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Guidelines for the characterization of dispersion stability

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National foreword

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**Guidelines for the characterization of
dispersion stability**

Lignes directrices pour la caractérisation de la stabilité des dispersions



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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
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Foreword

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The committee responsible for this document is ISO/TC 24, *Particle characterization including sieving*, Subcommittee SC 4, *Particle characterization*.

Introduction

Stability with respect to changes in relevant product specifications and product performance is important in industry and for end users.

Various terminologies are used to reflect different phenomena as well as different user perspectives. In the literature and in practice, one frequently finds terms such as dispersion, suspension or emulsion stability, demixing or separation stability, sedimentation or creaming stability, physical stability, colloidal stability, and kinetic stability.

This Technical Report focuses on instability driven by thermodynamics and does not include phenomena that are due to, e.g., radiation, chemical or enzymatic reactions¹⁾ or are related to the growth/metabolism of biological organisms like bacteria. These phenomena are often described as photo, UV or irradiation stability, thermal or chemical stability of one or the other constituent, enzymatic or microbial stability, etc.

The Technical Report concerns general aspects of stability test methods, acceleration procedures and data evaluation. In addition, recommendations of instrument manufacturer, information from the scientific or user community as well as from regulatory bodies are intended to be taken into account.

1) Chemical and physical properties are often interrelated.

Guidelines for the characterization of dispersion stability

1 Scope

This Technical Report addresses the stability characterization of liquid dispersions (suspensions, emulsions, foams and mixtures thereof) for applications, such as new product design, optimization of existing products, quality control during processing and during usage of the product. The stability of a dispersion in the sense of this Technical Report is defined in terms of the change in one or more physical properties over a given time period. Stability can be either monitored (determined) in real time or predicted on the basis of physical quantities related to stability. In the case of very stable dispersions, procedures that accelerate the changes under consideration or accelerated aging tests administered over a shorter time scale can be appropriate. Shelf life can be estimated based on the observed rate of the change in the physical property and the user-required specifications for the product. Guidelines are given for choosing relevant measurements that can be used for the ranking, identification and quantification of instability.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

2.1

agglomeration

assembly of particles in a dispersed system into loosely coherent structures that are held together by weak physical interactions

Note 1 to entry: Agglomeration is a reversible process.

Note 2 to entry: Synonymous with coagulation and flocculation.

[SOURCE: ISO 14887:2000,¹ 3.1, modified — text altered; IUPAC Gold Book,² modified]

2.2

aggregation

assembly of particles into rigidly joined structures

Note 1 to entry: Aggregation is an irreversible process.

Note 2 to entry: The forces holding an aggregate together are strong, for example covalent bonds or those resulting from sintering or complex physical entanglement.

Note 3 to entry: In common use, the terms aggregation and agglomeration are often applied interchangeably.

[SOURCE: ISO 14887:2000,¹ 3.2, modified — text has been altered; ISO 26824³]

2.3

coalescence

disappearance of the boundary between two particles (usually droplets or bubbles) in contact, or between one of these and a bulk phase followed by changes of shape leading to a reduction of the total surface area

Note 1 to entry: The flocculation of an emulsion, namely the formation of aggregates, may be followed by coalescence.

[SOURCE: IUPAC Gold Book²]

2.4 creaming

rise (separation) of the dispersed phase in an emulsion due to the lower density of the dispersed phase (droplets) compared to the continuous phase

Note 1 to entry: Creaming velocity has a negative sign as particle movement is opposite to the acting force.

2.5 dispersion

in general, microscopic multi-phase system in which discontinuities of any state (solid, liquid or gas: discontinuous phase) are dispersed in a continuous phase of a different composition or state

Note 1 to entry: If solid particles are dispersed in a liquid, the dispersion is referred to as a suspension. If the dispersion consists of two or more liquid phases, it is termed an emulsion. A suspoemulsion consists of both solid and liquid phases dispersed in a continuous liquid phase.

[SOURCE: Hackley *et al.*⁴; IUPAC Gold Book,² modified]

2.6 dispersion stability

ability to resist change or variation in the initial properties (state) of a dispersion over time, in other words, the quality of a dispersion in being free from alterations over a given time scale

Note 1 to entry: In this context, for instance agglomeration or creaming represents a loss of dispersion stability.

[SOURCE: IUPAC Gold Book²]

2.7 flocculation

assembly of particles in a dispersed system into loosely coherent structures that are held together by weak physical interactions

Note 1 to entry: The term flocculation is used frequently to denote agglomeration facilitated by the addition of a flocculating agent (e.g. a polyelectrolyte).

