



## Stability testing of herbal products

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### ABSTRACT

Herbal medicinal drug may be single active constituent or entire herb source is considered as medicinal product. Most of herbal drug products used are group of constituents. Stable drug product maintains their identity, strength, therapeutic effect within given specifications throughout the shelf life. Herbal medicinal products are of different nature thermolabile to volatile. Stability testing of herbal products is a complicated issue because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known. The stability testing of herbal products check the quality of herbal products which varies with the time under the influence of environmental factors, such as temperature, humidity, light, oxygen, moisture, other ingredient or excipient in the dosage form, particle size of drug, microbial contamination, trace metal contamination, leaching from the container, etc. and also provide statistics for the determination of shelf lives. Therefore evaluation of the parameters based upon chemical, physical, microbiological, therapeutic and toxicological studies can serve as an important tool in stability studies.

**Key words:** Herbal drugs, stability testing, storage condition

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### INTRODUCTION

Herbal drugs constituents are of different kind and have many constituents. The finished products of herbal medicine generally have low concentration of active constituent(s). Stability testing of herbal drugs is a challenging risk, because the entire herb or herbal product is regarded as the active matter, regardless of whether constituents with defined therapeutic activity are known [1]. The most important aspect in the evaluation of the stability study of a product is its storage condition. The purpose of a stability testing is to provide proof 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 and to establish a recommended storage condition and shelf-life. Based on the climatic conditions only storage conditions can be determined.

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. With the help of modern analytical techniques like spectrophotometry, 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.

### Role of markers

Markers are chemically known compounds, which may or may not have therapeutic effect, use to calculate the quantity of herbal medicinal ingredients in herbal medicinal products. The choice of the marker [2] has to be justified. Finding the “right” analytical marker is a crucial need for stability testing of HMPs. Typical sources for finding markers are:

1. Monographs and drafts (EDQM Pharmeuropa).
2. Experience, transfer from other plants/constituents.
3. Literature research about known constituents.
- 4 Scientific research.

The search for suitable and new marker substances is an important interface between scientific research and the use of the results in HMP-industry’s routine quality control. The isolation and structure elucidation of chemically defined substances in a plant, drug and/or drug preparation not only helps to better understand the active principle of an HMP. It can enhance analytical quality control.

Table 1. Types of extract and marker (Guideline on Quality of HMPs/THMPs)

Extract	Specification	Marker
Standardized	Content, tolerance	Efficacious constituents (such as silymarines in <i>Silybum marianum</i> )
Quantified	Defined range	Activer marker (contributing to the therapeutic activity, for example hypericines in <i>Hypericum perforatum</i> )
Other	Related to the Validated analytical range	Analytical marker (for analytical purposes, such as valerenic acids in <i>Valeriana officinalis</i> )

### Analytical methods for Herbal products

The analysis of herbal preparations is mostly done by running high performance liquid chromatography (HPLC) [3] or gas chromatography (GC) and thin layer chromatography (TLC) methods, quantitative determinations by UV-visible spectroscopy or combinations of these. HPLC and GC methods can be used for identification and purity testing, as well as the detection of single compounds for assay, is possible during one analysis. LC and GC mass coupling [4] are the also tools for determination but, they are highly sophisticated and expensive methods.

### Shelf-life

The determination of shelf life of herbal medicinal drug products is same as chemically defined APIs, but special nature of herbal product should be taken into consideration. It is recommended that in case of a herbal medicinal product containing a natural product or a herbal drug preparation with constituents of known therapeutic activity, the variation in component during the proposed shelf-life should not exceed  $\pm 5\%$  [5,6] of the initial assay value, unless justified to widen the range up to  $\pm 10\%$  per cent or even higher. The low marker concentration in the finished product, justify the wider range.

Additionally, due to the influences of climate, harvesting and biological variance, the natural variation of the marker content needs to be taken into account. For example, the linearity of the method may be tested over a range of 40-160 per cent of the marker’s expected content in the extract and/or product. During stability testing, a setting up of the limits to  $\pm 10\%$  per cent is accepted for the finished product, by the justification of matrix effects (placebo), the lack of precision and selectivity (combination products) and the low analyte concentrations. Considering that the marker content cannot be defined to a specified level, the relative changes from the starting value are specified (95-105 per cent or 90-110 per cent ‘from the initial value).

### Challenges in Stability testing of herbal medicinal product

Evaluating the stability [7] of HMPs presents a number of challenges when compared to chemically defined substances. In particular:

1. Active substances (herbal substances and/or herbal preparations) in HMPs consist of complex mixtures of constituents and in most cases the constituents responsible for the therapeutic effects are unknown.

