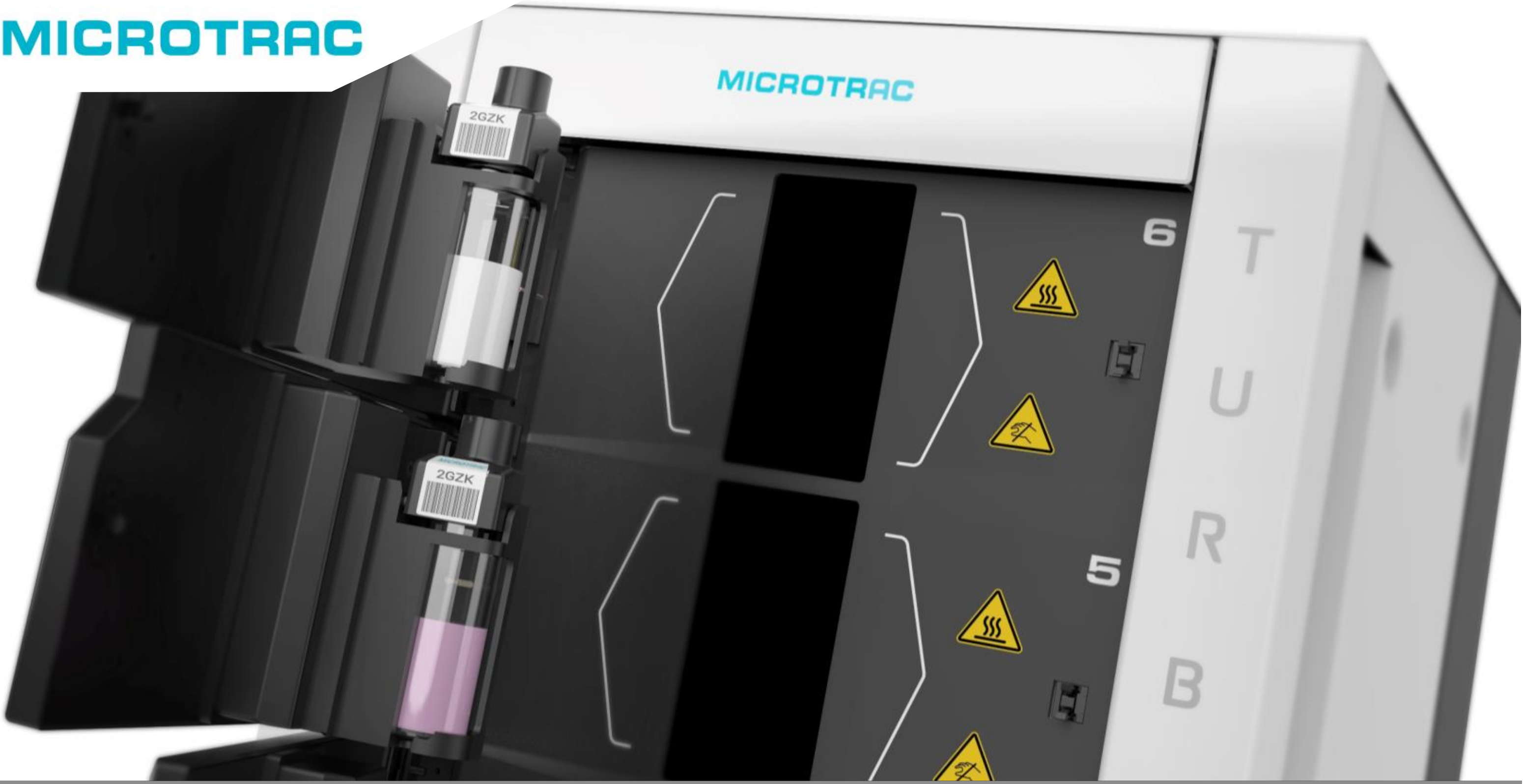


SHELF-LIFE PREDICTION BY TURBISCAN
Method & Case Study

Context

Shelf-life is an essential parameter to guarantee product performance, quality, and safety over its lifetime. Predicting shelf-life based on early data acquisition or by accelerating the destabilization process is one of the main challenges of new product development. Shelf-life prediction is a complex topic that associates accelerated stability testing (temperature, mechanical stress) and data extrapolation based on mathematical models. This note covers and explains how shelf-life can be predicted using the TURBISCAN technology based on the **ISO/TR13097**.