Note 2 to entry: See 2.1.

2.8 flotation

migration of a dispersed solid phase to the top of a liquid continuous phase, when the effective particle density is lower relative to the continuous phase density

Note 1 to entry: It may be facilitated by adhering gas bubbles, for example dissolved air flotation, or the application of lipophilic surfactants (e.g. in ore processing).

2.9 particle

minute piece of matter with defined physical boundaries

Note 1 to entry: A physical boundary may also be described as an interface.

Note 2 to entry: A particle may move as a unit.

[SOURCE: ISO 14644-5:2004,⁵ 3.1.7, modified — Note 1 is different and Note 2 has been added; ISO/TS 27687:2008,⁶ modified — Notes 1 and 2 have been altered and Note 3 has been deleted.]

2.10 Ostwald ripening

dissolution of small particles and the redeposition of the dissolved species on the surfaces of larger particles

Note 1 to entry: The process occurs because smaller particles have a higher surface energy, hence higher total Gibbs energy, than larger particles, giving rise to an apparent higher solubility.

[SOURCE: IUPAC Gold Book²]

2.11

phase inversion

phenomenon whereby the phases of a liquid-liquid dispersion (emulsion) interchange such that the dispersed phase spontaneously inverts to become the continuous phase and vice versa, under conditions determined by the system properties, volume ratio and energy input

[SOURCE: Yeo *et al.*⁷]

2.12

phase separation

process by which a macroscopically homogeneous suspension, emulsion or foam separates into two or more new phases

[SOURCE: Yeo *et al.*⁷]

2.13

sedimentation

settling (separation) of the dispersed phase due to the higher density of the dispersed particles compared to the continuous phase. The accumulation of the dispersed phase at the bottom of the container is evidence that sedimentation has taken place

Note 1 to entry: In the case of a dispersed liquid (emulsion), droplets can sediment if their density is higher than that of the continuous liquid phase (e.g. water in oil emulsion).

[SOURCE: IUPAC Gold Book²]

2.14

shelf life

recommended time period during which a product (dispersion) 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 usage

[SOURCE: Gyeszly⁸]

3 Basics of stability

3.1 Stability — Summary

Stability is the capacity of a dispersion to remain unchanged with respect to predefined stability criteria over a given time under stated or reasonably expected conditions of storage and use. It depends therefore on the application. For instance a cosmetic emulsion may be considered stable if no oil phase formation is observed during a period of three years. On the other hand, natural fruit juice can exhibit pulp settling without any reduction in quality. There is no universal method or technique to quantify all stability aspects due to the complexity of stability related phenomena. Therefore, it is always necessary to define:

- a) stability metrics: properties of the state or behaviour of a dispersion which should be monitored according to the demanded specific product qualities.
- b) stability criteria: deviations from the initial properties at production date, which are acceptable.

Shelf life is defined in terms of the alteration of stability metrics. In general, faster alteration leads to shorter shelf life.

In order to meet the predefined stability criteria of very stable products, analytical techniques having high resolution/sensitivity need to be used and procedures can be required in order to accelerate the alteration. However, because of the interrelated physical, physico-chemical and chemical properties of a liquid dispersion, adequate acceleration methods should be chosen and validated in the context of a specific product.

3.2 Characteristic features with regard to dispersion stability

Generally speaking, dispersions are thermodynamically unstable.^[9] However, for a dispersed system, the rate of change in its state may be acceptably low and therefore it exhibits kinetic stability. Kinetic stability may be improved by electrostatic, steric or electrosteric stabilization, or particle coating, as well as by pickering or rheological additives to the continuous phase.

The state of dispersion stability depends upon numerous interrelated physical, physico-chemical and chemical parameters, and its nature is therefore complex. The parameters may be categorized as follows:

- a) volume or mass concentration of dispersed phase (e.g. spatial homogeneity, diluted or concentrated);
- b) state of the continuous phase (e.g. density, viscosity, surface tension, chemical potential, quality of solvent);
- c) state of the dispersed phase (e.g. size, shape and density distribution, as well as viscosity of droplets, deformability of particles, structure of particulate surface);
- d) interaction between particles/droplets (e.g. electrostatic and van der Waals force, steric and depletion force);
- e) interaction between dispersed and continuous phase (e.g. wettability, interfacial tension, surface and volume rheology, solubility, dissolvability, network formation).

