



## A REVIEW ON STABILITY STUDIES OF UNANI FORMULATIONS

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### ABSTRACT

World health organization (WHO) has recognized the effectiveness of traditional system of medicine and its safety. According to WHO report, over 80% of the world population relies on traditional medicine largely plant based for their primary healthcare needs. Stability testing of herbal products is a challenging task, because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known. The objective of a stability testing is to provide evidence on how the quality of the herbal products varies with the time under the influence of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipients in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container, etc. and to establish a recommended storage condition, retest period and shelf-life. Unani system of medicine employs single drugs, simple preparations and compound preparations (using herbs, minerals and animal products in one and the same medicine) so the task of evolving standards and shelf life is enormous. There is no scientific ground, whatsoever; to fall back and as a composite strategy had to be evolved. Therefore evaluation of the parameters based upon chemical, physical, microbiological, therapeutic and toxicological studies can serve as an important tool in stability studies.

**Keywords:** Stability Studies, Shelf-life, Storage conditions, Unani Formulations.

### INTRODUCTION

Herbs are in extensive use in the traditional practices of different countries since time immemorial. In the European countries and also the African folklore, herbs are used empirically for the treatment of various diseases. In other countries like India, Tibet and China, use of herbal drugs has a rational explanation. Whether these herbs are used empirically or rationally; these are effective, based on centuries of experience and free from any adverse toxic effects<sup>1</sup>. As we observe in our routine life that all the objects get spoiled after a specific period. All the living beings go through a cycle of birth, growth, reproduction and death. All the non living substances that are grown or manufactured go through a life span in which they are influenced by environment. Everything made by human hands from the sublime Parthenon to the trivial milkshake is subject to decay. There is no existence of such a substance in world which is imperishable. If there is functionally relevant quality attribute of a drug product that changes with time, evaluation of this change falls within the purview of the pharmaceutical scientists and regulatory authorities who quantify the stability and shelf life of drug product<sup>2</sup>. Understanding the stability characteristics of drug substances and drug products is a critical activity in drug development and the above quote by Carstensen undergoes the need to learn of potential stability problems as soon as possible during development<sup>3</sup>. In order to assess the stability of a compound, one needs an appropriate method. The development of stability-indicating analytical method, particularly an impurity method, is a "chicken and egg" type of problem. That is, how does one develop an impurity method to detect degradation products when one does not know what degradation products are? Stress testing studies can help to address this dilemma. Stressing the parent compound under particular stress conditions can generate samples containing degradation products. These samples can be used to develop suitable analytical procedures<sup>3</sup>. Stability studies should be performed

on at least three production batches of the herbal products for the proposed shelf-life, which is normally denoted as long term stability and is performed under natural atmospheric conditions<sup>4,5</sup>. Stability data can also be generated under accelerated atmospheric conditions of temperature, humidity and light, which is referred to as short term stability and the data so obtained is used for predicting shelf-life of the product. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. With the help of modern analytical techniques like spectrophotometer, HPLC, HPTLC and by employing proper guidelines it is possible to generate a sound stability data of herbal products and predict their shelf-life, which will help in improving global acceptability of herbal products<sup>5</sup>. As a result of stability testing a re-test period for the active substance or a shelf life for the pharmaceutical product can be established and storage conditions can be recommended<sup>4</sup>. Stability studies of drugs are necessary for betterment of patients for clinical efficacy of formulations and for drug regulatory requirements. In Unani classical literature Unani Scholars mentioned the different expiration dates of various Unani single and compound formulations. First of all parameters have to be determined and formats designed for recording field and laboratory data on the identification of drugs, establishment of physical and chemical characters, characters of compound preparations with reference to tests adequately indicative of qualitative and quantitative availability of specific, potent and consequently, costly ingredients. In view of the fact that a large number of preparations are currently being used by the Unani physicians, statistical assessment has to be made on priority basis to determine representative drugs of the various classes of Unani medicine for standardisation<sup>6</sup>. Classical Unani practitioners shared a lot from their experience regarding the identification of crude drugs, their authentication methods and about their clinical efficacy. They also mentioned the method of compound drug formulations and their possible