What is Shelf-life and stability?

The technical Report ISO/TR 13097, Guidelines for the characterization of dispersion stability, addresses most questions around stability testing & prediction and gives recommendations about tests. According to **ISO/TR 13097**, shelf-life is defined as "the recommended period during which a product can be stored, throughout which the defined quality of a specified property of the product remains acceptable under expected (or specified) conditions of distribution, storage display, and use." In other words, a dispersion is considered stable if its properties remain within an acceptable range at storage conditions.

Most commonly, shelf-life is determined by bottle tests and visual observation. These tests are practical and simple but can take a long time and depend on the operator, causing long "GO/NO GO" decisions on product and process development.

Accelerated Stability Tests

A variety of test methods exist, here are the recommendations of ISO/TR13097 for the ideal test method.

Instrumental direct methods

Instrumental methods are **objective** and **traceable** and are preferred. Additionally, they detect destabilization far earlier than conventional visual observation, and "these methods can be used for measuring shelf-life" thanks to their high sensitivity and reproducibility.

Furthermore, the ISO/TR13097 recommends working on the **native state**: non-diluted & non-perturbated and so "to select a method that does not require sample preparation, so that the sample is analyzed in its original state".

Accelerated methods

Different methods can be categorized as follows:

- Thermal acceleration: storing and testing the stability at higher temperatures (usually between 25°C and 50°C) or by using thermal cycles.
- Mechanical acceleration: use of centrifugation or vibration to test the product.
- Physico-chemical perturbation: adding substances (solvent, acid..) to vary sample composition and test the resistance to this change.

Accelerated studies should be done with caution considering "its limits and its correlation to normal shelf-life conditions and/or typical usage".

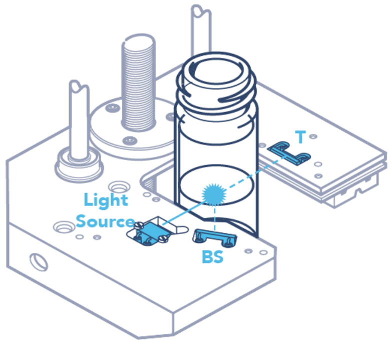
Thermal acceleration is the most used method with the benefit of studying stability in storage and shipping conditions.

Mechanical stress is artificial and non-realistic stress. It can induce additional phenomena that are not observed under normal conditions (especially on non-Newtonian samples) and despite the efficiency of quickly separating the dispersion, the stability estimation may be unrealistic [1][2].

TURBISCAN technology

TURBISCAN technology, based on **Static Multiple Light Scattering (SMLS)** is the leading technology for **direct dispersions stability testing**.TURBISCAN meets ISO/TR13097 recommendations by using optical scanning that quantifies and studies dispersions in their **native state** enabling **thermal acceleration** when needed.

SMLS technology consists of sending light pulses (at 880nm) into a sample to measure the amount of scattered light (Transmission and Backscattering). The reading head moves vertically along the sample cell and acquires the signal every 20µm. Measurements are made over time and variations in the backscattering and transmission levels, due to sample instability, are recorded. The signal is directly linked to the evolution of particle concentration (φ) and size (d) by the Mie theory.



$$BS = f\ (\varphi, d, np, nf)$$

Figure 1. TURBISCAN measurement head

TURBISCAN monitors any changes in physical stability (coalescence, creaming, sedimentation, phase separation...) up to 200x faster than the naked eye and without any dilution.

The **TSI** (TURBISCAN Stability Index) is an automatic calculation directly implemented in the software that sums all destabilizations into a single number. Therefore, the higher the TSI value, the more unstable the product (for more information, download the application note 0220_F_TURBISCAN).