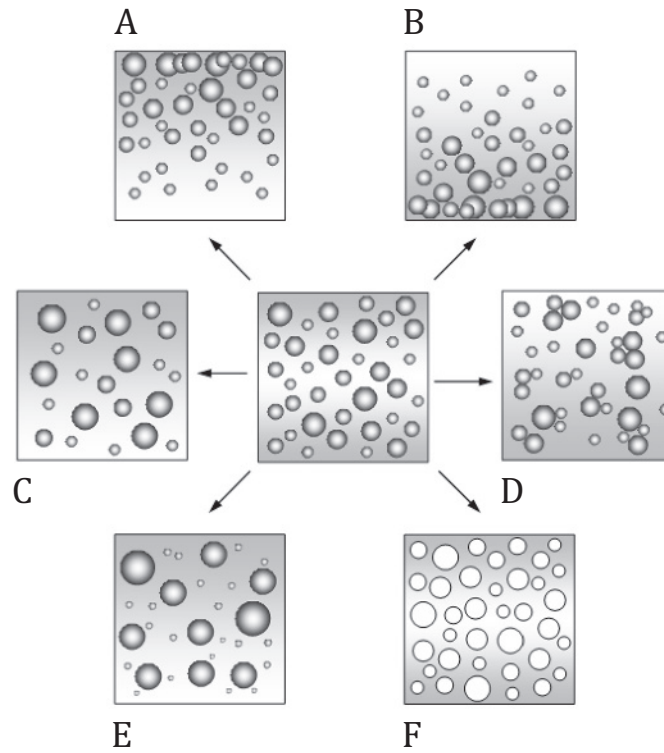
The volume concentration of the dispersed phase of a dispersion is one of the primary requirements of any product design and it should be homogenous within the entire product during the entire life span. In general, the higher the volume concentration, the higher the physical stability (e.g. less phase separation).

Formulators have to achieve product specifications and sufficient dispersion stability as demanded by the application or customer. This is accomplished by choosing the state of the dispersed phase (e.g. size distribution, shape, density match, restrictions to oversize, surface charge and coating) and the appropriate behaviour of the continuous phase. Traditionally, electrostatic stabilization has been principally used. Today, polymeric additives are commonly employed to tailor properties of the continuous phase of innovative products. Two essential aspects with regard to dispersion stability are particle-particle interactions and interactions between the dispersed and continuous phase. Tuning of particle interactions is an important tool to stabilize a dispersion. Electrostatic, steric and depletion stabilization or combinations of these are the most commonly used approaches. The theoretical foundation of these approaches is based on the classic DLVO (Derjaguin, Landau, Verwey, Overbeek) theory (see Overbeek^[10]) and more recently, the extended DLVO theory.^[11] In general, any specific interaction energy between two particles (e.g. double layer interaction, van der Waals attraction, steric interaction) is calculated as a function of the particle distance. The dependence on the distance is interaction specific. The different interaction energies are additive and the resulting energy-distance curve allows for stabilization evaluation.^[11] It should be emphasized that products today (e.g. paints, nutritional suspoemulsions, cosmetic multiple emulsions) often consist of several dispersed phases, and that the continuous phase may contain many constituents.

This complex structure of dispersions implies that a single parameter is generally insufficient to characterize or predict the stability state of a dispersion.

3.3 Alteration of the state of a dispersion

[Figure 1](#) and [Figure 2](#) schematically display a selection of primary and secondary mechanisms, respectively, which, over time, change the state of the dispersed phase and/or homogeneity of the dispersion. They are indicators of loss of stability. Additionally, aged dispersions may undergo phase separation that is obvious by visual observation. Destabilization mechanisms are sequenced simply for the sake of clarity and cannot be distinguished in most practical cases.



Key

A creaming, flotation

B sedimentation

C coalescence

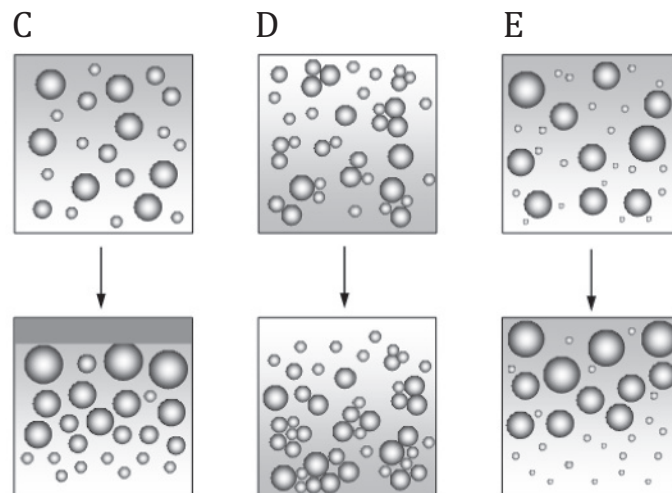
D flocculation, agglomeration

E Ostwald ripening

F phase inversion

Modified from source, [12][13]