expiration dates<sup>7</sup>. Jalinoos (Galen) who was attached to the Roman court and all time influential writer was the first who mentioned in his book Kitabul Murakkabath that all powders retain their potency not more than two months whereas that of the Hab and Qurs is more than the shelf life of Sufoof. Apart from these, shelf life of Sharbath is also mentioned in it which is about 1 year<sup>8</sup>. Ali bin Abbas Majoosi author of Kamil us Sana'a has mentioned expiry dates of many Qurs, Tiryakh, Majoonth, Aflooniya, Ayarijath<sup>9</sup>. Unani Scholars mentioned the stability periods of Unani formulations based on their keen observations and organoleptic parameters. Therefore, the acute observations of the Unani Scholars need to be substantiated with empirical evidence using scientific methodologies<sup>10</sup>. While preparing and processing medicinal recipes, it was always kept in mind that, as far as possible, the medicine should be useful in treatment of several ailments, therapeutically very potent, palatable and long life. Thousands of such recipes and their particular experience are described in Unani texts<sup>11</sup>.

### Definitions

Stability and shelf life is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality and purity throughout the retest or expiration dating period. Physical, chemical and microbiological data are generated as a function of time and storage conditions (e.g., temperature and relative humidity [RH])<sup>12-14</sup>. The United States Food and Drug Administration (FDA) require indication for every drug product of a shelf-life on the immediate container label. Since the true shelf-life of a drug product is typically unknown, it has to be estimated based on assay results of the drug characteristic from a stability study usually conducted during the process of drug development<sup>13,14</sup>.

### General need for Stability testing

Medicines cannot be used after a period of time. Some can be kept only for a short time. In 1984, Rhodes listed six general reasons for limited time for which medicines can be kept. These are

- Loss of Drug (Such as Hydrolysis or Oxidation)
- Loss of Vehicle (Such as Evaporation of water or other volatile ingredients)
- Loss of Uniformity (Such as caking of a suspension or creaming of an emulsion)
- Change of Bioavailability (particularly with tablets where ageing can reduce availability)
- Change of Appearance (Such as colour changes)
- Appearance of toxic and irritant products (as a result of chemical change)
- Microbiological activity

It is important to recognize and be aware of the potential for instability in both manufactured and extemporaneous products. There is a need to specify storage conditions and a shelf life, to ensure effective stock control and pay attention to the packaging used in dispensing<sup>15</sup>. Although the reasons for stability testing are

- Our concerns for patients welfare
- To protect reputation of the producer
- Requirement of regulatory agencies
- To provide a database that may be of value in the formulation of other products<sup>2</sup>

### Historical content

Stress testing and accelerated stability testing were often used interchangeably in the pharmaceutical industry. In a classic article by Kennon the effect of increasing temperature (from room temperature to 85°C) on the rates of degradation of pharmaceutical products was discussed in the context of predicting shelf life of pharmaceuticals. This article provided the basis for many articles that followed. For example, the articles by Yang and Roy and Witthaus were extensions of Kennon's original work. Their work led Joel Davis of the FDA to propose what has become known as the Joel Davis Rule, i.e. 3 months at 40°C/75% Relative Humidity is roughly equivalent to 24 months at room temperature (25°C). Interestingly, Cartensen has pointed out that prior to Joel Davis Rule, the historical rule of thumb had been that 5 weeks of storage at 42°C is equivalent to two years of storage at room temperature. This rule has been derived from work done in 1948 on stability of vitamin A and it assumes the same activation energy as found for vitamin A. Many other important contributions have been made over the years with regard to kinetic evaluations of drug stability from accelerated stability view point, A paper by Singh and Bakshi in 2000 provides the most, through the collection of references to various degradation studies of drug products, documenting the diversity of conditions and approaches to stress testing. This paper attempts to provide a classification system (Extremely Labile, Very Labile, Labile, Stable) based on a defined systematic approach<sup>3</sup>. Shiekh ur Raees Bu Ali Sena in his book Al Qanoon has mentioned that the drugs are very efficacious like those of Tiryakhat due to many important constituents in it, which last for a longer period of time. It can get spoiled sometimes when not prepared properly where in, it gets fermented which results in alteration of temperament and reduces the shelf life. Ibn Sena has also mentioned regarding the shelf life of Tiryakhe Farooqh in his book Al-Qanoon Fit-tib<sup>16</sup>. Abdul Hasan bin Sahal Rabban Tabri (810-895 A.D) has mentioned in his compilation "Firdousul Hikmat" about Tiryakhe Akbar should be preserved in Silver vessel for six months or one year then used. Then its potency remains for thirty years or even more.<sup>17</sup> Hakim Amanullah Khan was a famous physician and great scholar, writer of the book "Ganje Badaward" which consists of three parts Miftah, Ganjur and Telism. Miftah consists of 16 chapters in which chapter 2 is regarding the collection and storage of drugs and Chapter 12 describes shelf life of drugs.<sup>18</sup> Abu Hassan Ali Bin Abbas Majoosi has mentioned in "Kamilus Sana'a" in chapter no. 6 about the shelf life of Tiryakh and Majoonth it has been mentioned that Tiryakh should be used after twelve years or a minimum of seven years of manufacturing to get the maximum effect of the drug. Some of the scholars have mentioned that Tiryakh should be used after five years of manufacture and can be used up to thirty years when it is fresh and very potent and after thirty years it is considered to be old and loses its potency and completely loses its potency by sixty years. It has also been mentioned that Tiryakh from seven years to thirty years should be used in snake bites or scorpion bites as it is considered to be highly efficacious, once it has reached thirty years it can be used in other diseases which are not life threatening as its potency decreases. Writer of Kamil-us-Sana'a has mentioned the shelf life of various formulations in his writing as described below: Aqraase Asqheel, Aqraase Afaai, Aqraase Andrakhoon, Tiryakhe Arba'a have the shelf life from 2 months to 2 years