Shelf-life prediction

To determine or predict shelf-life, the essential points are the stability **metric** and the stability **criteria**. The most common stability metric is the overall product visual homogeneity, and its criteria is whether it is a visible or invisible destabilization. A visual loss of homogeneity will highly impact product perception and most likely its properties: UV-protection of sunscreen, vaccine efficiency, wall coverage of paint, flavor in beverages…

How to predict shelf-life based on stability metrics?

The ISO/TR13097 specifies two main routes for shelf-life prediction: **comparative** and **predictive studies**.

The **predictive studies** consist of modeling and extrapolating the data (linear, log, polynomial…) to check if the stability metric remains within the stability criteria for the desired amount of time.

However, even though theoretical models are available to predict some stabilizing properties such as colloidal interactions (DLVO) or migration behavior (Stokes prediction yield stress and rheological assessment), they are not currently well adapted to predict stabilizing behavior of complex systems resulting from multiple parameters, often non described by theory (non-DLVO forces). In that way, using such methods to predict the stability of real dispersions can lead to important misleading results.

On the other hand, comparative studies consist of comparing the evolution of the stability metric with a reference sample (similar formulation or a benchmark with known stability or shelf-life). This approach is very robust, does not require strong mathematical extrapolation, and can be applied to all types of dispersions. It is the most pragmatic, fast, and secure method to achieve shelf-life prediction.

Shelf-life prediction by TURBISCAN Case Study

Seven formulations with different surfactants were analyzed with the TURBISCAN to predict their shelf-life after 3 months at 40°C. The samples are directly transferred in the vials, without any sample preparation, and analyzed for 7 days at 40°C at rest. The evolution of global stability is followed by the TSI. The higher the value, the lower the stability. The TSI kinetic is compared to a reference sample, known, and considered as stable, i.e., passing the 3 month visual test at 40°C.

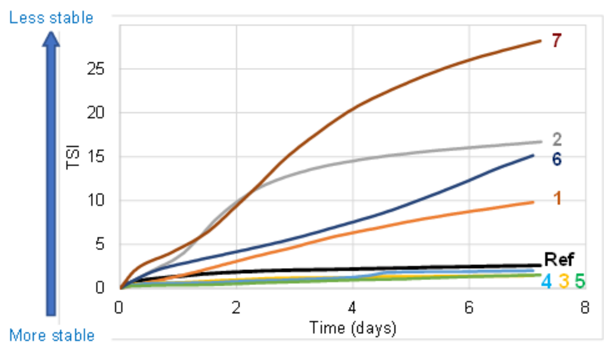


Figure 2. TSI kinetics with TURBISCAN

From this graph, we can classify the sample in two categories in function of their TSI kinetic compared to the reference sample:

X Samples having a **faster** TSI evolution: 7-2-6-1

The stability of these samples is evolving faster and will have a lower stability than the reference sample

✓ Samples having a **slower** TSI evolution: 4-3-5

The Stability of these samples is evolving slower than the reference and will have stability better or, in the worst-case scenario, as good as. We can easily predict these samples will **pass** the 3 months stability test.

This conclusion is obtained based on 7 days measurement and a similar conclusion could have been made after only 2 days versus 3 months based on visual observation.

The TSI is a perfect candidate as a replacement for the current stability metric: it plots the **entire** stability evolution of the sample as a function of time and is a quantifiable, operator-independent

parameter that can be calculated in just one click.

CONCLUSION

To accelerate the stability studies, the TURBISCAN approach is to associate :

- The extreme sensitivity of the **SMLS technology**
- Work on the **native sample** without any additional stress
- Use the **thermal stress** to accelerate even more the stability measurement and/or to simulate shipping and storage conditions **Predict the shelf-life** based on comparison with a reference product

For all these reasons, the TURBISCAN has been the leading technology, since 1994, to measure real stability of formulation and dispersion and fully complies with ISO TR13097.

[1] **DJ. McClement et Al. Critical review of Techniques and Methodologies for Characterization of Emulsion Stability.**

[2] **P. Snabre et al. Size Segregation in a Fluid-Like or Gel-Like Suspension Settling under Gravity or in a Centrifuge.**