# Val Joly (16-20 June 2014)

**Introduction to drug discovery**

**1) Bases of solid state pharmaceutics**

- **Introduction into Pharmaceutical Technology (M-P Flament 2x45')**

**Introduction to Pharmaceutical Technology**

The purpose begins with generalities on the conception of drug dosage forms with the importance of the drug knowledge (influence of the physical and chemical properties) and the formulation approaches: choice of the drug, of the administration route, the dosage form, the excipients and the manufacturing process. Then, the importance of the excipient properties will be discuss, with the notion of functionality of excipients. Conventional solid dosage forms and advanced drug delivery systems will be present with different examples.

- **Controlled Drug Delivery (J. Siepmann 2 x 45 min)**

**Advantages, Underlying mechanisms, Practical examples**

The two lectures will give an introduction into the field of "Controlled Drug Delivery", addressing particularly the various potential advantages
and the underlying mass transport mechanisms of this type of advanced pharmaceutical dosage forms. Several practical examples will be used to
illustrate the great benefits these systems can offer. These will include oral controlled drug delivery systems (e.g., polymer coated pellets and
tablets) as well as parenteral dosage forms (e.g. biodegradable microparticles).

**2) The Physical state of pharmaceuticals.**

- **Crystal, polymorphs, amorphous state. Stability, solubility (M. Descamps 4x45')**

**Condensed state of Pharmaceutical compounds.**

- Review of the main modes of characterization of the condensed matter
- Duality crystalline/ amorphous states, role of disorder, crystal polymorphism.
- Relative stability of physical states, metastability, instability.
- Kinetics of phase transformations, nucleation, vitrification
- Calorimetric glass transition, aging, kauzman paradox
- Glass transition and molecular mobility: relaxation non Arrhenius, non-exponential, nonlinear.
- Notions of amorphous stabilization, solid solutions, confinement…

- **Co-crystals (W. Jones 1x45')**

"Multicomponent crystals (and in particular cocrystals) offer considerable potential in the area of pharmaceutical materials. The talk will overview the various experimental approaches to preparing them (including the choice of coformer in any experimental screen) and some examples of how specific physical properties such as stability and solubility have been overcome via their use. "

**3) Preparation & Manipulation techniques of pharmaceuticals:**

- **Lyophilization (A. Hédoux: 1x45')**

**Freeze-drying of pharmaceuticals and biopharmaceuticals**

Freeze-drying is widely used to improve the stability and long-term storage stability of labile drugs. It is a time- and energy intensive process that could take days if the cycle is not optimized. Physical phenomena associated with the manufacturing process (phase transformations of water, heat and mass transfer) are analyzed in order to understand the influence of the set up parameters (shelf temperature, pressure chamber, freezing time) or experimental material (formulation, fill volume, container, equipment ...), on the process. This analysis allows us to understand how to optimize the cost of the procedure while ensuring the standards required for the quality of the freeze-dried product. It will be shown that Raman spectroscopy can be used to monitor the structural stability of proteins during a freeze-drying cycle

- **Compression (M-P Flament: 2x45'), Film coating (S. Muschert & Y. Karrout: 1x 45 min) and Spray drying (M. Hamoudi: 1x45')**

**Compression** : ( M-P Flament)

The first part focuses on the bases of compression with (i) the mechanisms of tablet formation, (ii) the physical phenomena of compression and (iii) the interest of the instrumentation of the tablet machines. The second part describes the problems encountered during the fabrication of tablets from an industrial point of view and will discuss on the influence of the formulation and of the technological parameters. Then, the last part will present some applications with the difficulties and possible solutions: multi-particular tablets, mini-tablets for paediatric use

**Film Coating :**Susanne Muschert, Youness Karrout

This presentation will give an overview on equipment and techniques used in polymeric film coating and provides also large variety of possible advantages of film coating such as time-controlled drug delivery, taste masking, moisture protection, improved esthetic appearance and site specific drug delivery to targeted segments of GIT. This is why numerous drug products on the market are film coated dosage forms, manufacturing techniques and characterization methods are of utmost practical importance.