2. The situation is further complicated when two or more herbal substances and/or herbal preparations are combined in a HMP. In many cases where combinations of herbal substances and/or herbal preparations are present in HMPs, they have similar constituents and this gives rise to even more analytical challenges.

3. In addition, many herbal substances/herbal preparations are known to be unstable.

Taking into account these special features of HMPs, adequate quality concepts have been established. As part of a total control strategy for herbal substances, herbal preparations and HMPs, a set of test criteria including qualitative and quantitative parameters has been recognized as quality indicating. With regard to stability tests, chromatographic fingerprints as well as appropriate methods of assay via marker substances represent the fundamental part of this concept, laid down in shelf-life specifications. Notwithstanding the appropriateness of this approach, its realization is often associated with analytical problems and high costs.

In summary, HMPs have a number of characteristics that clearly differentiate them from chemically defined medicinal products and therefore specific stability guidance needs to be established, which covers particular aspects that existing specific herbal guidelines and general guidelines on stability do not address.

#### **Mechanisms involved in change product**

Loss of activity, Change in concentration of active component[8], Alteration in bioavailability, Loss of content uniformity, Loss of elegance, Formation of toxic degradation product, Loss of packaging integrity.

**Importance of Stability testing:** It evaluates the efficacy of a drug. Stability studies [9] are used to develop suitable packaging information for quality, strength, purity & integrity of product during its shelf life. It is used for determination of the shelf life.

**Stress testing:** Stress testing help to identify the degradation product, which can help to establish the degradation pathway. Stress tests are usually considered unnecessary for herbal drug & its preparation.

1. For herbal drugs and herbal drug preparations, a testing under accelerated or intermediate conditions may be omitted. This should apply to finished products as well, because it is known that most products fail at 30°C/65 per cent relative humidity (RH) and at 40°C/75 per cent RH in particular. Herbal drug substances at only 25°C/60 per cent RH, with no requirement for intermediate/ accelerated testing.

2. If intermediate conditions are tested, the three-month time-point is omitted (that is, 0, 6, 9 and 12 months). In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times.

#### **Selection of batches:**

Long term testing is to be provided with on at least two batches of the drug substance and three batches [10] of drug product. In some cases of combination products, it is hardly possible to provide the required two batches of each extract at the same time due to different harvesting times. This should be taken into consideration when planning the schedule for stability study.

#### **Predictable changes in Herbal medicinal Product**

Following predictable changes [11] may occurs in herbal medicinal product during storage and in shelf life determination: Hydrolysis, Oxidation, Racemization, Geometric isomerization, Temperature, Moisture and Light

**Hydrolysis:** Reaction with water takes place results in degradation of product.

**Oxidation:** Due to addition of electro negative atom (o), Removal of electro positive atom, radicals formation results in decomposition of natural products.

**Racemization:** Racemization is the process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer. The compound then alternates between each form while the ratio between the (+) and (-) groups approaches 1:1, at which point it becomes optically inactive.

**Geometric isomerization:**

Geometric isomerization: Products can be change in trans or cis form. One form may be more therapeutically active.

**Polymerization:** There is combination of two or more identical molecule to form much larger & more complex molecule.

**Temperature:** The rate of most chemical increase with increase in temperature. So that “Tropical” area must be taken in consideration during preparation of the formula of the herbal substance.

**Moisture:** Moisture absorbed on to the surface of solid drug will often increase the rate of decomposition, if it is susceptible to the hydrolysis.

**Light:** Many type of chemical reaction induced by exposure to light of high energy. Autoxidation of volatile oil / fixed oil takes place and substance becomes colored.

### CONCLUSION

Stability testing of Herbal products with known chemical constituents is same as chemically defined APIs but the major herbal medicinal products are complex in nature. So one should take accounts of particular requirements and conditions. Major studies are same for both herbal medicinal and chemically defined products. The specific features for herbals are as follows:

1. Two batches of the drug substance and three batches of drug product
2. No three-month testing-point at 30°C/65 per cent RH for the drug product
3. Herbal drug substance at only 25°C/60 per cent RH, with no requirement for intermediate/ accelerated testing
4. Assay of marker substances for ‘quantified’ and ‘other’ extracts Choice of methods, combination of methods and fingerprints
5. Assay  $\pm 5$  per cent or  $\pm 10$  per cent from the initial value for quantified and other extracts (rather than for the declared value, as for standardized extracts and chemical APIs)
6. A requirement for ongoing stability-studies

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