STABILITY STUDY OF DOSAGE FORM: AN INOVATIVE STEP


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ABSTRACT
Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development. Importance of various methods followed for stability testing of pharmaceutical products, guidelines issued for stability testing and other aspects related to stability of pharmaceutical products have been presented in a concise manner in the present review. Stability of different pharmaceutical dosage forms is studies. Dosage forms in which include the suspension, emulsion, aerosols, solid dosage form, ointment, creams, capsules & other. Stability data innovative to prove the quality of the product till expiry & Evaluation of quality. Stability of Pharmaceutical Product Capacity of a drug substance or drug product in a given packaging system to remain within established specifications to maintain its Quality (identity, strength, purity/impurity, potency) and deliver the desired Performance throughout the retest or expiration period.

Keywords: Stability, Stability studies, Stability testing, suspension, emulsion, aerosols, ointment, creams, capsule.

INTRODUCTION
Stability is defined as the time lapse during which the drug product retain same properties and characteristics that it possessed at the time of manufacture. The stability of product is expressed as the expiry period or technically as shelf life. Expiration period is a valuable quality attribute for all pharmaceutical dosage forms. The expiration date should be
preferably accompanied by detail of specific storage. Adequate stability data acquired stability data acquire by manufacture should be available to support the expiration period and storage condition specified.

The stability of finished pharmaceutical products depends, on the one hand, on environmental factors such as ambient temperature, humidity and light, and, on the other, on product-related factors, e.g. the chemical and physical properties of the active substance and of pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system and the properties of the packaging materials For established drug substances in conventional dosage forms, literature data on the decomposition process and degradability of the active substance are generally available together with adequate analytical methods. Thus, the stability studies may be restricted to the dosage forms. A stable emulsion system in which the globules retain their initial character and remain uniformly distributed through the continuous phase.

**Stability studies are necessary for the following reason**

- Product instability of active drug may lead to under medication due to lowering concentration of the drug in dosage form.
- During decomposition of active drug toxic products may be formed.
- Instability may be due to changing in physical appearance though the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study. The goal of chemical kinetics is to elucidate reaction mechanism, In stability studies, the objective is establish an establish an expiry date.

**TYPE OF STABILITY**

**Five stabilities of drug must be considered**

1. Physical stability
2. Chemical stability
3. Microbiological stability
4. Therapeutic stability
5. Toxicologic stability

1. Physical: The original physical properties, including appearance, palatability, uniformity, dissolution and suspend ability are retained.
2. Chemical: Each active ingredient retains its chemical integrity and labeled potency within
the specified limits.
3. Microbiologic: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. Therapeutic: The therapeutic effect remains unchanged.
5. Toxicologic: No significant increase in toxicity occurs.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), Selecting the proper container for dispensing (glass vs. plastic, clear vs. amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms. Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature. In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order, or the order with respect to each reactant.3

1.3 FACTORS AFFECTING DRUG STABILITY
1. Temperature
2. PH
3. Moisture
4. Light
5. Concentration

1. Temperature
High temperature accelerates oxidation, reduction and hydrolysis reaction which lead to drug degradation.

2. PH
Acidic and alkaline pH influences the rate of decomposition of most drugs. Many drugs are stable between pH 4 and 8. Weekly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionized.
So if the pH of a drug solution has to be adjusted to improve solubility and the resultant PH leads to instability then a way out of this tricky problem is to introduce a water miscible Solvent into the product.
3. **Moisture**
   a. Water catalyses chemical reactions as oxidation, hydrolysis, and reduction reaction
   b. Water promotes microbial growth

4. **Light**
Affects drug stability through its energy or thermal effect which lead to oxidation

5. **Concentration**
Rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution.\(^4\)

**METHODS**
Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidity) is used in order to determine the type of degradation products which may be found after long-term storage. Testing under less rigorous conditions i.e. those recommended for long-term shelf storage, at slightly elevated temperatures is used to determine a product’s shelf life and expiration dates.

The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product.

