Automated Chemical & Physical Stability Testing

Introduction

During the last decade, the physical properties of new drug candidates have become more and more challenging. A significant number of new drug candidates have poor water solubility and it is a considerable challenge to convert these active pharmaceutical ingredients (api) into a formulated product. One key element for successful formulation development of poorly soluble compounds is a profound knowledge of the physical and chemical properties and stability of drug candidates in their pure and formulated states.

Over the past years, RPD TOOL has developed a comprehensive set of workflows, hard- and software tools as well as dedicated consumables for supporting formulation R & D, taking into account the challenges resulting from the physical properties of new drug candidates.

One example is our automated ***Storage Stability Workflow*** *under normal and accelerated conditions which provides the analytical data required to:*

- *Understand the chemical degradation pathways of the drug substance.*
- *Understand the physical stability of the drug substance.*
- *Aid in developing the api specification including storage condition.*
- *Provide data for shelf-live estimation of the drug substance.*

Workflow

Our standardised storage stability workflows can be automatically performed on our dedicated platforms ***StabScreen xHTS, SpecScreen xHTS*** *and/or* ***ChromScreen xHTS****. Additional softarwe packages automatically apply user pre-defined assessment rules to the generated analytical data and provide the user with an evaluation report of the test samples stored on the system.*

Using our approach, the storage stability workflow starts with the production of a set of formulation candidates which are then stored under normal and more challenging conditions. While the data generated from samples stored under accelerated - but not unrealistically severe - conditions enables an initial indication of api shelf-life, the results from samples stored under normal conditions can subsequently be used to verify and to increase the precision of the shelf-live.

specification. Table 1 shows an overview of typical storage conditions:

Temperature	Humidity	Storage time	Analysis
40 °C	*0, 25, 65, 75% RH*	*0, 4, 12, 26 weeks*	*Chem. & phys. stability*
30 °C	*0, 35, 65, 75% RH*	*0, 4, 12, 26, 52 weeks*	*Chem. & phys. stability*
25 °C	*0, 40, 60, 75, 85% RH*	*0, 4, 12, 26, 52 weeks*	*Chem. & phys. stability*
5 °C	*dry*	*0, 4, 12, 26, 52 weeks*	*Chem. & phys. stability*
-20 °C	*dry*	*0, 4, 12, 26, 52 weeks*	*Chem. & phys. stability*

Table 1: RPD TOOL's standard storage conditions for storage stability studies.

Physical storage stability

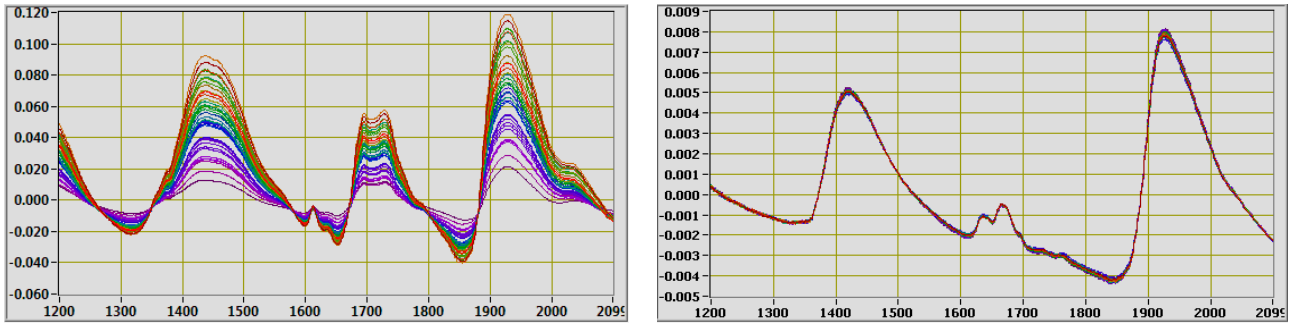
The physical properties of drug substances during storage can be changed by the following factors:

- *hygroscopic behaviour,*
- *morphological transformation of the drug,*
- *changes in visual appearance (e.g. discolouration at elevated temperature),*
- *changes in particle size distribution of the drug.*

In order to provide information about the physical storage stability of the drug and formulation candidates as early as possible, RPD TOOL has developed a set of non-destructive techniques which can be applied periodically to the stored samples.