with no extended shelf life, Tiryakhe Ghararah, Tiryakhe Masruditoos, Tiryakhe Shalisa have shelf life from 6 months to 7 years, Majoone Quibazul Mulk, Majoone Arastoon, Flooniyae Roomi, Flooniyae Farsi have the shelf life from 3 months to 3 years, Majoone Kibrit, Majoone Kaknaj have shelf life from 6 months to 3 years with no extended shelf life, Dawae Kurkum, Majoone luk, Majoone Afroosia, Majoone Athqhi and Sanjareena have the shelf life of 2 months to 1 year with extended shelf life of 6 months, Dawaul Misk Shireen, Dawaul Misk Talkh, Fanjnosh, Itrifal, Amroosia have the shelf life from 2 months to 2 years, Ayarijat Kabir, Shadritoos have shelf life from 1 year to 4 years with no extended shelf life, Purgative drugs have shelf life of up to 2 ½ months, Afloonina has shelf life up to 2 months, tablet up to 6 months, Qurse Kaukab has shelf life up to 6 months to 2 years, Zimad and Marham has shelf life up to 6 months, all types of syrups have shelf life from 2 days to 2 years with extended shelf life of 2 years<sup>9</sup>. The therapeutic efficacy of oil reduce once odour is altered, oils retain their therapeutic efficacy until their odour gets changed. But Roghane Balsan and Aabe Kafoor increases in potency with period of time. However Jalinoos has reported that Aabe Bihi did not undergo any change for as long as seven years<sup>9</sup>. Mohammed Hadi Khan Mohammed Husain narrated details about period of stabilization of compound drugs and their shelf life. "Period of stabilization of compound drugs is considered as that period in which a compound formulation achieve their Kaifiyat (efficacy) and Mizaj e sanvi (secondary temperament); according to this Tiryakh Farooq should be used six or seven years after their preparation. Some ancient Atibba (Physicians) advocated the use of Tiryaqe Farooq after six months. However other compound preparations due to difference in their ingredient are divided into four categories (Tabquaat).

#### **Shelf lives of compound drugs are also categorized into four classes**

##### **First category**

Compound formulations are those which have the shelf life of five to ten years, after that they lose their potency e.g. Mathroditoos, Afloonina Farsi and Roomi, Barshasha and other Barsh, Ayarije Loghazia, Ayarije Arkaghnees and other compound formulations.

##### **Second Category**

Compounds formulations are those which have shelf life, efficacy and potency for three to four years, for example, Amroosia, Arastoon, Anquaroya, Ayarijat, Tiryaqe Teen, Tiryaqe Ghauza, Ramehran, Dawaul Mulk, Dawaul Kurkum, Sanjarina, Soteer, Majoone Astamkhiyoon, Majoone Amber, Majoone Quaisar and similar compounds.

##### **Third category**

Compounds drugs which have shelf life, potency and efficacy for two years, come under this category e.g. Sharbat, Itrifilat, Jawarishat, Aqras like Qurse Kaukab, Qurse Asqueel, Qurse Kaknaj, Ruboob and Majoone Sagheer. According to Jalinoos Rub and Sharbate Bihi which retain their taste and do not change can be used for seven years.