The main objectives and uses of stability testing are show in table

<table>
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<th><strong>Objective</strong></th>
<th><strong>Type of study</strong></th>
<th><strong>Use</strong></th>
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<tr>
<td>To select adequate formulation &amp; container-Closure system</td>
<td>Accelerated</td>
<td>Development of the product</td>
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<td>To determine shelf life &amp;storage condition</td>
<td>Accelerated &amp; Real time</td>
<td>Development of the product &amp; of the registration dossier</td>
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<tr>
<td>To substantiate the claimed shelf life</td>
<td>Real time</td>
<td>Registration dossier</td>
</tr>
<tr>
<td>To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product</td>
<td>Accelerated &amp; Real time</td>
<td>Quality assurance in general, including quality control</td>
</tr>
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</table>
IMPORTANCE

- The primary reason for stability testing is the concern for the well-being of the patient suffering from the disease for which the products is designed.
- Apart from degradation of the unstable product into toxic decomposition products, loss of activity up to a level of 85% of that claimed on the label may lead to failure of the therapy resulting in death. Because of this concern, it has become a legal requirement to provide data for certain types of stability tests for the regulatory agencies before approval of a new product.
- Second important concern is to protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market.

TYPES OF STABILITY TESTING

1. Real-Time stability testing

Real-time stability testing is normally performed for longer duration of the test period in order to allow significant product degradation under recommended storage conditions. The period of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs and must permit one to distinguish degradation from inter-assay variation. During the testing, data is collected at an appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity.

The reliability of data interpretation can be increased by including a single batch of reference material for which stability characteristics have already been established. Stability of the reference material also includes the stability of reagents as well as consistency of the performance of the instrument to be used throughout the period of stability testing. However, system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation must be monitored.
ICH Climatic zone and Long term condition

<table>
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<tr>
<th>Climatic zone</th>
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<th>Major countries Region</th>
<th>Mean annual partial water press.</th>
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<tr>
<td>1</td>
<td>Temperate</td>
<td>Europe, Russia</td>
<td>&lt;15°C/&lt;11hPa</td>
<td>21°C/45%RH</td>
</tr>
<tr>
<td>2</td>
<td>Subtropical &amp; Mediterranean</td>
<td>Japan , Southern Europe</td>
<td>&gt;15°C-22°C/&gt;11-18 hPa</td>
<td>25°C/60%RH</td>
</tr>
<tr>
<td>3</td>
<td>Hot &amp; Dry</td>
<td>Iraq, India</td>
<td>&gt;22°C/15°hPa</td>
<td>30°C/35%RH</td>
</tr>
<tr>
<td>4a</td>
<td>Hot &amp; Humid</td>
<td>Iran, Egypt</td>
<td>&gt;22°C/15°C/27hPa</td>
<td>30°C/65%RH</td>
</tr>
<tr>
<td>4b</td>
<td>Hot &amp; very humid</td>
<td>Brazil, Singapore</td>
<td>&gt;22°C&gt;27hPa</td>
<td>30°C/75%RH</td>
</tr>
</tbody>
</table>

Shelf life determination based on real time testing

Another method which involves real time testing and statistical analysis, followed for determining shelf life. 1. Keep three batches for stability study at least for 1 year at one fixed temperature. 2. Test them at 0, 1, 3, 6, 9, and 12 months for drug content. At each testing time test a number of samples, so that you have a mean and a standard deviation value of the result. 3. Now plot the graph of % drug content on Y axis and time on X axis along with confidence intervals. Where the lower 95% confidence curve intersects minimum potency, there you fix the shelf life.7

2. Accelerated stability testing

Definition: In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input required to cause product failure is determined. This is done to subject the product to a condition that accelerates degradation. This information is then projected to predict shelf life or used to compare the relative stability of alternative formulations.

This usually provides an early indication of the product shelf life and thus shortening the development schedule. In addition to temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package. In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed simultaneously. Because the duration of the analysis is short, the likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing. Further, in accelerated stability testing, comparison of the unstressed product with stressed material is made within the same assay and the stressed sample recovery is expressed.
as percent of unstressed sample recovery. For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures.