**Spray drying :** M.Hamoudi

Spray drying is a successfully employed method in pharmaceutical technology to prepare microspheres for controlled drug delivery systems.
Other common methods to produce microspheres are emulsification solvent evaporation, emulsification solvent extraction, or phase separation.
Comparing these methods, spray drying is a simple, rapid, reproducible and easy to scale-up technique. It is a one stage process, allowing mild
temperature conditions. The spray-drying technique is less dependent on the solubility of the drug (e.g. hydro solubility) and the polymer. In the
last two decades, polymers based on lactic acid and glycolic acid and their copolymers have attracted much interest as carriers in the
preparation of different medical devices and drug delivery systems. These polymers meet the necessary criteria of excellent biocompatibility,
biodegradability, and non-toxicity in humans - either in surgery or in drug delivery systems.

**4) Characterization techniques of pharmaceuticals:**

- **Calorimetry** (J-F. Willart: 1x45')

This course is dedicated to Differential Scanning Calorimetry (DSC). It will be divided in three parts:

(i) Basic principles and implementation of a DSC experiment

(ii) Characterization of pharmaceutical materials using DSC

(iii) Presentation of advanced DSC techniques: Temperature modulated DSC, Isothermal DSC, and Hyper DSC.

- **Dielectrics relaxation spectroscopy (E. Dudognon: 1x45' + N. Correia: 1x45' )7**

**Dielectric spectroscopies applied to pharmaceutical compounds: What can we learn from?**

In this course, we will present the principles of the Dynamic Dielectric Spectroscopy and its variant the Thermo-Stimulated Currents technique.

We will show that these two complementary techniques allow the study of molecular movements with characteristic relaxation times varying from $10^{-9}$ to $10^{3}$ s, *i.e*., from the more localised (secondary relaxations) to the more delocalised motions (relaxation associated to the dynamic glass transition). By varying the temperature, the evolution of these motions can be followed from the liquid to the glassy states. The temperature dependence of the associated relaxation times allows to establish the relaxation map that is the fingerprint of the material.

Through studied cases taken in the pharmaceutical field (API or excipients), we will show that dielectric spectroscopies can bring information about the stability of amorphous materials as they allow, for example, to determine the influence of water, the influence of physical ageing or to follow the kinetics of crystallization.

The use of dielectric spectroscopies can also bring a valuable contribution to understand the exotic behaviour of some materials as caffeine.

- **Raman scattering (A. Hédoux: 1 x 45')**

**Raman spectroscopy in molecular compounds: application to pharmaceuticals and biopharmaceuticals.**

After the description of the principle of the Raman effect, the different parts of the Raman spectrum distinctive of molecular materials will be presented. A special attention will be given to the contribution of complementary investigations of the low-frequency and fingerprint regions to the structural description of disordered states and to the understanding of phase transformation mechanism. Applications of combined low- and high frequency investigations to pharmaceuticals and biopharmaceuticals will be presented.

- **X-Ray (P. Derollez: 1x45') + PDF (G. Cuello: 1x45')**

**Contribution of powder X-ray diffraction in the determination of the crystal (micro)structure of drugs and food. P.Derollez**

The presentation will focus on the contribution of X-ray diffraction in the analyze of the structural and microstructural features of crystal powders. We will see what information are contained in a diffraction pattern and how extract them. Then, the results of some examples on drugs and food products (indomethacin, lactose) will be shown and the correlation between the microstructural effects (size of crystallites, micro-deformations) and the existence of a hydrogen-bond network will be discussed.

**Neutron diffraction and PDF analysis – G. Cuello**

Neutron scattering techniques, and particularly neutron diffraction, will be presented. An introduction to Pair Distribution Function (PDF) analysis will be given, showing how this technique can provide information about the short range order (few angstroms) of amorphous materials. This is of particular interest when working with complex molecular systems where the bonds between different molecular units are sometimes more important than the molecular structure itself. Examples of the molecular liquids and amorphous will be given.