##### **Fourth Category**

Compounds drugs which come under this class have their shelf life of minimum two to six months and maximum one year. For example Huboob, Roghaniyat, Zaroorat, Safoofat,

Marham and Safoofe Muqliyasa and other similar compound formulations<sup>19</sup>. The Tiryakh are compared to the life cycle of man where he passes through the stages of infancy, childhood, youth, senility and death the same way the life cycle of Tiryakh has been explained, it becomes child after six months or a year after manufacture, then after that period it becomes adolescent and potency continues to increase up to ten years if in hot regions and twenty years if in cold regions and then stops to grow. Its potency lasts effectively up to ten or twenty years. After twenty to forty years its potency is reduced and then its Tiryakh properties disappear. Then after thirty to sixty years it becomes like any other Majoon which are less effective than Tiryakh<sup>20</sup>. Hakeem Akbar Arzani has mentioned in Qarabadin Qadri about the shelf life of Unani formulations like Itrifile Zamani, Mufarreh Har and Barid, Qurse Androon, Sikanjabeene Shakri, Tiryakhe Arbaa, Qurse Kaukab have shelf life up to 2 years and Ayarij if in the form of Safoof has shelf life of 3 months, if mixed with Shehad it is 4 years, if in the form of Qurs it is 6 months, Ayarije Faiqhra has shelf life of 30 years to 50 years, Barshasha up to 5 years, Siyadritoos, Fulooniya, Majoone Falasifa, Majoone Lehsun, Sharbathe Unnab, Sikanjabeen, Mufarreh Azam, Sikanjabeene Asli has shelf life up to 4 years, Roghane gul, Mufarrehat, Majoone Najaah Qurse Kafoori has shelf life up to 1 year, Mufarreh Abresham, Itrifile Kabeer, Habbe Zahab have shelf life upto 3 years, Mufarreh Soosanbari have shelf life up to 20 years and Qurs has a shelf life of 6 months and etc.<sup>21</sup> Hakeem Kabeeruddin in his compilation Bayaze Kabir has mentioned regarding Barshasha that it retains its potency for 5 years<sup>22</sup>. Hakeem Azam khan in his compilation Qarabadeene Azam has mentioned regarding the potency of Tiryakhe Arba'a as 2 years, and that of Siyadritoos as 4 years<sup>23</sup>. In NFUM shelf lives of Unani formulation has been mentioned they are as follows. Murabbajat and Gulkhand should be preserved only one season, Extracted or medicated oils can be preserved for one to two years, Saiyalat like (Arq, Qutur, Sikanjabeen, Sharbat) can be preserved and used for one year, When Maghziyat are ingredients in Safoof they should be used within six months, Safoof retain their potency for one year. Kushtajat maintain their potency indefinitely. The older the Kushta is better the effect.<sup>24</sup> Hakeem Dr. Hari Chand Multani has mentioned regarding the compilation of Hakeem Farooq Naeem Khan about shelf lives of compound formulations in his book Hindustan wa Pakistan ki jadi bootiyan that Jawarishat and Majoonat have shelf life up to three to five years, Khamirajat have shelf life up to five years if the consistency is correct, Sharbat and Arqiyat have shelf life up to three years, Hab o Qurs have shelf life up to three to five years, Safoof has shelf life up to one year if free from moisture<sup>25</sup>. Tibbi pharmacopoeia approved from board of Unani and Ayurvedic System of medicine, Pakistan Act II 1965 has described regarding the Stability of drugs, Expiry of drugs, Murakkabat and Antidote stabilization.<sup>11</sup> Government of India has recently issued a gazette notification regarding shelf life or date of expiry for ASU medicines. In the Drugs and Cosmetics Rules, 1945, after rule 161A, the following rule shall be inserted, namely: 376S GI / 09-2 161B. 1 This notification clearly says that the date of expiry of Ayurveda, Siddha and Unani medicines shall be conspicuously displayed on the label of a container or package of an ASU medicine. It further says that medicine should not come in to circulation after the said date of expiry. 764(E) 15.10.2009 the potency of ASU preparations is lost / reduced after a certain period of time. Hence to make full use of these



