STANDARDISATION AND QUALITY CONTROL OF MULTIHERBAL FORMULATIONS

BY

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HERBAL DRUGS

ARE – FINISHED LABELLED PRODUCTS THAT CONTAIN ACTIVE INGREDIENTS SUCH AS AERIAL OR UNDERGROUND PARTS OF PLANT OR OTHER PLANT MATERIAL OR COMBINATIONS THEREOF, WHETHER IN THE CRUDE STATE OR AS PLANT PREPARATIONS.

ARE NOT – THE MEDICINES THAT CONTAINING PLANT MATERIAL COMBINED WITH CHEMICALLY DEFINED ACTIVE SUBSTANCES INCLUDING CHEMICALLY DEFINED ISOLATED CHEMICAL CONSTITUENTS OF PLANTS.

(As Defined by World Health Organization)
HERBAL DRUGS

CLASSIFIED AS –

- Phytomedicines or Phytopharmaceuticals sold as Over The Counter (OTC) products in modern dosage forms such as Tablets, Capsules & Liquids for oral use.

- Dietary Supplements containing Herbal Products, also called Neutraceuticals available in modern dosage forms.

- Herbal Medicines consisting of either Crude, Semi–Processed or Processed Medicinal Plants.
HERBAL DRUGS

SINGLE OR CRUDE DRUGS

MULTI HERBAL FORMULATIONS
HERBAL DRUGS

SINGLE / CRUDE DRUGS

- ALL MAINLY WHOLE, FRAGMENTED OR CUT PLANTS, PLANT PARTS USUALLY DRIED FORM, BUT SOMETIMES FRESH

- ALSO INCLUDE ALGAE, FUNGI & LICHENS

- CERTAIN EXUDATES THAT HAVE NOT BEEN SUBJECTED TO A SPECIFIC TREATMENT
HERBAL DRUGS

MULTIHERBAL FORMULATIONS

FORMULATIONS ARE OBTAINED BY SUBJECTING HERBAL INGREDIENTS TO VARIOUS MANUFACTURING PROCesses SUCH AS –

- EXTRACTION
- DISTILLATION
- EXPRESSION
- FRACTIONATION
- PURIFICATION
- CONCENTRATION
- FERMENTATION
HERBAL DRUGS

KEY PARAMETERS

- STANDARDISATION
- QUALITY EVALUATION
HERBAL DRUGS

STANDARDISATION

ADJUSTING THE HERBAL DRUG PREPARATION TO A DEFINED CONTENT OF A CONSTITUENT OR A GROUP OF SUBSTANCES WITH KNOWN THERAPEUTIC ACTIVITY RESPECTIVELY BY ADDING EXCIPIENTS OR BY MIXING HERBAL DRUG EXTRACTS
HERBAL DRUGS

QUALITY EVALUATION

A SYSTEMATIC EXAMINATION OF THE EXTENT TO WHICH AN ENTITY (PART OR PRODUCT) IS CAPABLE OF MEETING SPECIFIED REQUIREMENTS. THE RESULT OF QUALITY EVALUATION MAY BE USED FOR QUALIFICATION, APPROVAL AND REGISTRATION OR ACCREDATION PURPOSES.

A QUALITY EVALUATION MAY BE USED TO DETERMINE MANUFACTURING QUALITY CAPABILITY.
HERBAL DRUGS – QUALITY EVALUATION

- ABSOLUTELY REQUIRED FOR -
  - AUTHENTICITY
  - PURITY
  - SAFETY

- QUALITY EVALUATION –
  - QUALITY CONTROL
  - QUALITY ASSURANCE

- THE WHO AND NUMBER OF COUNTRIES DEALING WITH HERBAL DRUGS FORMULATED VARIOUS PROTOCOLS FOR STANDARDISATION AND QUALITY EVALUATION
HERBAL DRUG STANDARDIZATION

THE TRIPLE ‘P’ BASED PROTOCOLS

- PHARMACOGNOSTICAL
- PHYSICO – CHEMICAL
- PHYTOCHEMICAL

RESIDUAL ANALYSIS
HERBAL DRUGS - STANDARDISATION

**PHARMACOGNOSTICAL**
- Taxonomical
- Morphological
- Anatomical
- Biological
- Biochemical
- Biotechnological

**PHYSICO - CHEMICAL**
- Ash Values
- pH
- Optical Rotation
- Specific Gravity
- Hardness
- Disintegration Time
- Elemental Composition

**PHYTOCHEMICAL**
- Extractive Values
- Chemical Profiling
- TLC Fingerprinting
- Markers
  - Bio-active
  - Biologically
  - Chemical
- HPTLC / HPLC Based Quantifications

**Residual Analysis**
- Heavy Metals
- Pesticides
- Toxins
- Radio-actives
- Fumigants
- Pathogens
- Fungicides
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

THE BOTTLENECKS

- USE OF MULTIPLE INGREDIENTS
- INCONSISTENCY OF FINISHED FORMULATIONS
- OVERLAPPING OF CHEMICAL & CHROMATOGRAPHIC PROFILES
- STABILITY OF FORMULATIONS
- DIFFICULTY IN DEVELOPING STANDARDS.
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

