STABILITY TESTING OF HERBAL DRUGS

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Stability Studies

• Stability testing is an obligatory requirement in the registration process for all medicinal products, including Herbal Medicinal Products (HMPs).

• The HMPs are subjected to systematic stability testing in order to establish and ensure consistent therapeutic efficacy and safety throughout their shelf life. The tests are performed to define storage conditions and the product’s shelf-life.

• Stability testing is an important component of herbal drugs and products development process.

• Drugs regulatory agencies across the globe have recommended guidelines for the conduct of stability studies of HMPs, which require that stability data should be included during product registration.

• Numerous chemical constituents in an herbal drug are liable to varied chemical reactions under the influence of conditions during shelf life.

• These reactions can change chemical composition of the HMPs and finally altered therapeutic profile.

• The challenges in stability of HMPs are chemical complexity, chemical variability in crude drug, selection of marker, influence of enzymes etc.
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The need for Stability Studies

- Well-being of the patient and manufacturer by ensuring product quality
- For selection of adequate formulation, determination of shelf-life and storage conditions
- Preparation and substantiation of the claimed shelf-life for the registration dossier
- To provide evidence on how quality of drug/product varies with time under influence of environment
Regulatory Basis of Herbal Drug Stability Testing

• Guidelines provided by drugs regulatory agencies such as European Medicine Agency (EMEA, 2010), International Conference on Harmonization (ICH, 2003) and World Health Organization (WHO, 2009) require stability data of any product prior its approval.

• Various approaches for assessment of shelf life include assay of markers (active or analytical), biological assays, and/or chromatographic chemoprofiling or fingerprinting of control and stability samples of a product under different stability conditions.
Scientific Basis of Herbal Drug Stability Testing

- Stability studies on herbal drugs involve quantitative monitoring of active constituent and or analytical marker.
- Constituents belonging to different chemical groups in an HMP may undergo varied intra-molecular or inter-molecular reactions under the influence of heat, humidity and/or light during its manufacture, transportation and storage.
- These interactions between different groups are liable to produce products that may be more or less active and/or toxic.

**Example:**

- Polyphenols with proteins and polysaccharides via H-bonding and hydrophobic interactions
- Reversible complexes
- Decreased level of free polyphenols

Contd.
- Water solubility of tannins is increased in the presence of water soluble glycosides as with paeniflorin and glycyrrhizin.
- Alkaloids are precipitated in the presence of tannins.
- Polysaccharides, tannins and lignins form mono-dentate and bi-dentate complexes with heavy metal ions.
- Cations form strong complexes with Polysaccharides in alkaline medium but weak complexes in other media.

So it is required to ensure that the overall chemical composition of a drug remains unchanged during its shelf-life.
Vinca rosea (Catharanthus roseus)

Effect of UV light on total contents of Vinca rosea

UV- light

• Presence of UV light B increases total flavanoid content
• VINBLASTIN rapidly biotransforms to VINCRIISTINE in presence of UV-A light.
• presence of UV-A light increases concentration of VINBLASTIN
Herbal Drugs and Preparation

1. Standardized Extract
   • Silymarines in *Silybum marianum*

2. Quantified Extracts
   • Hypericines in *Hypericum perforatum*

3. Others
   • Drug-Extract Ratio

Herbal products are complex in nature due to a high number of constituents of different chemical classes. Classified entirely on basis of the active pharmaceutical ingredients. EMEA, has subdivided herbal preparations into three categories based on the active constituents in the product.
Mechanisms affecting Stability

**HYDROLYSIS**
Reaction with water leads to degradation of compound.

**LIGHT**
Many chemical changes due to exposure to light. Auto oxidation of volatile oils.

**OXIDATION**
Addition of oxygen, radical formation and decomposition of product.

**MOISTURE**
Absorption of moisture on solid surface increases decomposition.

**GEOMETRIC ISOMERIZATION**
Trans and cis forms, one form may be more therapeutically active.

**TEMPERATURE**
Chemical changes increase with increase in temperature.
ICH zones and long-term stability conditions

<table>
<thead>
<tr>
<th>CLIMATIC ZONE</th>
<th>CLIMATE</th>
<th>COUNTRIES</th>
<th>MAT/ MAPWP</th>
<th>LONG TERM TESTING CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Temperate</td>
<td>UK Northern Europe, US</td>
<td>&lt;15°C/ &lt;11hPa</td>
<td>21°C/ 45%RH</td>
</tr>
<tr>
<td>II</td>
<td>Subtropical &amp; Mediterranean</td>
<td>Japan, Southern Europe</td>
<td>&gt;15-22°C/ &gt;11-18hPa</td>
<td>25°C/ 60%RH</td>
</tr>
<tr>
<td>III</td>
<td>Hot &amp; Dry</td>
<td>Iraq, India</td>
<td>&gt;22°C/ &lt;15hPa</td>
<td>30°C/ 35%RH</td>
</tr>
<tr>
<td>IVa</td>
<td>Hot &amp; Humid</td>
<td>Iran, Egypt</td>
<td></td>
<td>30°C/ 65%RH</td>
</tr>
<tr>
<td>IVb</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>
Types of Stability testing methods

- **Accelerated Testing:** Product subjected to high temperature, humidity, light, etc. 40ºC/ 75% RH. At 3rd and 6th month.