Figure 1 — Primary destabilization phenomena of the state of liquid-solid or liquid-liquid dispersions



Key

- C coalescence
- D flocculation, agglomeration
- E Ostwald ripening

In case C, coalescence may progress to build up a continuous liquid phase again on top of the creaming layer for oil-in-water emulsion.

Figure 2 — Secondary alteration phenomena due to destabilization of a dispersion

There are three main categories that provoke an alteration of the state of a dispersion over time.

- a) Mechanical-driven processes: phase separation, i.e. creaming or flotation (see key item A of [Figure 1](#)) and sedimentation (see key item B of [Figure 1](#)) are driven by gravity, but other forces, such as mechanical, electric or magnetic can also give rise to concentration inhomogeneity within the product.
- b) Thermal-driven phenomena: Ostwald ripening (see key item E of [Figure 1](#)) and phase inversion (see key item F of [Figure 1](#)) are purely diffusion or thermally driven processes. The extent depends on the given physico-chemical properties of the two phases.
- c) Interaction-force-driven processes: in case of coalescence (see key item C of [Figure 1](#)), flocculation, agglomeration and aggregation (see key item D of [Figure 1](#)), the particles need to collide with each other or at least come within range of a mutual attractive force. For such processes, thermal and/or mechanical energy are necessary to initiate destabilization. Network formation or gelation may take place at particle volume concentrations above some threshold levels.

Stability analysis consists of monitoring, over an appropriate time, the alteration of the dispersion state (e.g. loss of homogeneity via sedimentation, creaming, particle size alteration, flocculation or coalescence). These are the stability metrics. On the other hand, stability criteria define the acceptable deviations in the metrics (e.g. sediment height, cream layer thickness, shift of particle size distribution, flocculation/agglomeration rate, coalescence rate, and appearance of oversized particles or the extent of developed new phases).

4 Characterizing the change of the state of a dispersion

4.1 General comments

In practice, after determining the stability metric(s), it is necessary to select an appropriate test method. It is recommended, if possible, to select a method that does not require sample preparation, so that the sample is analysed in its original state. The state of a dispersion is complex, and any sample preparation can alter the native state.

4.2 Direct methods

4.2.1 Visual observation

This approach has been applied for centuries to examine the time behaviour of a dispersion and to estimate its shelf life. The dispersion is placed in a test-tube, a test-bottle or into the container in which the product is delivered to the end-user and placed into storage. Alterations are visually observed at appropriate time intervals of days, weeks or months. Qualitative results are reported as “yes/no” alterations or “more/less” than a preset threshold or reference sample. Visual tests are simple and low cost, but require substantial storage space; they are time consuming, subjective (result depends on operator) and not traceable (unless linked to photographic images). It should be mentioned that often not only the stability in the sense of this Technical Report, but also the general appearance of a stored product is evaluated, and that some regulatory bodies demand such procedures be performed in the final containment vessel.

4.2.2 Instrumental methods

Results of instrumental methods are, in contrast to visual observations, objective and traceable. They also exhibit higher sensitivity, reproducibility and data storage. Appropriate measuring techniques have to be chosen in accordance with stability metrics according to the application. Scanning and spatially resolving techniques are appropriate in particular to detect phase separation. In addition, position resolved data help to discriminate between phase separation and phase changes. Different techniques are available, which are sensitive to alterations in the state or behaviour of the dispersion.