Importance:
- All medicinal products decompose with time. Paradoxically, when this decomposition is being assessed the skilled formulator becomes a victim of his own expertise, as a good formulation will take a long time to decompose.

- Instability in modern formulations is often detectable only after considerable storage periods under normal conditions.

- To assess the stability of a formulated product it is usual to expose it to high stress, i.e. condition of temperature, humidity and light intensity that cause break down.

- High stress conditions enhance the deterioration of the product and so reduce the time required for testing.

3. Retained sample stability testing
This is a usual practice for every marketed product for which stability data are required. In this study, stability samples, for retained storage for at least one batch a year are selected. If the number of batches marketed exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage. In this study, the stability samples are tested at predetermined intervals i.e. if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. This conventional method of obtaining stability data on retained storage samples is known as constant interval method. Stability testing by evaluation of market samples is a modified method which involves taking samples already in the market place and evaluating stability attributes. This type of testing is inherently more realistic.

METHODOLOGY

- **STABILITY STUDIES OF VARIOUS DOSAGE FORM**
- SUSPENSION
- SOLID
- CAPSULE
- SEMISOLID
AEROSOL
EMULSION

SUSPENSION STABILITY
Pharmaceutical suspensions are thermodynamically unstable system, so they always tend towards the ultimate loss of stability. What one examines at a time is only the apparent stability of the product.

Stability of suspension can be considered in two ways:

Physical Stability
The definition of physical stability in context of suspensions is that the particles do not sediment for a specific time period and if they sediment, do not form a hard cake. To achieve this desired target, one must consider the three main factors affecting the physical stability.

Particle-Particle Interaction and Its Behaviour (Derjaguin, Landau, Verwey & Overbeek)
Theory of attractive & repulsive forces in context of lyophobic colloids viz., DLVO theory. This theory allows us to develop insight into the factors responsible for controlling the rate at which the particles in the suspension will come together to produce aggregate to form duplets or triplets. The process of aggregation will accelerate the sedimentation and affect the redispersibility. For this, the potential energy curves may be used to explain the sedimentation behaviour which generally is indicative of the interaction of the two charged surfaces which gives rise to two types of suspension systems i.e. deflocculated and flocculated. In deflocculated suspension systems, the particle dispersed carry a finite charge on their surface. When the particles approach one another, they experience repulsive forces. These forces create a high potential barrier, which prevent the aggregation of the particles. But when the sedimentation is complete, the particles form a closed pack arrangement with the smaller particles filling the voids between the larger ones. And further the lower portion of the sediment gets pressed by the weight of the sediment above. And this force is sufficient to overcome the high energy barrier. Once this energy barrier is crossed, the particles come in close contact with each other and establish strong attractive forces. This leads to the formation of hard cake in a deflocculated system. The re-dispersion of this type of system is difficult as enough work is to be done in order to separate the particle and create a high energy barrier between them.
The another type viz., the flocculated system in which the particles remain in the secondary minimum, which means that the particles are not able to overcome the high potential barrier, so they remain loosely attached with each other. So, the particles here still experience a high energy barrier, but are easily re-dispersible.

**Chemical Stability**

Most of the drug materials although insoluble, when suspended in a liquid medium has some intrinsic solubility, which triggers the chemical reactions such as hydrolysis, to occur leading to degradation. So, the particles that are completely insoluble in a liquid vehicle are unlikely to undergo chemical degradation. The Chemical stability of the suspensions is governed by the following facts:

It is assumed that the decomposition of the suspension is solely due to the amount of the drug dissolved in aqueous phase. This solution will be responsible for drug decomposition and more drugs will be released from insoluble suspended particles within the range of solubility. It behaves like a reservoir depot. So, the amount of the drug in the solution remains constant inspite of the decomposition with time, thus, primarily suspensions behave as a zero order. But once all the suspended particles have been converted into the drug in the solution, the entire system changes from zero order to first order, as now the degradation depends upon the concentration in the solution. Thus, it can be said that suspension follows apparent zero-order kinetics.

