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POLYMORPHISM OF PHARMACEUTICALS – SIGNIFICANCE AND SELECTED IDENTIFICATION METHODS

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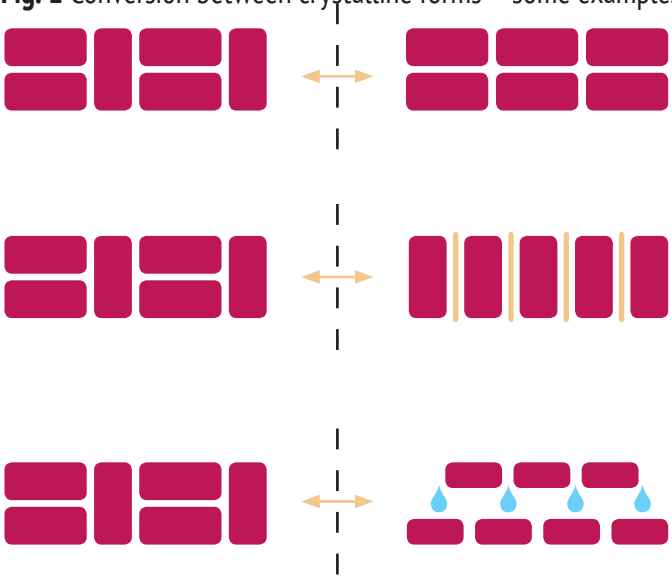
The pharmaceutical industry is a special field, where all stages have to be performed with utmost precision. Even the slightest step has to be carefully planned and documented. Risk assessment allows for avoiding serious problems at further stages of drug production, when consequences of errors may be already irreversible. One of situations that have to be considered at the developmental stage of a pharmaceutical is the occurrence of adverse polymorphic form of active pharmaceutical ingredient (API).

Polymorphism is an ability of a solid substance to occur in at least two crystalline forms. The phenomenon depends on thermal history of a material, and therefore various polymorphic forms of the same substance happen to be present in a single pharmaceutical product.

Uncontrolled transitions of polymorphic forms of API may occur during nearly all engineering processes, and even during storage of tablets. The following factors may influence development of polymorphisms: a type of solvent, the level of dispersion of mixture ingredients, crystallization temperature, cooling rate, presence of impurities, mixing and solution saturation level. It is estimated that over 50% API used in the pharmaceutical industry are present in more than one crystalline form.

Fig. 1 Conversion between crystalline forms – some examples:



During engineering processes one crystalline form may be transformed into another, more thermodynamically stable one.

Dissolution of solids may be associated with a phenomenon of pseudopolymorphism – that is formation of various cystalographic forms of the same substance with a solvent incorporating into the crystalline structure. The process leads to formation of solvates.

Hydrates are a particular case of pseudopolymorphism. They are formed when water molecules are incorporated into a crystalline structure, for example by absorption of steam.

Knowledge of properties of polymorphic API and of some additional substances at the early stage of development of a pharmaceutical product helps avoid numerous errors both during production and authorization of a medicinal substance, and also ensures its best quality and activity, and optimized physical properties.

The currently valid process of marketing authorization of a generic drug involves an obligatory API polymorphism analysis. It happens that a particular polymorphic form of a drug is patented by its primary manufacturer. Early analysis of polymorphisms allows for avoiding problems associated with violation of patent rights of another company.

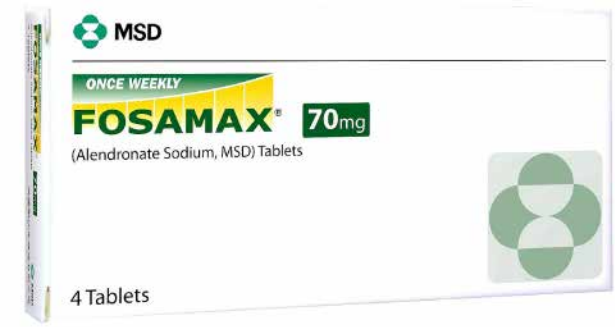
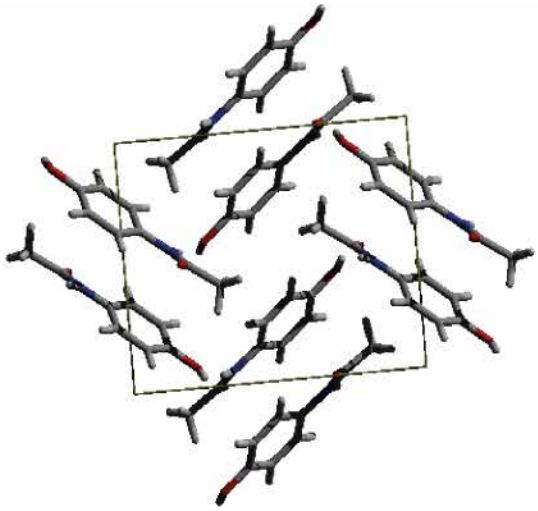