**NMR (M. Geppi: 1x45')**

In this lesson the possible applications of NMR, and in particular, solid-state NMR spectroscopy, to pharmaceuticals will be described.
After a short introduction to the basic principles and methods of solid-state NMR, the applications of this technique to APIs, excipients, complexes and formulations will be described also through suitable examples taken from the literature.
Such applications range from very detailed studies of the structural and dynamic properties of crystalline API's to the investigation of complex amorphous formulations, concerning for instance phase properties, interactions and miscibility among the different components.
The differences and complementarity of solid-state NMR respect to other common techniques, such as calorimetries, X-ray diffraction, electronic microscopies and dielectric spectroscopy will also be briefly treated.

**Modelling (F. Affouard: 1x45')**

**Molecular modelling of pharmaceuticals :**

This training will introduce the physical principles underlying the main methods of numerical simulation in the study of molecular materials of pharmaceutical and agrochemical interest. Theoretical concepts will be illustrated by practical examples that will allow participants to easily understand how numerical approaches can tackle several issues concerning structural, dynamical and thermodynamical properties of model drugs: probe of the structural organization induced by hydrogen bonds association, analyses of the complex molecular mobilities, prediction of the physical stability,… This course will show how to use the best suited numerical method with the necessary degree of modeling for a given physical problem. The main softwares for computing, data analysis, visualization and animation will be also presented.

## Practical demonstrations: Lille1 (2.5 hours) + Lille2 (2.5 hours)

| | Mon.<br>16th June | Tue.<br>17th June | Wed.<br>18th June | Thu.<br>19th June | Frid.<br>20th June |
|---|---|---|---|---|---|
| 8:30 – 9:15 | | Compression I<br>(M-P Flament) | Dielectrics I<br>(E. Dudognon) | Trip to Lille | Co-Crystals<br>(W. Jones) |
| 9:15 – 10:00 | Meeting at Lille1 Campus<br>(CERLA Building) | Compression II<br>(M-P Flament) | Dielectrics II<br>(N. Correia) | | Molecular Modelling<br>(F. Affouard) |
| 10:00 – 10:30 | | Coffee break | Coffee break | Practical works(2.5h)<br>Lille1: X-ray, Calorimetry, Raman, Dielectrics<br>Lille 2:<br>Compression<br>Film coating<br>Spray drying | Coffee break |
| 10:30 – 11:15 | Trip to Val Joly | Calorimetry<br>(J.-F. Willart) | NMR<br>(M. Geppi) | | Physical states III<br>(M. Descamps) |
| 11:15 – 12:00 | | Raman scattering<br>(A. Hédoux) | Lyophilization<br>(A. Hédoux) | | Physical states IV<br>(M. Descamps) |
| 12:00 – 13:30 | Lunch | Lunch | Lunch | 12:30-14:30 :<br>Lunch at Lille1<br>Transfert Lille1/Lille2 | Lunch |
| 13:30 – 14:15 | Introduction into Pharmaceutics I<br>(M-P Flament) | Film coating<br>(S. Muschert & Y. Karrout) | Physical states I<br>(M. Descamps) | | Trip back to Lille |
| 14:15– 15:00 | Introduction into Pharmaceutics II<br>(M-P Flament) | Spray-drying<br>(M. Hamoudi) | Physical states II<br>(M. Descamps) | Practical works(2.5h)<br>Lille1: X-ray, Calorimetry, Raman, Dielectrics<br>Lille 2:<br>Compression<br>Film coating<br>Spray drying | |
| 15:00 – 15:30 | Coffee break | Coffee break | Free | | |
| 15:30 – 16:15 | Controlled Drug Delivery I<br>(J. Siepmann) | X-Ray<br>(P. Derollez) | | | |
| 16:15– 17:00 | Controlled Drug Delivery II<br>(J. Siepmann) | PDF approaches<br>(G. Cuello) | | | |
| 17:00 – 19:30 | Free | Free | | Trip back to Val Joly | |
| 19h30 – 21h00 | Welcome party | Dinner | Banquet | Dinner | |

21-5-2014