preparations and as per textual reference, ASUDTAB has recommended Shelf life / Expiry date for ASU drugs. Shelf life / Expiry date under rule 161(B) has been amended in respect of Ayurveda, Siddha and Unani medicines. The Final Notification has been issued on 15th October, 2009.<sup>26</sup> Shelf life or date of expiry of Unani dosage forms are as follows: Hab, Qurs, Majoon / Dawa, Khamira, Itrifal, Tiryaq, Burood / Surma / Kohal, Raughaniyat, Marham / Zimad / Qairooti, Sharbat / Sikanjabeen, Jawarish, Capsule have shelf life up to 3 years, Laooq, Laboob, Halwa, Mufarreh / yaqooti, Ayarij / Safoof, Murabba have shelf life up to 2 years, Kushta, Nabeez have shelf life up to 5 years, Safoof (Namak wala / containing salt), Arq, Qutoor, Murabba have shelf life up to 1 year<sup>26</sup>.

### **Stability Studies for Finished Pharmaceutical Ingredients General**

The design of the stability studies for the finished pharmaceutical product (FPP) should be based on knowledge of the behavior and properties of the Active Pharmaceutical Ingredients (API) and their stability studies and on experience gained from pre formulation studies and investigational FPPs<sup>27-36</sup>.

#### **Selection of batches**

Data from stability studies should be provided on at least three primary batches of the FPP. The primary batches should be of the same formulation and packed in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate production batches and provide product of the same quality meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot-scale batches and the third one can be smaller, if justified. Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied<sup>27-31</sup>.

#### **Container closure system**

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information respectively<sup>27-36</sup>.

#### **Specification**

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative) and functionality tests (e.g. for a dose delivery system). Analytical procedures should be fully validated and stability-indicating whether and to what extent replication should be performed will depend on the results of validation studies<sup>27-36</sup>. Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. A single primary stability batch of the FPP should be tested for

antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf-life for verification purpose, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content<sup>36</sup>.

#### **Testing frequency**

For long-term studies frequency of testing should be sufficient to establish the stability profile of the FPP. For products with a proposed shelf-life of at least 12 months the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter through the proposed shelf-life<sup>29,32,33,34</sup>. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9, 12 months), from a 12-month study is recommended<sup>27-36</sup>. Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified<sup>37</sup>.

#### **Storage conditions**

In general a FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.<sup>27-36</sup>

In general "significant change" for an FPP is defined as

1. A 5% change in assay from its initial content of API (s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (Note: Other values may be applied if justified to certain products such as multivitamins).
2. Any degradation product exceeding its acceptance criterion.
3. Failure to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. colour, phase separation, resuspendibility, caking, hardness and dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams and partial loss of adhesion for transdermal products) may be expected under accelerated conditions and as appropriate for the dosage form
4. Failure to meet the acceptance criterion for pH, or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units<sup>36,38</sup>.

#### **FPPs packaged in impermeable containers**

Parameters required to classify the packaging materials as permeable or impermeable depend on the packaging material characteristics such as thickness and permeability coefficient.

The suitability of the packaging material used for a particular product is determined by its product characteristics generally considered moisture-impermeable containers include glass ampoules. Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Stability studies for products stored in impermeable containers can be conducted under any controlled or ambient relative humidity condition.<sup>39,40</sup>

### Stability commitment

1. When available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf-life. Where the submission includes long-term stability data from the production covering the proposed shelf-life, a post-approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:
2. If the submission includes data from stability studies on at least the number of production batches, a commitment should be made to continue the long term studies through the proposed shelf-life and the accelerated studies for six months.
3. If the submission includes data from stability studies on fewer than the number of production batches, a commitment should be made to continue the long-term studies through the proposed shelf-life and the accelerated studies for six months and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf-life and on accelerated studies for six months.
4. If the submission does not include stability data on production batches, a commitment should be made to place the first two or three production batches on long-term stability studies through the proposed shelf-life and on accelerated studies for six months.
5. The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.<sup>27-36</sup>

### Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include appropriate results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). The purpose of the stability study is to establish a shelf-life based on testing a minimum of batches of the FPP and label storage instructions applicable to all future batches of the FPP manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.<sup>27-36</sup> Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the statistical analysis. However, a tentative shelf-life of 24 months may be established provided the following conditions are satisfied:

- The API is known to be stable (not easily degradable);
- Stability studies as outlined above have been performed and no significant changes have been observed;

- Supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more; and
- The manufacturer will continue to conduct real-time studies until the proposed shelf-life has been covered and the results obtained will be submitted to the national drug regulatory authority<sup>27-36</sup>.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

### Statements/Labelling

A storage statement should be established for the labelling based on the stability evaluation of the FPP. There should be a direct link between the label storage statement and the demonstrated stability of the FPP. An expiry date should be displayed on the container label like for accelerated study; the statement can be "Do Not Store at 25°C", to support the stability study<sup>39</sup>. In addition "Protect from moisture" should be added as applicable. In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging.