MULTIPLE INGREDIENTS

EVERY INGREDIENT NEED TO BE STANDARDISED
INCREASE OF CONSTITUENTS LOAD
DISAPPEARANCE OF INGREDIENT CHARACTERS IN FORMULATIONS
OVERLAPPING CHEMICAL AND CHROMATOGRAPHIC PATTERNS
STABILITY OF INGREDIENTS VS FORMULATION STABILITY
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

FORMULATION INCONSISTENCY

LARGE VARIATIONS IN DIFFERENT SAMPLES OF SAME FORMULATION

VARIATIONS IN INGREDIENTS

VARIATIONS IN QUANTITY OF INGREDIENTS

NO UNIFORM MANUFACTURING PROTOCOLS
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

FORMULATION INCONSISTENCY

A CLASSICAL EXAMPLE

RASAYANA FORMULATION

54 INGREDIENTS

T₁ T₂, T₄ T₅ : COMMERCIAL FORMULATIONS; T₃ : MAJOR INGREDIENT
MULTIHERBAL FORMULATIONS

STANDARDISATION & QUALITY CONTROL

FORMULATION INCONSISTENCY

A FORMULATION WITH 5 INGREDIENTS

T₁, T₄, T₅ : COMMERCIAL FORMULATIONS
T₂, T₃ : MAJOR INGREDIENT

A FORMULATION WITH 18 INGREDIENTS

T₁, T₂, T₆, T₇, T₈, T₉, T₁₀ : COMMERCIAL FORMULATIONS
T₃, T₄, T₅, T₆, T₇ : MAJOR INGREDIENTS
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL
STABILITY OF FORMULATIONS

THE MULTIHERBAL FORMULATIONS CONSISTING OF SEVERAL ACTIVE AND INACTIVE CONSTITUENTS ARE AMENABLE FOR TRANSFORMATION AND POSE SERIOUS PROBLEMS TO THE STABILITY OF FORMULATIONS
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL
THE ESSENTIAL COMPONENTS

MULTIHERBAL FORMULATIONS

INGREDIENTS QUALITY

STABILITY

STANDARDISATION

SOPs OF MANUFACTURING PROCESS

SAFETY

EFFICACY
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL
THE PROTOCOLS

QUALITY EVALUATION (AUTHENTICITY) OF INGREDIENTS
(TRIPLE ‘P’ BASED SCREENING)

SOP DEVELOPMENT FOR MANUFACTURING PROCESS OF
MULTIHERBAL FORMULATIONS
(EXTRACTION, DISTILLATION, CALCINATION, FERMENTATION ETC.)

STANDARDISATION OF FORMULATIONS
(TRIPLE ‘P’ BASED, ESPECIALLY CHEMICAL & CHROMATOGRAPHIC
PROFILING, MARKER COMPOUNDS, QUANTITATIVE STUDIES)
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

THE PROTOCOLS

STABILITY STUDIES
(SHELF LIFE EVALUATION BASED ON PHYSICO-CHEMICAL,
MICROBIAL & HPTLC/HPLC FINGER PRINTS)

SAFETY
(Toxicological DATA & DOCUMENTED EXPERIENCE)

EFFICACY
( PHARMCOLOGICAL SCREENING DATA & DOCUMENTED
TRADITIONAL USE)
MULTIHERBAL FORMULATIONS

MARKER COMPOUNDS

RELIABLE QUALITY CONTROL STANDARDS

MARKERS ARE CHEMICALLY DEFINED CONSTITUENTS, WHICH MAY OR MAY NOT HAVE THERAPEUTIC ACTIVITY AND ARE OF HIGH SIGNIFICANCE FOR CONTROL PURPOSE

A : CHEMICAL MARKERS
B : BIO MARKERS
C : BIO - ACTIVE MARKERS (THERAPEUTIC MARKERS)
MARKER COMPOUNDS

THESE ARE –

- PURE, SINGLE ISOLATED COMPOUNDS
- SECONDARY METABOLITES
- MOSTLY WITH TERPENE, STEROID, ALKALOID, FLAVONOID AROMATIC & HETEROAROMATIC FRAMEWORKS
- HAVING ALCOHOLIC, CARBONYL, OLEFINIC, ACID, ESTER & AMIDE FUNCTIONALITIES

HIGHLY USEFUL FOR SINGLE / CRUDE DRUGS

MAY OR MAY NOT SURVIVE IN MULTIHERBAL FORMULATIONS
MARKER COMPOUNDS

- PURE, SINGLE ISOLATED COMPOUNDS
- SECONDARY METABOLITES
- MOSTLY WITH TERPENE, STEROID, ALKALOID, FLAVONOID AROMATIC & HETEROAROMATIC FRAMEWORKS
- HAVING ALCOHOLIC, CARBONYL, OLEFINIC, ACID, ESTER & AMIDE FUNCTIONALITIES

