Pharmaceutical Sciences

1. **Molecular diagnosis & analytical chemistry**
   - Physicochemical evaluation
   - Method validation and ICH stability

2. **Molecular Pharmaceutics**
   - Early formulation
   - Drug rescue: Formulation Search Engine

3. **Innovative Formulation**
   - Lipid-based formulations: SEDDS/SMEDDS, liposomes…
   - Functionalised Polymers
   - Cyclodextrin complexes …

4. **Equipment & Technologies**
   - Physico-chemistry and analytical chemistry
   - Formulation characterisation
Physicochemical Evaluation

Drug design orientation

• pKa: Potentiometric titration, UV scans using Sirius technology

• logP and logD: Sirius technology or innovative liquid-liquid micropartition technique*

• HSA binding: Affinity chromatography using a Human Serum Albumin column

• Solubility & Stability
  – In buffers
  – In ingredients
  – In human gastrointestinal fluids from healthy volunteers
Physicochemical Evaluation

Correlation of determined parameters and literature values

- \( \log P(\text{oxl}) = 0.97\log P(\text{lit}) + 0.01 \)
  - \( R^2 = 0.954 \)

- \( \log D_{7.4}(\text{oxl}) = 0.95\log D_{7.4}(\text{lit}) + 0.15 \)
  - \( R^2 = 0.942 \)

- \( y = 0.92x - 0.86 \)
  - \( R^2 = 0.9628 \)

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- LogP and LogD pH 7.4 values determined by micropartition chromatography vs. literature values
- HSA Percentage Protein Binding (PPB) determined by affinity chromatography vs. literature values
Method validation and ICH stability

For API and Drug Product

- Research:
  - Pre-stability and forced degradation
  - HPLC-UV and HPLC-UV-MS method development

- GPL compliance:
  - HPLC-UV method validation
  - HPLC-UV impurity profile
  - ICH stability in climatic chambers
  - Reporting

- Empower data acquisition and treatment software

[Link to ICH website]
Early Formulation

Optimal formulation for animal dosing

- Solutions, suspensions, emulsions …

- Preliminary stability testing

- Preliminary tolerability tests
  - Absence of critical adverse effects
  - Absence of biased pharmacological effects

- Database
  - Formulation composition
  - Volume of administration tolerated in animals
Drug rescue: Formulation Search Engine

**Formulation for an improved bioavailability**

- Attractive approach combining molecular diagnosis and molecular pharmaceutics
- Application to pharmaceuticals and cosmetic agents
- Optimized probability of success for poorly soluble and effluxed drugs
- Requires only a gram-scale amount of active ingredient
- Reduced turn-around-time
- Oral and topical formulations
- GRAS ingredients
# Drug rescue: Formulation Search Engine

## Chronology of events

1. **Molecular diagnosis**  
   Identification of key parameters for drug formulation strategy:  
   \( pK_a \), lipophilicity, solubility, absorption, metabolism…

2. **Molecular pharmaceutics**  
   Formulation screening and ranking using in vitro cell models:  
   Feasibility study, solubility, stability, absorption using Caco-2 cells…

3. **Proof of concept in animals**  
   Selection of the most promising formulations before scale-up  
   Determination of PK parameters following administration
Drug rescue: the example of HMR1297

Before FSE

1 - Molecular diagnosis

- Poor plasmatic PK profile in rats following oral gavage
- Potential market: 0 $
- Poor Solubility
- Poor Permeability
- Monkey: fa ~ < 1%
- Dog: fa ~ < 1%
- Rat: fa ~ < 1%
- Degradation in the GI tract
- F.S.E
- P-gp Efflux Mechanism
- fa: orally absorbed fraction

Patent - WO 2006/018501
Drug rescue: the example of HMR1297

2 - Molecular pharmaceutics

Potential market: 1 bn $

Monkey: fa ~ 100%

Dog: fa ~ 100%

Rat: fa ~ 100%

Enhanced Solubility

Enhanced Permeability

P-gp Efflux Inhibition

Limited Degradation in the GI tract

fa: orally absorbed fraction

F1 & F2

3 - Proof of concept in animals

Improved plasmatic PK profile in rats following oral gavage

Patent - WO 2006/018501
Pharmaceutical optimisation of successful PK study formulations

Mini-ternary diagrams for optimal self-emulsifying systems selection

Optimal composition area selection according to:
- Formulation appearance
- Droplet size distribution
- Droplet size populations
- Drug stability and formulation stability
Lipid-based formulations: SEDDS/SMEDDS

Self-Emulsifying and Self-Microemulsifying Drug Delivery Systems

- Form emulsions and microemulsions once diluted with water
- Used to improve solubility and enhance oral absorption
- Successful approach for more than 10 chemical drugs
- Database containing 200 lipid-based formulations
- Suitable for pharmacological and toxicological studies and clinical use
Innovative Formulations

Functionalisied polymers for encapsulation

Pharmaceutical applications
- To improve solubility for optimal oral or topical absorption
- To improve stability and protect compounds against degradation
- To design pH-dependant sustained release formulation
- To modulate rheology of topical application
- To protect the stomach against cytotoxic compounds

Cosmetic applications
- To improve solubility for topical applications: fragrance, active ingredients, dyes
- To improve stability
- To improve formulation characteristics

Environmental applications
- Heavy metals encapsulation in water
- Toxic water soluble component elimination
- Lipophilic compound elimination

Some examples
- Dissolution of heavy metals, dyes, oils, terpens, aspirin
Functionalised polymers

Encapsulation main principle

1) Basic solution
2) Drug (D)

1) pH<2
2) pH>5

Aqueous solution of drug with controlled viscosity (syrup)
Cylodextrin Complexes

**Cyclic glucose oligosaccharides**

- Drugs are encapsulated in the hydrophobic core
- Encapsulated drugs are more soluble in water
- Used to enhance oral bioavailability
- Used to mask undesired flavours

Crystal structure of rotaxane (blue) with a cyclodextrin (green)

Main core of α-cyclodextrin
Physicochemistry and analytical chemistry

**GlpKa-DPAS**
- pKa measurement
- Sirius Analytical

**DSC (Differential Scanning Calorimetry)**
- Melting point measurement
- Polymorphism study
- TA Instruments

**5 HPLC-UV and 1 UPLC-UV systems**
- Drug characterisation and quantification
- Waters

**1 LC-UV-MS**
- Drug impurity profile analysis
- Agilent-Micromass
Formulation characterisation

Nanosizer and Coulter Sizer 3
• Droplet or solid particle size measurement
• Malvern – Beckman

Optical microscope
• Particle shape studies
• Leica – Olympus

Dissolution bath
• Dissolution profiling
• Distek – Sotax

3 climatic chambers and 4 ovens
• API and drug product forced degradation studies
• ICH stability
• Memmert