- a) Optical measuring principles are designed to monitor the changes of the state of dispersion by recording transmission and/or back scattering intensities. They are applicable to dispersions such as emulsions, suspensions and foams. Recorded intensities depend on instrumental design (e.g. wavelength, optical path length (see ISO 10934-1:2002^[14]) and the properties of the sample (e.g. volume concentration, particle size, shape, refractive index). A wide range of volume concentrations may be analysed by choosing the analysis method with appropriate optical path for low concentration transmission or back scattering with long path length and for high concentration, back scattering or transmission with short path length. If near-infrared sources are used, in most cases measured intensities do not depend on the optical properties (absorbance) of the continuous or dispersed phase. Instruments are available using transmission and/or backscattering sensors combined with spatial resolution from a few micrometres up to tens of micrometres, and measuring intervals from seconds to days.
- b) X-ray transmission methods including industrial computed tomography are tools for high volume concentration, but they are practically restricted to dispersed phases of atomic numbers >12 (carbon). Transmitted X-ray intensity depends only on the mass concentration and not on the particle size itself, as in case of light waves. Spatial resolution and measuring intervals are comparable to optical methods.
- c) Acoustic and electroacoustic spectroscopies (i.e. ultrasonic methods) offer another penetrating wave approach. Similar to light, attenuation of acoustic waves or in some cases changes of sound velocity are analysed to characterize the state of dispersion. Generally, these methods require somewhat higher volume concentrations (e.g. of order a few percent volume fraction). Quantitative analysis requires appropriate equations and material specific parameters. Scanning instruments are used because the current spatial resolution of sensors is limited.
- d) Measurements of electrical properties, such as conductivity or permittivity, can be used to characterize inhomogeneity (e.g. particle concentration) within the dispersion.

Direct methods operate in real time and require minutes to months to identify nascent destabilization phenomena. Nevertheless, sensitivity and accuracy of instruments provides the capacity to detect alterations in the state of samples far earlier than visual observations. The techniques described above do not require any sample preparation to measure the kinetics of dispersion state alterations. These methods can be used for measuring shelf life.

4.3 Correlative methods

Correlative methods focus on determination of a single physical parameter of the state of a dispersion that is known to correlate with stability of the dispersion. For example one of the following parameters may be measured and compared with pre-defined acceptable values:

- a) density differences;
- b) mean particle size;
- c) particle size distribution;
- d) electrophoretic mobility, zeta potential;
- e) concentration of particles/droplets larger than a stated size value;
- f) rheological parameters.

NOTE Various standard methods have been developed for each of these measurements, and the details can vary according to industry, type of material and application. It is up to the user to determine which of the available standards is most relevant and to adhere to that standard when making the measurement.

The advantage of this approach is that the evaluation may be performed immediately after the formulation of a new dispersion or after processing the product. A representative sample is needed, and the measurement technique may require sample preparation, which can alter the state of dispersion. Care should be taken to validate such procedures.

Correlative measurements provide quantitative values corresponding to one physical measurand. It characterizes the corresponding property at the time of the measurement and does not yield kinetic information. Due to the complexity of the state of dispersion (cf. 4.2), at the time of publication of this Technical Report, no theory exists to calculate or predict the time course of the dispersion state alteration or even predict shelf life based on a single physical parameter obtained at any single point in time.

4.4 Procedures to accelerate the evaluation of long-term stability

4.4.1 Purpose

Shorter evaluation time in research and development (R&D) and pre-shipment quality control (QC) is a challenge for highly stable dispersions (e.g. cosmetics, dispersions for construction, agrochemicals). Although instrument manufacturers have increased the sensitivity to detect minor alterations of the dispersion state, the acceleration of the naturally occurring, thermodynamically based destabilization process has to be achieved in order for the methods of [Clause 3](#) to be appropriate. Depending on the cause of naturally occurring alterations of the state of the dispersion, different procedures may be chosen to increase the rate/velocity of these alterations. A combination of procedures is advantageous in some cases. In general, these procedures are based on experience and should be used with caution.

Accelerated testing should be considered regarding its limits and its correlation to normal shelf life conditions and/or typical usage. It should be mentioned that accelerated testing itself may induce additional destabilization phenomena that are not observed under normal conditions of storage and use.

4.4.2 Mechanical procedures

- a) Inclination principle: sedimentation and creaming are driven by gravity and their velocities depend on the friction between the separating dispersed and continuous phases in opposite directions. Counterintuitively, a phase separation may be accelerated by the fact that particles sediment or cream in an inclined measuring cell faster than if the tube is vertical (Boycott effect). The enhanced separation rate may be seen as a consequence of the fact that while in both vertical and inclined separation, the particles sediment in the vertical direction. In the former case, the particles can settle only on the bottom of the sample cell, but in the latter situation, the majority of particles settle on the upward-facing cell wall.^[15] Depending on cross-section, inclination angle, volume

concentration and material properties, the necessary observation time to detect a given separation may be reduced by a factor of 2 to 20.

