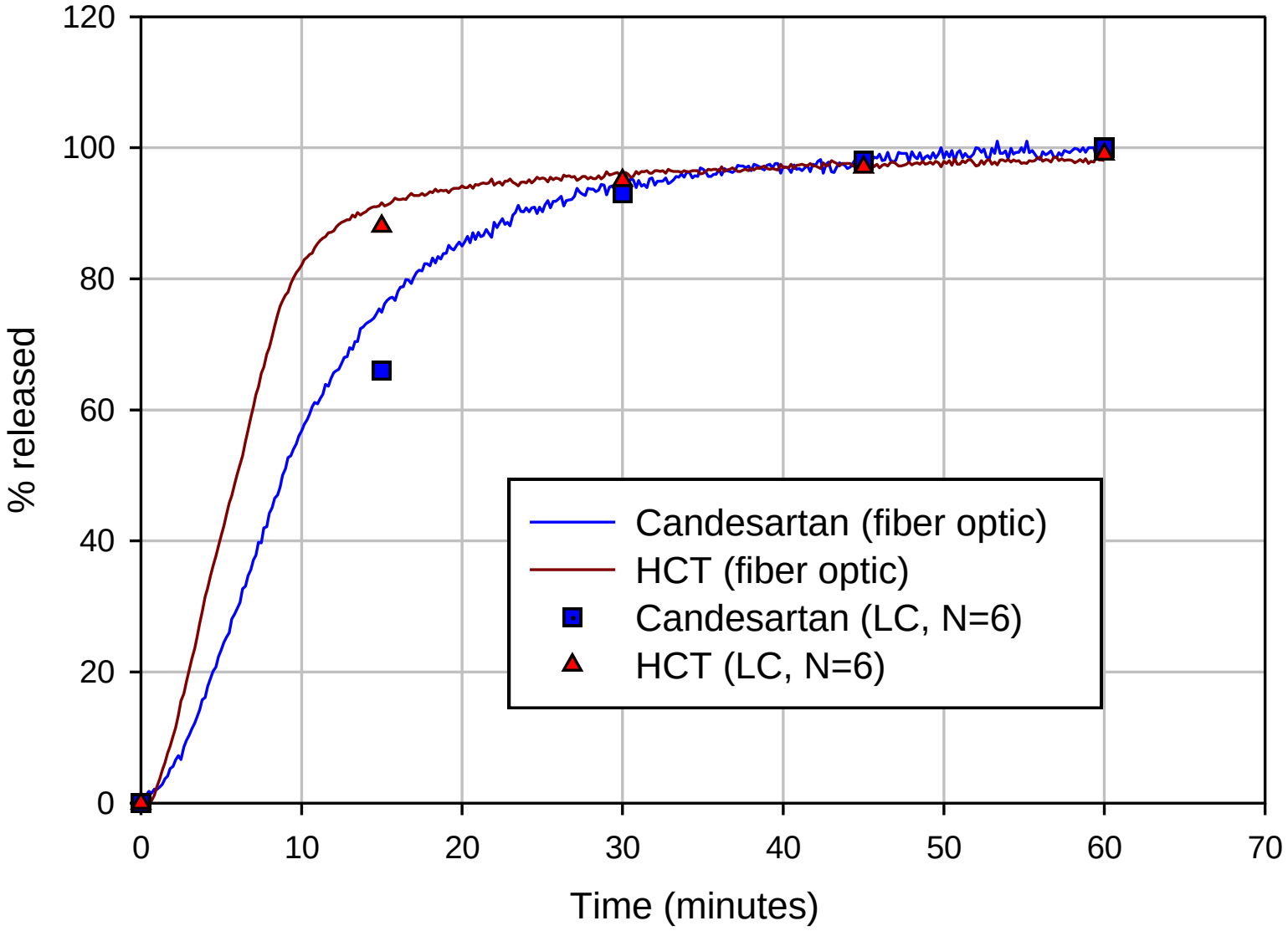


Lücker P et al, J Clin Pharmacol 1990;30:S28-S32

Dissolution vessel

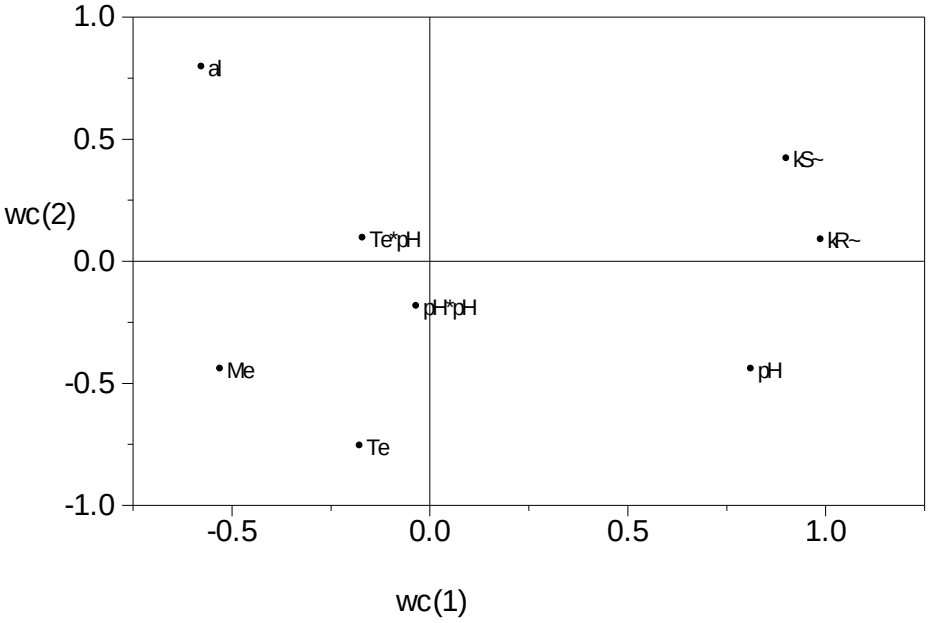


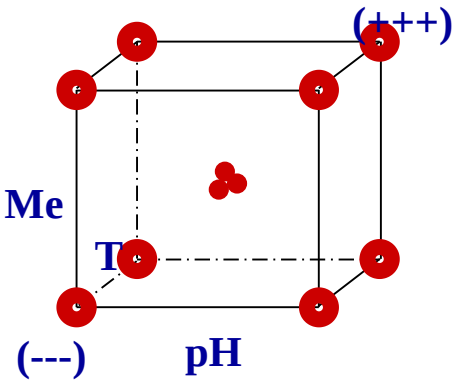
Fiber optic measurement

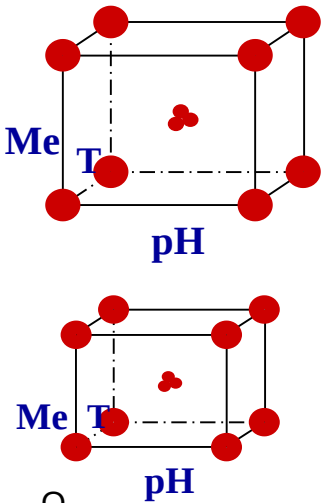


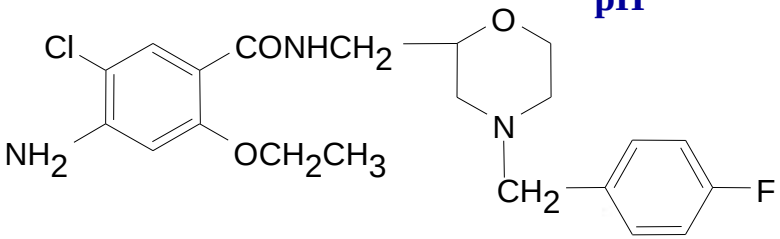
Chemometrics – Design of Experiments (DoE)

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
- Generate excellent science

Line manager
- Development of team and individuals
- Support medicine development

Project manager
- Lead medicine development project(s)
- Handle project budget

Thank you for your attention!