The suspension is stable till the system follows zero order, but once it enters the first order kinetics, the degradation is rapid. But, if the suspension is concentrated, the system will require more time to convert from zero order to first order. And this is the reason that a concentrated suspension is often stable enough to market, but a dilute is not. But a concentrated suspension affects the physical stability of the suspension. So, the manufacturing pharmacist should optimize both physical & chemical parameters of the dispersed particles to achieve the desired stability of the suspensions.

**CONCLUSION**

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CAPSULE STABILITY

Physical Stability
Relative to the effect of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil, with a gelatin shell having a dry glycerin to dry gelatin ratio of about 0.5 to 1 and a water to dry gelatin ratio of 1 to 1, and that is dried to equilibrium with 20 to 30 % RH at 21 to 24 c. The physical stability of soft gelatin capsules is associated primarily with the pick-up or loss of water by the capsule shell. The above control capsule should have satisfactory physical stability at temperatures ranging from just above freezing to as high as 60 c.

As the humidity is increased, within a reasonable temperature range, the shell of the unprotected control capsule should pick-up moisture in proportion to its glycerin and gelatin. The total moisture content of the capsule shell, at equilibrium with any given relative humidity within a reasonable temperature range.

High humidities (>60% RH at 21 to 24 c) produce more lasting effects on the capsules shell, since as moisture is absorbed, the capsules become softer, tackier, and bloated. The capsules do not leak unless the increased moister has allowed a deleterious ingredient in the capsule content to attack to gelatin. On return to optimum storage condition, the capsules are dull in appearance and most likely inseparably stuck together. And increased in temperature (>24 c), together with humidity (>45%), results in more rapid and pronounced effects and may even cause the unprotected capsules to melt and fuse together. Capsules containing water-soluble or miscible liquid bases may be affected to a greater extant than oil- based capsules, owing to the residual moisture in the capsule content and to the dynamic relationship existing between capsule shell and capsule fill during the drying process.

The capsule manufacturer routinely conducts accelerated physical stability tests on all new capsule products as an integral part of the product development program. The following tests have proved adequate for determining the effect of the capsule content on the gelatin shell, the tests are strictly relevant to the integrity of the gelatin shell and should not be construed as stability tests for the active ingredients in the capsule contents. The result of such tests are
used as guide for the reformulation of the capsule content or the capsule shell, or for the
selection of the proper retail package. The test conditions are (1) 80% RH at room
temperature in an open container, (2) 40 °C in an open container, (3) 40 °C in a closed container
(glass bottle with tight screw-cap). The capsules at these stations are observed periodically
for two weeks. Both gross and subtle effects of the storage conditions on the capsule shell are
noted and recorded. The control capsule should not be affected except at the 80% RH station,
where the capsule would react described under the effects of high humidity.

In the case of a newly developed product, the gross effect such as disintegration, leakers,
unusual brittleness or softening, apparent color fading, or discoloration are obvious. The
more subtle changes may be the loss of a volatile ingredient as detected by slight capsule
indentation. Or the slight darkening or widening of the capsule seams, or slight changes in
color hue. Capsules obtain show a “soft spot” at the site at which they lie next to the tray or
against another capsule. This spot is the result of slower drying and is of no consequence in
the control capsule, since such areas firm up and are not flaws in the capsule shell. On the
other hand, if such areas don’t become firm, usually because of action by the capsule content,
then physical stability problems can be anticipated during the shelf-life of the product. Such
defects must be corrected before the product can be considered for production. Correction of
such defects depends identifying their cause. Most defects can be corrected by appropriate
changes in gelatin or fill material formulations, but in some cases, different colorant, machine
speeds, and machine dies may have to be used. The experience and matured judgment of the
costume manufacturer is in valuable in the solution of such problem.

Chemists conducting the physical stability tests in the their own laboratories should keep two
important points in mind: (1) prior to testing, the capsules should be equilibrated to known
atmospheric conditions, preferably 20 to 30% RH at 21 to 24 °C. (2) evaluations of the results
of the previously described heat tests should be made only after the capsules have returned to
equilibrium with the room temperature.