- **Real Time (long-term) Testing:** Longer duration. 25-30ºC & 35-75% RH (depending on climatic zone), for 3rd, 6th, 9th, 12th, 18th, 24th, and 36th month.

- **Intermediate Testing:** Conducted when accelerated studies fail. At 25ºC for longer duration of time.

- **Stress Testing:** Includes effects of temperature, i.e., above 40ºC and ≥75% RH.

- **Forced Degradation Testing:** performed to provide intrinsic stability assessment of drug.
## Stability Testing Storage Conditions for drugs as per ICH and WHO

<table>
<thead>
<tr>
<th>Intended Storage Condition</th>
<th>Stability Test Method</th>
<th>Test temp. and humidity (period in months) as per ICH</th>
<th>Test temp. and humidity (period in months) as per WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room temperature</td>
<td>Long term</td>
<td>25±2°C/60±5% RH</td>
<td>25±2°C/60±5% RH or 30±2°C/65±5% RH or 30±2°C/75±5% RH</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>30±2°C/65±5% RH</td>
<td>30±2°C/65±5% RH</td>
</tr>
<tr>
<td></td>
<td>Accelerated</td>
<td>40±2°C/75±5% RH</td>
<td>40±2°C/75±5% RH</td>
</tr>
<tr>
<td>Refrigerated</td>
<td>Long term</td>
<td>5°C/ambient</td>
<td>5±3°C</td>
</tr>
<tr>
<td></td>
<td>Accelerated</td>
<td>25±2°C/60±5% RH (6)</td>
<td>25±2°C/60±5% RH or 30±2°C/65±5% RH</td>
</tr>
<tr>
<td>Freezer</td>
<td>Long term</td>
<td>-20°C/ambient (12)</td>
<td>-20°C/5±5°C</td>
</tr>
<tr>
<td>Method and climatic zone</td>
<td>Environment</td>
<td>Time points for sampling</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Long term for climatic zones I and IV</td>
<td>25°C/60% RH</td>
<td>3, 6, 9, 12, 18, 24, 36 months</td>
<td></td>
</tr>
<tr>
<td>Long term for climatic zones III</td>
<td>30°C/35% RH</td>
<td>3, 6, 9, 12, 18, 24, 36 months</td>
<td></td>
</tr>
<tr>
<td>Long term for climatic zone IVa/Intermediate for zones I and II</td>
<td>30°C/65% RH</td>
<td>3, 6, 9, 12, 18, 24, 36 months</td>
<td></td>
</tr>
<tr>
<td>Long term for climatic zone IVb/Intermediate for zones I and II</td>
<td>30°C/75% RH</td>
<td>3, 6, 9, 12, 18, 24, 36 months</td>
<td></td>
</tr>
<tr>
<td>Accelerated condition for all zones</td>
<td>40°C/75% RH</td>
<td>3, 6 months</td>
<td></td>
</tr>
</tbody>
</table>
Challenges in Stability Testing

Active substances in HMPs consist of complex mixtures of constituents & most of markers & their therapeutic effects are unknown.

Many herbal compounds are unstable hence, a set of test criteria including qualitative and quantitative parameters has been recognized as quality indicating.

In combined formulations, different substances having similar constituent give rise to analytical challenges. Different studies are conducted during one year for such changes.
## Selection of batches and Testing conditions

<table>
<thead>
<tr>
<th>FORMAL STABILITY STUDIES</th>
<th>LONG TERM STABILITY STUDIES</th>
<th>ONGOING STABILITY STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Conducted on at least three primary batches.</td>
<td>▪ On at least three batches performed under natural conditions.</td>
<td>▪ All products have to be tested at least one batch a year.</td>
</tr>
<tr>
<td>▪ Stability performed on each individual strength and container size till bracketing.</td>
<td></td>
<td>▪ Wherever appropriate, bulk products are also to be tested.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Applies to every dosage and packaging size and type.</td>
</tr>
</tbody>
</table>
Special conditions to take account for HMPs

Specification Limit:

➢ Limit of assay of ±5% of declared value shall be applied to standardized extracts.

➢ For drugs with low marker concentration, the range shall be widened to ±10% or even higher.

➢ Due to influence of climate, natural variation in markers shall be taken into account.

➢ Since marker content cannot be defined to a specific level, the relative changes from starting value are (95-105% or 90-110%) from initial value.

➢ An analytical marker is stable in herbal substances (monograph) and in solid dosage forms but unstable in liquid dosage form. This can be solved by various means: a stable marker shall be chosen, etc.
Protocols for Stability Testing

1. Selection of Batches and Samples
2. Test Attributes
3. Analytical procedures
4. Acceptance Criteria
5. Storage Conditions & Storage period
6. Testing Frequency
7. Sampling Plan
8. Container closure system
9. Evaluation
10. Statements labelling
Summary

➢ Herbal medicinal products like all other drugs, have to fulfil the legal requirements with regards to quality including stability testing.

➢ Due to their natural origin, the analytics of all types of extracts is challenged by a complex matrix requiring a complex sample preparation.

➢ There are generally no differences between specifications set up for HMPs and chemically defined APIs, whereas the special nature of the herbal products shall be taken into consideration.

➢ In many cases constituents have a low concentration, and also different concentration on different locations.
BIBLIOGRAPHY


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- Aspects of collection, Processing and Storage in ISM Manufacturing unit by Dr. Anil Sharma.


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Thank You