b) Mechanical energy

- 1) Centrifugation: it is known that centrifugation accelerates phase separation and therefore new or optimized formulations of a given dispersion type may be ranked according to their stability. The same is true for process optimization or QC of dispersion products. As ranking of monitored alterations of the chosen stability metrics at the same measuring conditions, mainly acceleration, is often sufficient, extrapolation to gravity condition would be of interest. According to [13] earth acceleration (gravity) g in Stokes law has to be replaced by centrifugal acceleration a . The latter depends on the square of the rotational speed and on the distance between the rotor centre and position of the sample region under consideration. The ratio of the centrifugal to gravitational acceleration gives the dimensionless relative centrifugal acceleration (RCA). The RCA-value indicates how much faster the terminal sedimentation or creaming velocity of the particles is in a centrifugal field, compared to gravity under otherwise identical conditions. In other words, centrifugation time multiplied by RCA estimates the appropriate time scale to detect the same changes of dispersion state under gravity. The above considered proportionality applies if the structure of the dispersion is not altered by the accelerated particle movement (Newtonian dispersion behaviour). In case of a non-Newtonian dispersion the destabilization rate is not linear versus RCA. Extrapolation to gravity behaviour (RCA = 1) has to be performed based on experimentally determined nonlinear fit equations for the given formulation type.
- 2) Mixing, vibration and agitation: destabilization phenomena can be accelerated by pragmatic mechanical approaches. On the one hand, collision frequency between particles increases (and is independent of the total interaction energy, e.g. according to the DLVO theory) the probability for particle-particle related destabilization phenomena to occur. The power of energy input is empirically chosen. The approach is restricted to comparison of similar designed dispersions, but stability testing may be shortened. On the other hand, these approaches generate an input of mechanical energy into the dispersed system and may induce complex flow patterns and shear fields. Generated mechanical forces may overcome repulsion energies between dispersed particles or break designed structures (e.g. stabilized films on emulsion droplets). As a consequence, agglomeration, flocculation, coalescence and/or network destruction occurs. The results may be interpreted in the sense of structural stability.

4.4.3 Thermal procedures

Temperature is probably the most common means to accelerate stability testing of a wide range of suspensions and emulsions. Samples are sealed and stored for hours, weeks or months at high temperatures (humidity is also often controlled) in a climatic exposure test cabinet. Applied temperature and storage time depend on the type of product. A range from 40°C to 50°C is often applied for cosmetics, 54°C for some agrochemicals and even up to 80°C for special crude oil product testing. The state of the dispersion is analysed at preset time intervals to detect destabilization phenomena as summarized in [Figures 1](#) and [2](#). Generally speaking, destabilization phenomena will be enhanced by elevated temperature: sedimentation and creaming due to a decrease in viscosity, Ostwald ripening and phase inversion due to a change in the thermodynamic potential (solubility), as well as flocculation, aggregation, agglomeration and coalescence due to intensified Brownian motion (increase of collisions) and elevating the efficiency of collisions between particles and droplets.

Empirical studies can correlate alteration of stability metrics at elevated temperature with alterations obtained at room temperature. For instance a company may specify that if a product is stored at 45°C for three months with no signs of destabilization then it may be deemed to be stable at room temperature for two years.

Generally speaking, the destabilization rate (i.e. alteration rate of the stability metrics) depends on activation energy E_a and decays according to the Arrhenius law. [17][18] Based on this law, destabilization rates may be predicted for a given temperature, if E_a is known. In order to measure E_a , the alteration rates of the corresponding stability metrics should be measured as a function of temperature and plotted against $1/RT$, where R is the universal Gas constant and T is the temperature, in Kelvin. The negative

slope of this graph equals E_a . The Arrhenius law assumes first-order kinetics. For other kinetics, more complicated relationships can apply.

In the past, changes had to be detected by naked eye observations (see [4.2.1](#)) and therefore traditional standard operational procedures had to use rather long test times to prove destabilization phenomena due to aging. The combination of storage at higher temperatures and sensitive instrumental methods can reduce temperature-exposure times.

Freeze-thaw-cycling is another approach to accelerate the testing. The rationality of this acceleration test has its roots in the fact that the free water (continuous phase) of the dispersion starts to freeze and the droplets become increasingly concentrated in the decreasing non-frozen part of the continuous phase. Droplets are, therefore, forced together and the liquid film between the droplets that prevents coalescence can break down due to increasing pressure. This approach is advantageous as it may be applied to dispersions immediately after new design steps or processing. For unstable dispersions having a tendency to coalescence, their state is changing much more rapidly compared to normal storage conditions above the freezing point.