SEMI-SOLID DOSAGE FORMS STABILITY

STABILITY OF CREAMS

Physical Stability

The most important consideration with respect to pharmaceutical and cosmetic emulsions
(creams) is the stability of the finished product. The stability of a pharmaceutical emulsion is
characterized by the absence of coalescence of the internal phase, absence of creaming, and
maintenance of elegance with respect to appearance, odor, color and other physical properties. An emulsion is a dynamic system, however, any flocculation and resultant creaming represent potential steps towards complete coalescence of the internal phase. In pharmaceutical emulsions creaming results as a lack of uniformity of drug distribution and poses a problem to the pharmaceutical compounder. Another important factor in the stabilization of emulsions is phase inversion which involves the change of emulsion type from o/w to w/o or vice versa and is considered as a case of instability. The four major phenomena associated with the physical instability of emulsions are flocculation, creaming, coalescence and breaking.¹

**Chemical Stability**

The instability of a drug may lead to the loss of its concentration through a chemical reaction under normal or stress conditions. This results in a reduction of the potency and is a well-recognized cause of poor product quality. The degradation of the drug may make the product esthetically unacceptable if significant changes in color or odor have occurred. The degradation product may also be a toxic substance. The various pathways of chemical degradation of a drug depend on the structural characteristics of the drug and may involve hydrolysis, dehydration, isomerization and racemization, decarboxylation and elimination, oxidation, photodegradation, drug-excipients and drug drug interactions. Factors determining the chemical stability of drug substances include intrinsic factors such as molecular structure of the drug itself and environmental factors such as temperature, light, pH, buffer species, ionic strength, oxygen, moisture, additives and excipients.

The application of well-established kinetic principles may throw light on the role of each variable in altering the kinetics of degradation and to provide valuable insight into the mechanism of degradation the chemical stability of individual components within an emulsion system may be very different from their stability after incorporation into other formulation types. For example, many unsaturated oils are prone to oxidation and their degree of exposure to oxygen may be influenced by factors that affect the extent of molecular dispersion. This could be particularly troublesome in emulsions because emulsification may introduce air into the product and because of the high interfacial contact area between the phases. The use of antioxidants retards oxidation of unsaturated oils, minimizes changes in color and texture and prevents rancidity in the formulation.
Microbial Stability
Topical bases often contain aqueous and oily phases, together with carbohydrates and proteins and are susceptible to bacterial and fungal attack. Microbial growth spoils the formulation and is a potential toxic hazard. Therefore, topical formulations need appropriate preservatives to prevent microbial growth and to maintain their quality and Shelf-life. Cream formulations may contain fats and oils with high percentage of unsaturated linkages that are susceptible to oxidation degradation and development of rancidity. The addition of antioxidants retards oxidation of fats and oils, minimizes changes in color and texture and prevents rancidity in the formulation.\(^\text{30}\)

STABILITY OF OINTMENTS
The ointments should remain stable from the time of preparation to the time when the whole of it is consumed by the user.

(i) To stop microbial growth preservatives are added. Preservatives for ointment includes: p-hydroxyl benzoates, phenol, benzoic acid, sorbic acid, methyl paraben, propyl paraben, quaternary ammonium compounds, mercury compounds etc.

(ii) The preservatives should not react with any of the component of the formulation. Plastic containers may absorb the preservative and thereby decreasing the concentration of preservative available for killing the bacteria.

(iii) Some ingredients like wool fat and wool alcohols are susceptible to oxidation. Therefore, a suitable antioxidant may be incorporated to protect the active ingredients from oxidation.

(iv) Incompatible drugs, emulsifying agents and preservatives must be avoided. The drugs which are likely to hydrolyze must be dispensed in an anhydrous base.\(^\text{30}\)

AEROSOL STABILITY

Concentrate Stability: This stability testing is usually run in glass containers because you do not want the container to be a contributing

Product and Container Stability: Once an acceptable formulation is achieved, start stability testing in the aerosol can, valve, dip tube, and gaskets. Upon the product

Low Temperature Stability: If the product is not freeze-thaw stable, directions such as “protect from Freezing” needs to be added to the product label.\(^\text{32}\)
SOLID DOSAGE FORMS STABILITY

