Why Thermal Analysis is Not Relevant for Storage Stability

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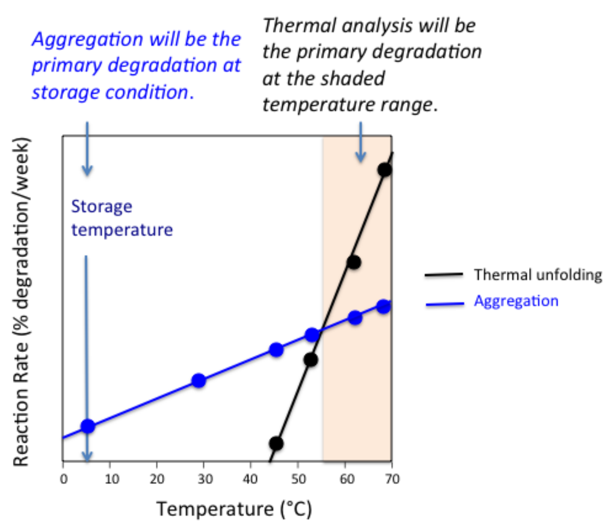
Proteins are molecules of delicate three-dimensional structures that are made of unique primary, secondary, tertiary, and even quaternary structures. Because of this, different proteins may be susceptible to different stresses during normal pharmaceutical operations such as process, manufacturing, storage, transportation, and delivery. Therefore, it is important to understand what the relevant stresses for each individual protein are. Heat, cold, agitation, shear, surface, freezing, dehydration, and light are examples of relevant physical stresses. Metal ions, destabilizing impurities, pH, active oxygen species, and free radicals are examples of some chemical stresses. The stresses introduced for formulation development studies have to be relevant to what the product will experience in real life.

For example, thermal unfolding is not relevant for the storage stability of proteins. Please take a look at the Figure below which represents what happens during the stability study of most proteins. The black line represents the unfolding of the secondary structure of proteins analyzed by thermal analysis (DSC).

Literature tells that the activation energy (temperature dependency of a reaction, the higher the more dependent) is around 100 Kcal/mole and is very temperature dependent. On the other hand, for most degradations observed during routine stability studies (5-40°C), the activation energy is only around 25-35 Kcal/mole (blue line).



When the stability of proteins is analyzed at the shaded area (55°C or higher), the thermal unfolding is the predominant degradation. However, the aggregation of partially unfolded species, real problem that we observed at actual storage (5-25°C), will not be observed due to the aggregation of completely denatured species.

Interestingly, the thermal unfolding never occurs at real storage condition. In other words, we may end up solving a problem that never occurs in real life if our decision is based on thermal analysis data. This is the reason why accelerated stability studies have to be done at temperatures below 45°C where the real problems are outstanding (unshaded area where blue line is greater than black line). Yes, it may take several months to collect sufficient amount of degradation products at temperatures below 45°C, but it is the only way to gather most relevant results.

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