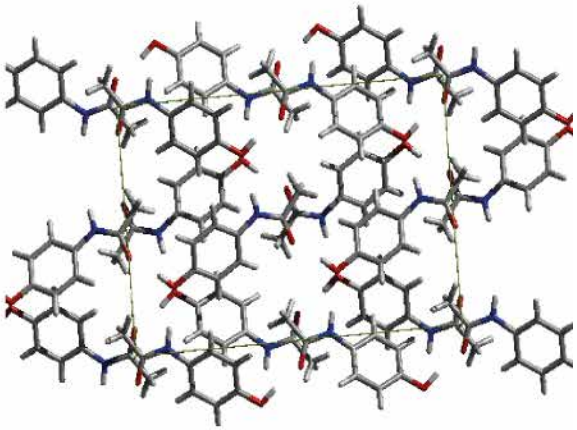
Photo 1 Fosamax (alendronic acid) – a drug first marketed by Merck. A competitor introduced another polymorphic form before expiration of the patent owned by Merck. [1]

Additionally, as a result of different arrangement of molecules, crystals may demonstrate different properties, including physical and chemical stability, hygroscopic properties, susceptibility to decomposition by light, melting point, hardness, solubility and solubility rate, or susceptibility to the tablet-formation process. Therefore, the choice of an appropriate polymorphic form at the stage of product development affects not only hygroscopic properties and final stability of a product, but also its bioavailability (most often associated with lower solubility) and toxicity of a drug.

Here is an example of the most commonly used analgesic drug – paracetamol [2]. The first form is significantly more thermodynamically stable at room temperature, compared to the second form. However the polymorph possessing the rhomboidal structure may be directly formed into tablets, and the askew form requires previous granulation, which increases engineering costs.



Rys. 2 Forma I



Rys. 3 Forma II

The great significance of polymorphism diagnostics in development of a pharmaceutical product was learned by scientists working for Abbott. The company introduced Norvir (ritonavir) – a protease inhibitor used in therapy of AIDS. Eighteen months later, in course of the post-marketing pharmacovigilance, it turned out that the used polymorphic form, despite its greater thermodynamic stability, was poorly soluble and was easily precipitated from solution, which resulted in significant loss of the drug bioavailability [3]. Although the company preformed re-formulation of the product and changed conditions of its manufacture, it incurred serious financial losses.

The phenomenon of polymorphism is also associated with excipients present in the solid form of a drug. Sorbitol – a commonly used excipient – may be an example. Only selected of its polymorphic forms may be formed into tablets, despite the fact that their physical properties are not greatly different.

SELECTED METHODS OF IDENTIFICATION OF POLYMORPHIC FORMS IN DRUGS

X-ray Diffraction

X-Ray diffraction analysis is one of the most popular methods used for the diagnostics of polymorphism. X-Ray Powder Diffraction (XRPD) is one form of that analysis. A powdered sample demonstrates a characteristic diffraction pattern with peaks at particular positions and of particular intensity. Based on that pattern it is possible to identify individual components of analyzed mixture. A diffractogram is unique for each polymorphic form, as it is a characteristic presentation of a substance demonstrating a particular packing.

The diffraction method is sensitive and precise. The technique allows for determination of quantitative composition of individual polymorphic forms in a given medicinal product.