Physical Stability
Conversion from one form to another and Crystallization, change in polymorphic form, desolation are common

Physical stability of the amorphous state
- Crystallization much more likely above Tg. General “guideline” is that amorphous materials are stable at temperatures 50 oC below Tg
- Stability of amorphous form greatly depends on how it was prepared. Presence of residual crystalline (defect sites) can be a source for nucleation. In general grinding/milling produces least stable amorphous form, followed by lyophilization/spray. Drying, followed by melt-quench

Physical stability of the crystalline state
- Polymorphic transformation and salvation/desolation biggest problems
- Stability of polymorphic form may depend upon temperature (monotonic vs. enantiotropic). Mixtures of polymorphic and pseudo polymorphic forms possible
- Presence of moisture can promote polymorphic and pseudopolymorphic transformations. Polymorphic and pseudo polymorphic changes are often observed upon scaling up a process

Chemical Stability
Can be intramolecular or intermolecular and Hydrolysis, oxidation, photolysis are possible.

Chemical stability of the amorphous state
- Reactivity much more likely above Tg. Above Tg, reactions in the amorphous state may be thought of as a continuation of reactions in the melt (follow same Arrhenius plot)
- Hydroscopic nature can promote hydrolysis reactions May also be more sensitive to oxidation and photochemical degradation
- It has been proposed that small amounts of amorphous material is the source of many stability problems observed (both physical and chemical.
- Spectroscopic methods - includes Raman Infrared, Solid-State NMR.

EMULSION STABILITY
A stable emulsion is one in which the dispersed globules retain their intial character and remain uniformly distributed throughout the continuous phase. Various types of deviation
from this ideal behavior can occur.

A stable emulsion may be defined as a system in which the globules retain their initial character and remain uniformly distributed through the continuous phase. The function of emulsifying agent is to form an interfacial film around the dispersed droplets; the physical nature of this barrier controls whether or not the droplets will coalesce as they approach one another. If the film is electrically charged then the repulsive forces will contribute to stability. The three major phenomenon associated with physical stability are

1. The upward or downward movement of dispersed droplets relative to the continuous phase, termed creaming or sedimentation, respectively.
2. The aggregation and possible coalescence of dispersed droplets to reform the separate, bulk phases. Inversion, in which an W/O emulsion and vice versa.

Some Thermodynamics
If two components are completely compatible they do not form an interface as it is the case for dilute gases or two mutually soluble liquids. In this case, the free energy of mixing is negative. It is exactly the opposite if two incompatible components forming an of formation must be positive.

This behavior finds its expression in a special form of the Gibbs-Helmholtz equation where US is the total surface energy for a given interface (S), σ is the interfacial tension, and T is the absolute temperature

\[ U^S = \sigma \cdot T \left( \frac{\partial g}{\partial T} \right)_S \leq 0 \]

The preparation of emulsions requires energy to disperse the organic phase (solvent or solution) in water. In order to get an idea about the thermodynamics the change in the Gibbs free energy of the system (ΔG), provided by the particular dispersing procedure at constant composition and pressure, can be expressed by:

\[ \Delta G = \Delta H - T \Delta S \]

The entropy (ΔS) is a measure of the extent of disorder in the system and hence measures the extent of size reduction of the organic phase (or increase in droplet number). The increasing disorder during the formation of an emulsion means a positive ΔS contributing to stability. ΔH is the enthalpy of the system and can be considered as the binding energy of the organic bulk material or the energy input needed to achieve a certain average droplet size.
If a volume change during the emulsification is neglected the enthalpy corresponds to the internal energy which is the sum of the work required to expand the interfacial area (ΔW) and an amount of heat which results from wasting a part of the energy input. The increase in the energy of an emulsion compared to the non emulsified components is equal to ΔW. This amount of energy can be considered as a measure of the thermodynamic instability of an emulsion.

$$\Delta W = \sigma \cdot \Delta A$$

ΔW is the free energy of the interface and corresponds to the reversible work brought permanently into the system during the emulsification process. This makes an emulsion very prone to coalescence processes which lead to a decrease in ΔA and subsequently in ΔW. The conclusion is straightforward that ultimate Stability against coalescence processes is only achieved if approaches zero.