\*Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

### Variations

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs. The results of these stability studies should be communicated to the regulatory authorities concerned<sup>40</sup>.

### Ongoing stability studies

The purpose of the ongoing stability programme is to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain, within specifications under the labelled storage conditions<sup>41</sup>. Any reworking, reprocessing or recovery operation should also be considered for inclusion.<sup>42</sup>

Table 1: ICH Stability Zones

| Zone     | Type of Climate                              |
|----------|----------------------------------------------|
| Zone I   | Temperate zone                               |
| Zone II  | Mediterranean/subtropical zone               |
| Zone III | Hot dry zone                                 |
| Zone IV  | Hot humid/tropical zone                      |
| Zone IVb | ASEAN testing conditions hot/higher humidity |

India comes under III, IV climatic zone but usually assigned to IV<sup>43</sup>.

### Stability indicating method

According to regulatory definition; a stability indicating method is one of a number of quantitative analytical methods that are based on the characteristic structural, chemical or biological properties of each active ingredient of a drug product so that the active ingredient content can be accurately measured. Therefore a stability indicating method is an analytical procedure that is capable of discriminating between the major active intact pharmaceutical ingredients (API) from

any degradation product formed under defined storage conditions during stability evaluation period. In addition it must also be sufficiently sensitive to detect and quantify one or more degradation products. With this criterion then, the discriminating “nature” of the method indicates the method to be stability indicating as well as stability specific.<sup>2,44</sup>

### Strategy of method development

- Information regarding physicochemical properties of API is invaluable to the method development process
- Solubilities should be determined in aqueous and organic solvents.
- Separation goals-quantitative, qualitative, isolation or purification of compound
- Selection of chromatographic mode.<sup>45,46</sup>

### Factors affecting product stability

#### Physical degradation

Components of pharmaceutical (drug substances and excipients) exist in various microscopic physical states with differing degrees of order. Examples are amorphous and various crystalline, hydrated, solvated states. With time, the drug or excipient may change from one state, usually unstable or metastable, to a more thermodynamically stable state. The rate of conversion will depend on the chemical potential corresponding to the free energy difference between the states and the energy barrier (like that for chemical reactions) that must be overcome for conversion to take place<sup>47</sup>. It was evident from the reported data that higher temperatures could have devastating effect on physical stability of preparation.<sup>48</sup>

#### Chemical Stability

Chemical degradation of the active constituent in a medicinal product often results a loss of potency for example, hydrolysis of the  $\beta$ -lactam ring of benzyl penicillin results in a lower anti microbial activity.<sup>49</sup> A variety of chemical reactions can result in the degradation of drug substances and excipients; the most common reactions are oxidation and hydrolysis. Sometimes more than one reaction may occur at the same time<sup>50</sup>. Each ingredient whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substances and dosage forms. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light, humidity, oxygen, carbon dioxide. The major dosage form factors that influence drug stability include particle size (especially in emulsions and suspensions), pH, solvent system composition (i.e. Percentage of “free” water and overall polarity) compatibility of anions and cations, solution ionic strength, primary container, specific chemical additives and molecular binding and diffusion of drugs and excipients. In dosage forms, the following reactions usually cause loss of active drug content and they usually do not provide obvious visual or olfactory evidence of their occurrence.

#### Hydrolysis

Esters and  $\beta$ -lactams are the chemical bonds that are most likely to hydrolyze in presence of water. For example, the acetyl ester in aspirin is hydrolysed to acetic acid and salicylic acid in presence of moisture, but in dry environment the hydrolysis of aspirin is negligible. The aspirin hydrolysis rate increases in direct proportion to the water vapour pressure in an environment.<sup>51,52</sup>

#### Epimerization

This reaction occurs rapidly when dissolved drug is exposed to a pH of an intermediate range (higher than 3) and it results in the steric arrangement of the dimethylamino group example Tetra cycline family.<sup>51,52</sup>

#### Decarboxylation

Some dissolved carboxylic acids such as p-amino salicylic acid, lose carbon di oxide from the carboxyl group when heated. The resulting product has reduced pharmacological action.<sup>51,52</sup>