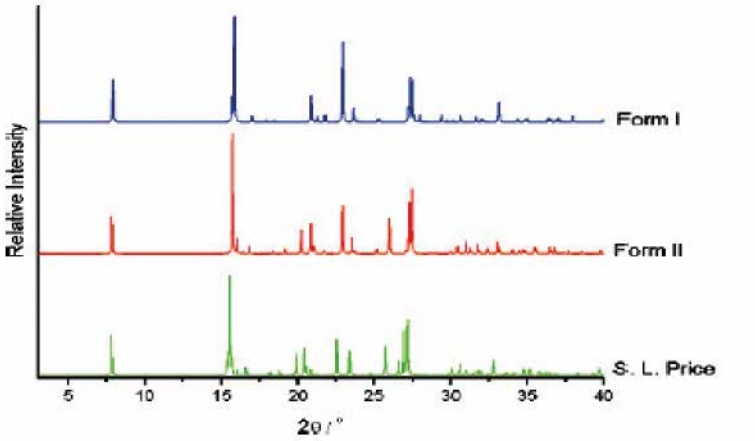


Fig. 4 Simulated powder diffractograms for individual polymorphic forms (forms I, II and II proposed by S.L. Price). An additional peak may be seen in the diffractogram of the form II and S.L. Price. The peak is located within 2Θ: 20 and 26°, compared to the diffraction image of the form I [2].

Raman spectroscopy (Raman effect)

Raman spectroscopy is a technique based on measurement of inelastic scattering of monochromatic light. Characteristic spectra enable identification of polymorphic forms. Raman spectroscopy is safe and requires no pre-processing of a sample. Moreover, by combination of a spectroscope and a confocal microscope, it is possible to present distribution of various polymorphic forms, e.g. on surface of a tablet.

IR spectroscopy

Infra-red spectroscopy is complementary to Raman spectroscopy. The technique allows for differentiation between anhydrous form of a substance and its solvate. Obtained spectra enable identification of polymorphic forms by comparison to data from database or a model.

Scanning Electron Microscopy

Those who would like to learn about differences between polymorphic forms may use scanning electron microscopy (SEM). High magnification and high resolution of image allow for determining the topography of a surface and types of crystals.

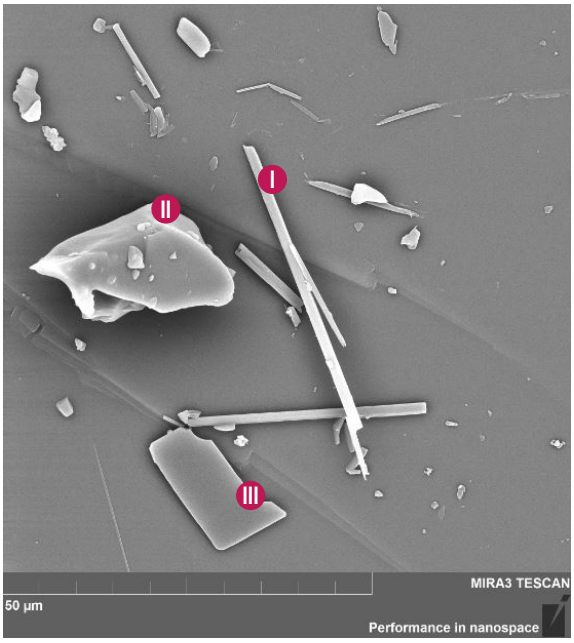


Photo 2 SEM images: three different polymorphic forms of the same substance. [4]

For greater confidence, the identification of polymorphic forms should be based on several complementary methods. The Jagiellonian Center of Innovation offers polymorphism analyses with all above-mentioned methods, as well as numerous additional analyses for the pharmaceutical industry, including chemical, biological, structural analyses, and drug form determination.

Literature:

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2. Sykuła A., Łodyga-Chrucińska E. 2006. Polimorfizm – jego wpływ na substancje farmaceutyczne, Zeszyty Naukowe Politechniki Łódzkiej, nr. 984
3. Stańczyk A., Stańczyk C. 2013. Polymorphism of pharmaceuticals, Lek w Polsce, vol 23 nr. 10
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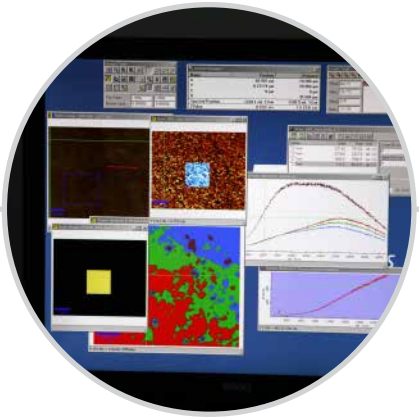

The Jagiellonian Center of Innovation was established in 2004 by the Jagiellonian University in Krakow with a view to developing and managing the infrastructure of the Life Science Park as well as providing a wide range of services to businesses and scientists engaged in life sciences. The JCI offering includes, among other things, rental of specialized laboratory space, capital support for innovative companies, contract research and clinical trial services, and a cosmetic production line.

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