Hygroscopicity

Near infrared spectroscopy (NIR) is a powerful technique for monitoring the water uptake kinetic and equilibration level in the samples stored under different conditions. Plot 1 shows an overlay of NIR spectra of hygroscopic and non-hygroscopic test samples stored at enhanced humidity, while Table 2 on the following page shows water content found for 10 formulation candidates stored under different conditions:



Plot 1: Overlay of NIR spectra of a hygroscopic (left) and a non-hygroscopic test sample (right). Blue: The rainbow colour of the spectra represents its chronological order from purple (beginning of storage) to red (end of storage). X-axis: Wavelength [nm]. Y-axis: Absorbance.

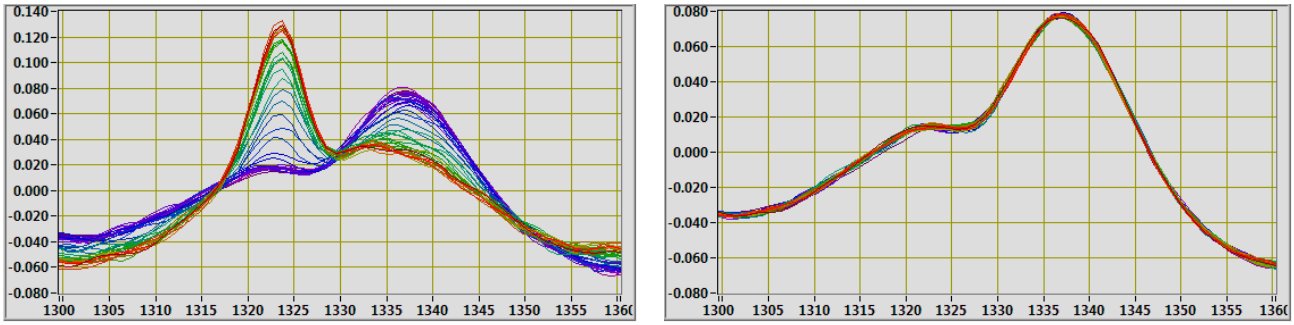
Formulation no.	20°C/dry	24°C/65% RH	40°C/dry	40°C/75% RH
1	0.1 %	0.5 %	0.1 %	0.8 %
2	0.1 %	1.0 %	0.1 %	1.5 %
3	0.2 %	0.2 %	0.2 %	0.4 %
4	0.1 %	0.4 %	0.1 %	0.6 %
5	0.1 %	2.5 %	0.1 %	3.5 %
6	0.1 %	5.0 %	0.1 %	7.0 %
7	0.2 %	0.5 %	0.2 %	0.9 %
8	0.1 %	0.1 %	0.1 %	0.3 %
9	0.5 %	10 %	0.4 %	8.0 %
10	0.1 %	0.1 %	0.1 %	0.2 %

Table 2: Water content at equilibrium state for 10 formulation candidates stored under different conditions.

In addition to the water content at equilibrium state, the water uptake kinetic can be calculated for each sample from the NIR spectra set if required. The kinetic profile of the water uptake can for example be used to provide recommendations about drug substance handling or to distinguish between unspecific water uptake and hydrate formation.

Morphological and pseudomorphological transformations

Due to the fact that the solid state has a direct impact on a drug substance's performance, bioavailability and chemical stability, a profound knowledge of the morphological and pseudomorphological stability of a drug substance in pure or formulated form is essential (cf. also ICH Q6A guideline). RPD TOOL monitors the (pseudo)morphological stability of drug and formulation candidates by periodic automated Raman spectra acquisition and analysis during storage of the drug substance and formulation candidates under different conditions. If necessary, XRPD spectra are additionally taken at selected time intervals. Plot 2 shows an overlay of Raman spectra acquired from a test sample with (left) and without (right) morphological change during storage.



Plot 2: Overlay of Raman spectra taken from a sample with (left) and without (right) morphological change during storage. The rainbow colour of the spectra represents its chronological order from purple (beginning of storage) to red (end of storage). X-axis: Wave number [cm^{-1}]: Y-axis: Raman intensity.

