Extended Abstract American Journal of Drug Delivery and Therapeutics 2021
Vol.8 No.3

Physical stability and drug crystallization in amorphous solid dispersions

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Abstract:
High-impact pharmaceutical drugs are constantly identified by (bio) medical research, with a high potential for the treatment of severe civilization diseases. However, such drugs often exhibit a very low solubility in water (and thus in biorelevant media). As they tend to crystallize during storage or after administration, they cannot be used for the development of the future-generation pharmaceuticals. Therefore, about 80% of the promising drugs currently under development never make it into a medicine. Several approaches exist to increase the bioavailability of drugs. Most of them aim at formulating the drug in a less-stable but better-soluble modification which is intended to be stabilized with the help of excipients, e.g. polymers. However, finding the right excipient for a given drug is quite difficult and today usually established by a “trialand- error” approach assisted by expensive high-throughput screening techniques. This results in tremendous costs for the development of advanced formulations and – when no appropriate formulation is found - even prevents a huge number of very promising drugs from being applied in a medicine at all. As pharmaceutical formulations usually have to be stored between manufacturing and use, it has moreover to be guaranteed, that their properties do not change during this period.

This is best ensured when they are thermodynamically stable, i.e. at drug concentrations being lower than the drug solubility in the formulation. The latter is to a great extend influenced by the kind of drug and excipients, by temperature, and by relative humidity. It will be shown that the influence of humidity on the drug solubility in ASDs as well as on their kinetic stability can be predicted using thermodynamic models (1-3, 5). This provides the information whether an ASD will crystallize (destabilize) at humid conditions or not. However, the investigation of crystallization kinetics is usually performed by timeconsuming long-term experiments with recurring investigations of crystallinity, e.g. by X-ray diffraction. In this work it will therefore also be demonstrated that the kinetics of drug crystallization in ASDs can be determined only based on simple water-sorption measurements combined with a state-of-the-art thermodynamic modeling of the drug solubility in polymers at humid conditions. The latter allows accounting for the mutual influence of water sorption and drug crystallization in the ASD and thus for simultaneously predicting the amount of absorbed water and crystallized drug. Knowing the experimental water sorption as function of time thus directly provides the ASD crystallinity without the need of additional X-ray measurements. Amorphous solid dispersions (ASDs) have been widely used in the pharmaceutical industry for solubility enhancement of poorly water-soluble drugs. The physical stability, however, remainsone of the most challenging issues for the formulation development. Many factors can affect the physical stability via different mechanisms, and therefore an in-depth understanding on these factors isrequired.

Pharmaceutical scientists are increasingly interested in amorphous drug formulations especially because of their higher dissolution rates. Consequently, the thorough characterization and analysis of these formulations are becoming more and more important for the pharmaceutical industry. Here, fluorescence-lifetime-imaging microscopy (FLIM) was used to monitor the crystallization of an amorphous pharmaceutical compound, indomethacin. Initially, we identified different solid indomethacin forms, amorphous and γ- and α-crystalline, on the basis of their time-resolved fluorescence. All of the studied indomethacin forms showed biexponential decays with characteristic fluorescence lifetimes and amplitudes. Using this information, the crystallization of amorphous indomethacin upon storage in 60 °C was monitored for 10 days with FLIM. The progress of crystallization was detected as lifetime changes both in the FLIM images and in the fluorescence-decay curves extracted from the images. The fluorescence-lifetime amplitudes were used for quantitative analysis of the crystallization process. We also demonstrated that the fluorescence-lifetime distribution of the sample changed during crystallization, and when the sample was not moved between measuring times, the lifetime distribution could also be used for the analysis of the reaction kinetics. The recrystallization of amorphous solid dispersions may lead to a loss in the

dissolution rate, and consequently reduce bioavailability. The purpose of this work is to understand factors governing the recrystallization of amorphous drug-polymer solid dispersions, and develop a kinetics model capable of accurately predicting their physical stability.

Recrystallization kinetics was measured using differential scanning calorimetry for initially amorphous efavirenz-polyvinylpyrrolidone solid dispersions stored at controlled temperature and relative humidity. The experimental measurements were fitted by a new kinetic model to estimate the recrystallization rate constant and microscopic geometry of crystal growth. The new kinetics model was used to illustrate the governing factors of amorphous solid dispersions stability. Temperature was found to affect efavirenz recrystallization in an Arrhenius manner, while recrystallization rate constant was shown to increase linearly with relative humidity. Polymer content tremendously inhibited the recrystallization process by increasing the crystallization activation energy and decreasing the equilibrium crystallinity. The new kinetic model was validated by the good agreement between model fits and experiment measurements. A small increase in polyvinylpyrrolidone resulted in substantial stability enhancements of efavirenz amorphous solid dispersion. The new established kinetics model provided more accurate predictions than the Avrami equation.