Crystalline Polymorphism, Habits, Agglomeration States and Amorphous Phases : An Overview of the Importance of the Solid State in Pharmaceutical Development

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A majority of pharmaceutical dosage forms is still today absorbed by the oral route. The active ingredient (AI) as well as the excipients are obtained in the solid state as crystalline, semi-crystalline and amorphous powders. Consequently, it is essential to control the physico-chemical characteristics of these powders in order to assure :

- good manufacturability of the pharmaceutical dosage form (PDF),
- acceptable stability of the AI in its formulation, as well as the one of the PDF itself,
- a constant release of the AI from its PDF over time, and possibly of its PDF overtime, and possibly of its bioavailability if dissolution is the limited step in the absorption. This point is of such particular importance that the Regulatory Authorities have put to the fore the necessity to set a bioequivalence study each time e.g a generic drug is to be submitted.

For that we need to control :

- the desired crystalline form of the molecule if it is susceptible to polymorphism,
- the external form of the solid particle or the habit (or facies),
- the degree of aggregation or agglomeration, the size distribution and other parameters such as surface area and porosity for instance.

All these features are the result of a complex process which is the crystallization process of a molecule from a solvent.

During the lecture, some definitions and thermodynamic concepts of polymorphism and pseudopolymorphism as well as considerations of habits and agglomeration states will be discussed rapidly (and the basis of the crystallization process recalled).

Then, we shall envisage through examples the main consequences of those physical characteristics in pharmaceutical development including :

- an example of how to choose the polymorphic form of an NCE to be developed,
- the relation between solubility or kinetics, dissolution and bioavailabililty with the possible roles played by the formulation,
- the influence of agglomeration on dissolution,
- the role of impurities in the crystallization process.

In the last part of the lecture, we shall briefly address the case of amorphous phases. These are more or less systematically present in the crystalline phases at every step following the crystallization of an AI or an excipient (filtration, drying, milling, etc…) Taking their high level of energy into account, they may be detrimental for the PDF developed. Then, it may be necessary to quantify the crystallinity (or conversely the amorphous content) of the powders, but amorphous phases and / or solid solutions of AI's can be used in a positive way to improve the dissolution / bioavailability of a poorly soluble drugs. We shall briefly discuss the case of two dielectric techniques (thermostimulated current and dynamic dielectric spectroscopies) which allow the measure of the amorphous content in the first case and the assessment of the physical state of an AI in its formulation in the second case.