4.4.4 Physico-chemical procedures

The vulnerability of the state of dispersion regarding its specific stability metrics is pragmatically “challenged” by adding substances that alter the physico-chemical conditions (e.g. electrochemical potential of the continuous or/and dispersed phase). In this way, specific destabilization phenomena are accelerated. Direct but correlative methods may apply. It should be underlined that these “ageing” tests can alter the conditions more severely than those encountered during the normal life span. Procedures to test stability relative to dilution, salt, pH or solvent changes, among others, have been utilized. For example, in the oil industry n-heptane induced separation is used to quantify asphaltene stability.

5 Prediction of the shelf life of a dispersion

5.1 General comments

Shelf life is defined as the lifetime of a product (food, medicine, inks, cosmetics, etc.) during which there are no changes or variations greater than allowed by the product specification, meaning that the product is sufficiently stable and any destabilization phenomena that naturally occur are within tolerable limits. Strictly speaking, shelf life is not only related to the storage time (shelf time), but covers the total life span, from the production, storage, distribution, to the end of usage period with the end-user. It can be that for a given part of the shelf life, certain conditions (e.g. temperature) are expected to be met.

There is no all-purpose method to calculate or predict shelf life of a dispersion. However by using appropriate techniques (see [Clause 4](#)) it is possible to analyse the time course of alteration of the dispersion state and to predict, in many cases, shelf life by data comparison or extrapolation.

5.2 Comparative analysis

For QC purposes and for optimizing product properties or product processing of an existing formulation, it is possible to use a reference product for which the kinetics of stability behaviour is well known and to compare the stability data of the reference sample with the results of the new optimized product using the same direct method and stability criteria. If the alteration rate is slower than the reference sample, the new product can be considered as stable. This approach is robust as no mathematical extrapolations are used, but it does not quantify the product shelf life. This approach can be used for virtually all types of dispersions and acceleration methods according to [4.4](#).

5.3 Predictive analysis

An important purpose of dispersion stability testing is to establish product shelf life for recommended storage, display and usage conditions. This is a three-step task. Firstly, experimental data should be provided showing how the considered stability metrics vary with time. These data are compiled

and presented for all time points. Based on linear or nonlinear regression analysis, the alteration rate or velocity of the corresponding property is obtained. If a linear regression applies, the analysis provides mean sedimentation or creaming velocities (e.g. $\mu\text{m}/\text{day}$), formation rates of a creaming layer or a sediment thickness, velocity of particle growth (due to Ostwald ripening or coalescence), or the formation rate of flocks or agglomerates.

Next, stability criteria have to be defined for the given dispersion product, specifying how much deviation in the stability metrics can be tolerated during processing, storage or usage. For example, a criterion can be the accepted thickness of a supernatant on top of a product due to phase separation.

The final step is to extrapolate the observed deviation course in the stability metric(s), e.g. via the regression analysis to that point in time where the acceptance stability criteria is exceeded, which by definition corresponds to the shelf life. Reliability of the shelf life prediction decreases as the time span of observation becomes much shorter than the shelf life. In drug product stability testing, the use of one-sided confidence intervals were recommended in order to improve the quality of the prediction.^[16]

Especially for very stable products, e.g. cosmetics, shelf life assessment is often the bottleneck in the design and commercialization of new products, and there is a need to accelerate stability testing according to 4.4. In this case shelf life prediction, as described above, cannot be obtained directly from the kinetic data based on regression, because “accelerated” data have to be “translated” to normal storage, display or usage conditions. A generic approach would be to start with an appropriate acceleration (e.g. elevated centrifugal acceleration or temperature). If a significant change of the dispersion state quantified by the chosen stability metrics attribute is observed, the experiment is repeated at an intermediate (lower) acceleration and so on. Based on the back extrapolated alteration velocities/rates at “normal” storage, display or usage conditions and the acceptance stability criteria, shelf life may be predicted as described above.^[16]

Shelf life prediction has to be performed with caution and should be based on a knowledge of the properties of the constituents and the product behaviour. On one hand, regression lines and extrapolation functions can be employed only for similarly formulated dispersion products and should preferably be validated by long-term testing. On the other hand, the shelf life of a product depends on many factors besides formulation type and processing conditions, such as packaging characteristics, distribution, storage temperature excursions and handling conditions.^{[17][18]}

Annex A (informative)

A compilation of relevant international and national standards

NOTE The descriptions given in this annex have been adapted from several standards.