**Gibbs - Marangoni Effect**
Convective motions due to differences in interfacial tension

![Fig no.1- local differences in \( \sigma \) at curve interfaces try to restore flat surface spontaneously](image)

Additional action of surfactants: generation and maintaining of a gradient of the interfacial tension (gradient of the interfacial density of surfactant molecules) across the droplet surface during undulations caused by thermal or mechanical stresses. The latter effect also contributes to the stability of emulsions and is strongly connected with the Gibbs - Marangoni effect.
Gibbs - Marangoni Effect
A closer look at an emulsion droplet (O/W)

![Gibbs-Marangoni Effect Diagram](image)

**Fig no.2 - Gibbs - Marangoni Effect**

**Bancroft’s rule**

„When water is the dispersing phase, the emulsifying agent should be a hydrophilic colloid (Höber). Höber does not draw the conclusion that the emulsifying agent should be an oleophile colloid in case the emulsion is to contain water in drops“

The liquid in which the stabilizer has a higher solubility forms the continuous phase.

**Degradation of Emulsions**

- phase separation
  (Creaming, sedimentation)
- Ostwald ripening
- aggregation processes
- (Flocculation, coagulation, coalescence)
- phase inversion

1) **Phase Separation**

Creaming of emulsion is the separation of dispersed globules in the form of concentrated layer on the top of emulsion. Mostly, oil are light and show upward movement to form
cream. The dense oil may show sedimentation. Creaming is not a serious instability problem if uniform redispersion can be achieved by shaking of the emulsion.

2) Phase Inversion
Phase inversion or emulsion type reversal is the change in type of emulsion from o/w to w/o and vice versa. Some reason of phase is as follows:
1. Change in phase volume ratio
2. Changing the emulsifier
3. Change in temperature
Phase Inversion Temperature PIT
- As the temperature increases, the water solubility of ethoxylated nonionic emulsifiers becomes poorer (the HLB decreases).
- There is a temperature (PIT) at which the hydrophilic and lipophilic characteristics of the emulsifier are equal (relative to the required HLB of the oil phase).
- At this temperature the emulsion will exhibit a phase inversion - The PIT should be at least 20°C higher than the storage temperature. Choose emulsifiers, and concentrations, to raise the PIT.

3) Aggregation processes
In this process, the emulsifier film around the globules is destroyed to certain extent. This step can be recognized by increased globule size and reduce number of globule.
Aggregation is observed due to:
- insufficient amount of the emulsifying agent
- altered partitioning of the emulsifying agent
- incompatibilities between emulsifying agents

4) Ostwald ripening
- Ostwald ripening requires to occur a certain solubility of the dispersed phase in the continuous phase.
- Direct contact between the droplets is not necessary as molecular diffusion through continuous phase lead to an increase in Dd.

OBJECTIVE OF STUDY
- The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as
temperature, humidity and light.

- To select adequate (from the viewpoint of stability) formulations and container closure Systems.
- To determine shelf-life and storage conditions.
- To substantiate the claimed shelf-life.
- To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product.

Main aim of accelerated stability study to predict the stability profile of a drug product that prediction of self life of the product before launching into market

CONCLUSIONS

- Pharmaceutical stability is a critical quality attribute. Any deviation from the established stability profile could affect the quality, safety and efficacy
- Thorough understanding of the stability of the drug substance and drug product is important to “build the quality in”
  - Design the optimal pharmaceutical product, define efficient API / DP process and establish appropriate specifications and expiry dates
  - Successful development, registration and commercialization
- Developing global stability programs are challenging due to climatic variations and differences in local regulatory requirements
- Plan well and use science based approach; consult the experts/regulators, as needed
  Stability studies should be planned on the basis of pharmaceutical R&D and regulatory requirements. Forced degradation studies reveal the intrinsic chemical properties of the API, while formal stability studies establish the retest date. The shelf life (expiry date) of FPPs is derived from formal stability studies. Variability and time trends of stability data must be evaluated by the manufacturer in order to propose a retest date or expiry

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