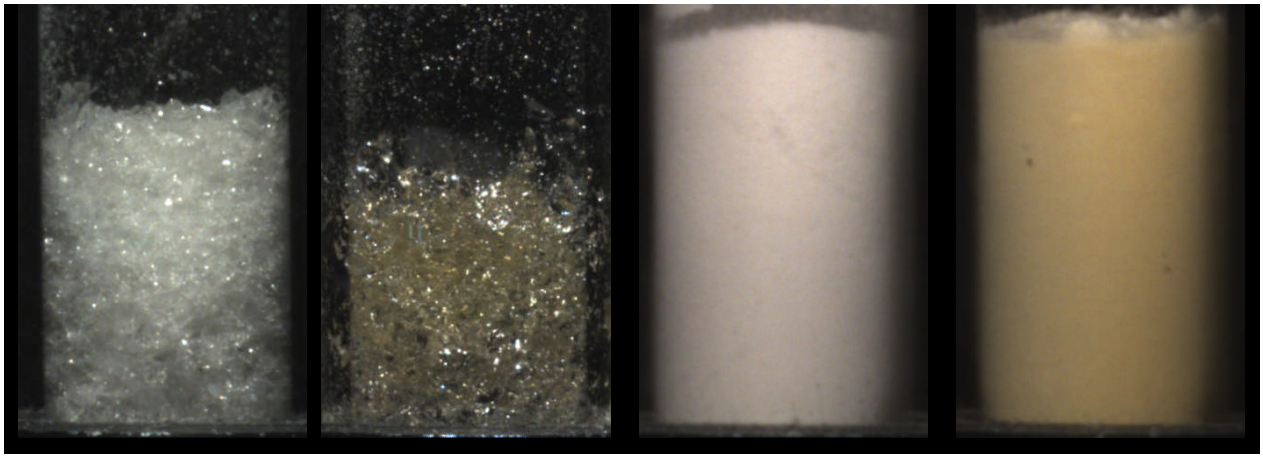
Our automated spectra analysis software automatically performs first level data evaluation including classification of the (pseudo)morphological stability of the formulation candidates into unstable (red), critical (orange) and stable (green) in respect of the corresponding storage conditions. Table 3 shows an example of the analysis of the Raman spectra sets generated during a four-week storage study from three formulation candidates stored under four different conditions.

Formulation no.	Storage condition	Week 1	Week 2	Week 3	Week 4
1	25°C/dry				
	25°C/60%RH				
	40°C/dry				
	40°C/75%RH				
2	25°C/dry				
	25°C/60%RH				
	40°C/dry				
	40°C/75%RH				
3	25°C/dry				
	25°C/60%RH				
	40°C/dry				
	40°C/75%RH				

Table 2: Classification into stable (green), critical (orange) and unstable (red) of the (pseudo)morphological stability of three formulation candidates stored for four weeks under different conditions

Visual appearance

Periodic picture acquisition under reproducible illumination with defined amplification guarantees the identification of changes in visual appearance, such as discoloration, changes in optical surface properties, etc.). The following Plot 3 shows an example of discoloration caused by chemical degradation during four weeks' storage:



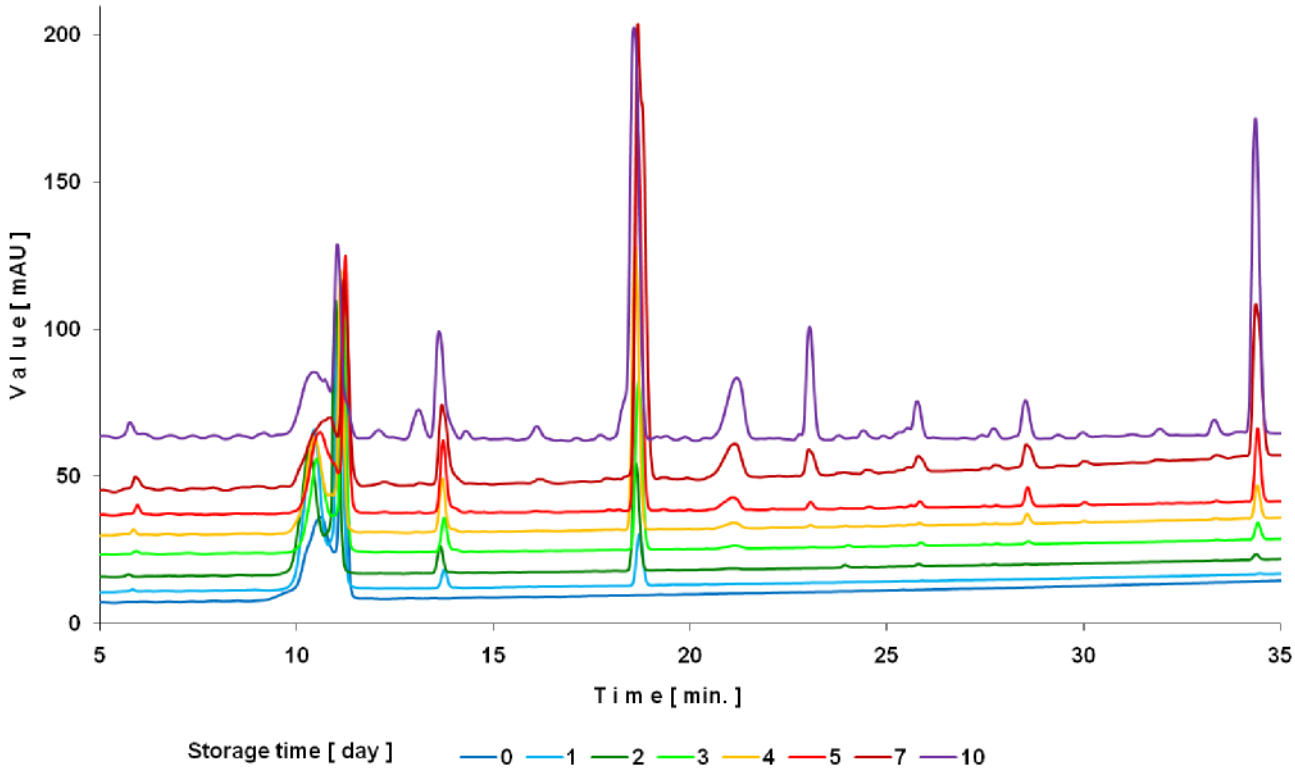
Plot 3: Pictures of two formulation candidates generated during four weeks' storage. From left to right: Solid disperse formulation prior to and after storage, powder mixture prior to and after storage.