- a) ISO 8780-1^[19] gives an introduction to the various methods described in the subsequent parts for dispersing pigments in a particular binder system. Methods for assessing the characteristics of the dispersion so produced are described in the ISO 8781^[20] series. The results allow one to draw inferences about the dispersion that can be obtained under manufacturing conditions.
- b) ISO 14887^[1]
- c) EN 13900-1^[21] provides an introduction to the various parts of EN 13900, which describe methods for dispersing pigments and extenders in plastics materials in order to determine their dispersibility. Methods of assessing the ease of dispersion are described in the subsequent parts of EN 13900. The various procedures described permit the making of comparisons between similar pigments (e.g. between a test sample and an agreed reference pigment).
- d) ASTM D1401-12^[22] is a test method that covers the measurement of the ability of petroleum oils or synthetic fluids to separate from water.
- e) ASTM D1791-93(2008)^[23] is a test method that is not absolute, but does give an indication of the useful shelf-life of a liquid water-emulsion floor polish. It indicates whether or not a polish will gel or remain a usable liquid over the desired storage life of the product. It should be noted that polishes of different composition types vary in useful storage life under identical storage conditions.
- f) ASTM D2337-01(2010)^[24]: waterborne coatings, when subjected to cycles of freezing and thawing, can undergo detrimental changes in application and performance characteristics. This test method evaluates the ability of multicolour lacquers to resist these changes. This test method covers the determination of the extent to which multicolour lacquers resist coagulation and coalescence, when subjected to freezing and subsequent thawing.
- g) ASTM D3342-90(2012)^[25]: each steel rolling mill and operation is particular as to the degree of stability of dispersion required to effect maximum efficiency of lubrication and cooling. This test method is designed to differentiate between coolants for this use. A similar situation is encountered with aluminium rolling mills, but significant differences in designated settling times be required outside the parameter of times used herein. Precision data have only been obtained relative to metastable dispersions for steel mill rolling oils.
- h) ASTM D3707-89(2010)^[26] is a test method that indicates the stability of the emulsion during storage and normal usage. This test method covers the stability of water-in-oil emulsions when held at a constant elevated temperature.
- i) ASTM D3709-89 (2010)^[27] is a test method that indicates the ability of the emulsion to withstand mild to moderately severe winter conditions of use and storage. Generally this significance would be limited to conditions where the emulsion reaches a minimum temperature of - 18 °C (0 °F).
- j) ASTM D3716-99 (2008)^[28] is a test that serves the purpose not to fully identify and characterize a polymer, but to identify a variety of basic parameters needed to predetermine the usefulness of the polymer in formulations as well as for QC purposes.
- k) ASTM D6930-10^[29] is a test method that is useful for determining, in a comparatively short time, the storage stability or settlement of an emulsified asphalt. It is a measure of the permanence of the dispersion as related to time, but it is not to be construed to have significance as a measure of other stability aspects involved in use.

- l) ASTM D 7061-06^[30] is a standard test method for measuring n-Heptane induced phase separation Asphaltene-containing heavy fuel oils as Separability Number by an optical scanning device
- m) ASTM D7112-09^[31]: automatic determination of stability parameters using a light back-scattering technique improves accuracy and removes human errors. In manual testing, operators have to visually compare oil stains on pieces of filter paper to determine if asphaltenes have been precipitated. This test method can measure stability and compatibility parameters, and determine stability reserve on different blends for particular applications to optimize the blending, storage, and use of heavy fuel oils
- n) ASTM D7149-05(2011)e1^[32] is a practice that provides a procedure for determining the stability of an adhesive to withstand five repeated cycles, or as otherwise specified, of freezing and thawing at a specific temperature
- o) ASTM F1105-09^[33] is a practice that determines the procedure to be used to ensure the long-term storage stability of aircraft cleaning and maintenance products in order to ensure their ability to meet the shelf-life requirements called up in specifications or contract documents. The subsequent testing requirements are detailed in the specification or contract
- p) CIPAC Method 2000, MT 184.^[34]
- q) ICH-Guidance for industry Q1A(R2)^[35] is a guidance document intended to define which stability data package for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan and the USA. It does not seek to address the testing for registration in or export to other areas of the world. The guidance document exemplifies the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that can be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

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