#### Dehydration

Acid catalysed dehydration forms, a product that lacks both antibacterial activity and causes toxicity.<sup>51,52</sup>

#### Oxidation

The molecular structures most likely to oxidize are those with a hydroxyl group directly bonded to an aromatic ring, conjugated dienes, heterocyclic aromatic rings, nitroso and nitrite derivatives and aldehydes. Products of oxidation usually lack therapeutic activity. Visual identification of oxidation for example the change from colourless epinephrine to its amber coloured products may not be visible in some dilutions or to some eyes.<sup>51,52</sup>

#### Photochemical decomposition

Exposure to primarily, UV illumination may cause oxidation (photo oxidation) and scission (photolysis) of covalent bonds. Ex. Nifedipine riboflavin is very liable to photo oxidation<sup>51</sup>.

#### Ionic strength

The effect of the total concentration of the dissolved electrolytes on the rate of hydrolysis reactions results from the influence of ionic strength on interionic attraction. High ionic strength of inorganic salts can also reduce the solubility of some other drugs.<sup>51,52</sup>

#### pH effect

The degradation of many drugs in solution accelerates or decelerates exponentially as the pH decreases or increases over a specific range of pH values. Improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug, resulting from hydrolysis and oxidation reactions. A drug solution or suspension may be stable for days, weeks or even years in its original formulations, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit from 4 to 3 or 8 to 9 could decrease the drug stability by a factor of ten or even greater.<sup>51,52</sup>

#### Interionic compatibility

The compatibility or solubility of oppositely charged ions depends mainly on the number of charges per ion and the molecular size of the ions.<sup>51,52</sup>

#### Solid state stability

Solid state reactions are relatively slow, thus the stability of drugs in solid state is rarely dispensing concern. The degradation rate of dry solids is usually characterised by first order kinetics or a sigmoid curve. Therefore, solid drugs with lower melting point temperatures should not be combined with other chemicals that would form a eutectic mixture.<sup>51,52</sup>



## Temperature

In general, the rate of a chemical reaction increases exponentially for each  $10^0$  rise in temperature. This relationship has been observed for nearly all drugs hydrolysis and some drug oxidation reactions. The actual factor of rate increase depends on the activation energy of the particular reaction. The activation energy is a function of the specific reactive bond and the drug formulation (e.g. solvent, pH, additives). As an example consider a hydrolysable drug that is exposed to  $20^0\text{C}$  increases in temperature, such as that from cold to controlled room temperature. The shelf life of the drug at controlled room temperature should be expected to decrease to one fourth to one twelfth of its shelf life under refrigeration.<sup>52</sup>

## Microbiological stability

In recent past 15 years ago, it was relatively common practice to give attention to the microbiological status of pharmaceutical products only if they were designed for administration by parenteral or ophthalmic routes. The situation has now changed and though we do not expect all pharmaceutical products to be sterile (that is totally devoid of all forms of life both vegetative and sporing), we do have concern about the microbiological status of all drug delivery systems. We have concern about the extent of total bio burden and we also have specific interest in excluding pathogens. Basically there are two possible ways in which the microbial status of pharmaceutical product can change significantly with time. First, micro organisms present in the product at the time of manufacture may reproduce and thus increase number of viable organisms. Thus a product, when assayed for total bio burden at the time of manufacture, is within the limits when tested after 6 months of storage, exceeds the maximum permitted bio burden. Second, if package integrity is compromised during distribution or storage, it is possible that the microbiological status of product may be adversely affected as a result of the growth of the micro organisms. In order to reduce or eliminate the first type of microbiological problem, attention should be given to quality of raw materials and the nature of the manufacturing facility and its operation. Certain raw materials that are often the source of micro organisms (both pathogenic and non pathogenic) are of natural origin e.g. corn starch, lecithin, thus there should be careful monitoring of the microbiological status of the raw materials, in terms of excluding contamination during the manufacture, such factors as positive pressure air flow, equipment design, personnel training and clear SOPs all have roles to play.<sup>2</sup>


## CONCLUSION

Natural medicines are continuously gaining attention as the therapy for many of the ailments in the modern era. Hence, it becomes the prime responsibility of the herbal drug manufacturer to provide adequate stability for long-term storage and safety for consumption by the patients. As the phyto formulation is a mixture of more than one active ingredient, care should be taken to the determination of the stability profile for natural medicines. A stable formulation will gain confidence in the modern patient compliance.

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