Particle size distribution, solubility and solubilisation rate

Complementary to the above-mentioned non-destructive techniques, additional destructive physical analyses of the stored samples can be performed after different storage times (i.e. 2 weeks, 1, 2, 6 months). Examples of these are the determination of particle size distribution in order to investigate crystal growth or agglomeration of the drug substance or determination of solubility and solubilisation rate as an important application test for drug substances.

Chemical storage stability

The determination of chemical storage stability is performed by fully or semi-automated chromatographic analysis (HPLC/UV or HPLC/MS) of test samples after different storage times. The chromatographic sample preparation stage consists of sample solvent extraction, removal of non-dissolved solids and, if required, dilution to the final concentration. Solvent extraction is performed with our extraction module and guarantees smooth, fast and complete dissolving/extraction of the drug substance from the formulation matrix. After extraction, the non-dissolved solid residues are removed by centrifugation and/or filtration. If required, a dilution stage for the clear solution completes the chromatographic sample preparation. For all stages of sample preparation, dedicated consumables are available and eliminate any risk of cross contamination. The chromatograms of Plot 4 of formulation samples analysed after 0, 1, 3, and 6 months' storage show the formation of several by-products with retention times of approximately 4.8, 23.5 and 24 min during storage.



Plot 4: Overlay of chromatograms of a test sample stored at 70°C/75% RH

Benefit

Regardless of whether you are looking for a fully or semi-automated approach to performing your storage stability studies, our hardware and consumables can significantly improve the efficiency of your storage stability workflow: Based on the experience gained during years of analytical services as well as from feedback from leading pharmaceutical companies, we are convinced that among others the following benefits are most relevant and can be achieved in all labs focused on formulation research and development:

- ***Quality improvement**: The analytical data generated on our fully-automated system sets a new standard in the reproducibility of different analysis methods compared with classical manual operation. In addition to improved data quality, our automated tools produce up to 50 % more analytical data than usually generated with classical manual operation.*

  For customers with lower sample throughput, we can also demonstrate that the semi-automated approach with our consumables and tools still enables a significant improvement in data quality and quantity compared with manual operation, even though not to the same extent as for a fully-automated system.

  It is obvious that the systematic improvement of data quality and quantity during formulation R & D activities finally leads to an improvement in product quality of the market formulation.
- ***Time saving**: Acceleration of drug development, regardless of whether the fully or semi-automated approach is being used. The use of our consumables, hardware and software eliminates or reduces the need for human intervention and makes it possible to perform several development activities in parallel. These improvements make it possible to cut the time required for formulation development by approximately 50 %.*
- ***Cost reduction**: A significant reduction in analytical costs generated during formulation R & D can be achieved with our tools and consumables. For the semi-automated approach, a cost reduction of >20 % compared with manual operation can expected. Using the fully-automated version of our storage stability system, a cost reduction of up to 70 % is achievable.*

We would be pleased to share the above-mentioned benefits with you and to discuss your requirements in more detail. Please do not hesitate to contact us for further details of our unique tools for the assessment of the chemical and physical storage stability of new drugs and formulation candidates.

Your RPD TOOL Team.