HIGHLY USEFUL FOR SINGLE / CRUDE DRUGS

MAY OR MAY NOT ‘SURVIVE’ IN MULTIHERBAL FORMULATIONS
MULTIHERBAL FORMULATIONS

FATE OF MARKER COMPOUNDS

CLUES FROM CHROMATOGRAPHIC PATTERNS

SOME MARKER COMPOUNDS SUFFER STRESS DURING THE MANUFACTURE OF MULTIHERBAL FORMULATIONS
MULTIHERBAL FORMULATIONS

MARKER COMPOUNDS

MARKER COMPOUNDS OF INGREDIENTS NOT NECESSARILY THE MARKERS FOR FORMULATIONS

SOME MARKERS UNDERGO TRANSFORMATIONS AND DECOMPOSE, VANISH OR GENERATE NEW MARKERS

MARKER COMPOUNDS SPECIFIC TO MULTIHERBAL FORMULATIONS NEED TO BE ISOLATED

FORMATION OF NEW MARKERS DEPENDS ON THE VARIOUS MANUFACTURING PROCESSES
# Multiherbal Formulations

### Analogy Between Manufacturing Process and Chemical Transformation

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Type of Formulation</th>
<th>Operation of Manufacture</th>
<th>Chemical Analogy</th>
<th>Transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vati/Gutika/Guggul</td>
<td>Mixing of Powdered Ingredients with or without Metallic Preparations, Resins and Excipients</td>
<td>Solid State Transformations with or without Metallic Catalysts</td>
<td>Rearrangements and Condensation Reactions</td>
</tr>
<tr>
<td>2.</td>
<td>Kashaya</td>
<td>Boiling of Plant Ingredients with Water</td>
<td>Hydration</td>
<td>Hydrolysis and Addition of Water</td>
</tr>
<tr>
<td>3.</td>
<td>Asava / Arista</td>
<td>Soaking of Plant Ingredients or their Extracts in Water with a Sweetening Agent and Inoculum Bearing Plants</td>
<td>Fermentation</td>
<td>Induces Microbial Transformations</td>
</tr>
<tr>
<td>4.</td>
<td>Grhita/Taila</td>
<td>Treatment of Plant Extracts in Ghee or Oil Under Controlled Conditions</td>
<td>Enzymatic Reactions</td>
<td>Trans Esterification or Hydrolysis</td>
</tr>
<tr>
<td>5.</td>
<td>Ksara / Lavana</td>
<td>Burning of Plant Ingredients with or without salts</td>
<td>Pyrolysis</td>
<td>Degradation and Decomposition</td>
</tr>
</tbody>
</table>
MULTIHERBAL FORMULATIONS

MARKERS MAJOR TRANSFORMATIONS

- HYDROLYSIS
  (Glycoside: Aglycone+Sugar; Ester: Acid+Alcohol; Amide: Acid+Amine)

- DEHYDRATION
  (Alcohols: Alkenes)

- ESTERIFICATION

- GLYCOSIDATION

- ISOMERISATION

- REARRANGEMENTS
MULTIHERBAL FORMULATIONS

MARKERS COMPOUNDS NEW CLASSIFICATION

- CHEMICALLY MODIFIED MARKERS
- HYBRID MARKERS
- PSEUDO MARKERS
- IMPURITY MARKERS
MULTIHERBAL FORMULATIONS

MARKERS COMPOUNDS NEW CLASSIFICATION

➢ CHEMICALLY MODIFIED MARKERS
  THESE MARKERS GENERATED BY -
  ❖ DEALKYLATION
  ❖ DEACETYLATION
  ❖ DEHYDRATION &
  ❖ ISOMERISATION

➢ HYBRID MARKERS
  ❖ THESE MARKERS GENERATED BY –
  ❖ CONDENSATION
  ❖ ESTERIFICATION
  ❖ GLYCOSILATION
MULTIHERBAL FORMULATIONS
MARKERS COMPOUNDS NEW CLASSIFICATION

- **PSEUDO MARKERS**
  - THESE ARE MOSTLY FORMED BY –
    - DEGRADATION
    - DECOMPOSITION
    - POLYMERISATION

- **IMPURITY MARKERS**
  - THESE ARE NEGATIVE MARKERS FORMED BY –
    - PYROLYSIS
MULTIHERBAL FORMULATIONS

IMPURITY MARKERS

THESE ARE PARTICULARLY USEFUL FOR LAVANA, KSARA, BHASMA WHICH ARE PREPARED BY BURNING THE PLANT INGREDIENTS.

T₁ AND T₂ ARE TWO LAVANA FORMULATIONS
MULTIHERBAL FORMULATIONS

MARKERS GENERATION

THE FOLLOWING ISOLATION & SPECTROSCOPIC TECHNIQUES ARE HIGHLY USEFUL

- GRAVITY COLUMNS, PREPARATIVE LAYERS
- FLASH / MPLC / HPLC
- LIQUID – LIQUID CHROMATOGRAPHY LIKE DCCC / HSCCC
- IR/UV/1D & 2D NMR, MASS
MULTIHERBAL FORMULATIONS

MARKERS QUANTIFICATION

THE FOLLOWING CHROMATOGRAPHIC TECHNIQUES ARE HIGHLY USEFUL

- TLC
- HPTLC / AMD
- HPLC
- GC & GC-MS
- TLC – FID/FPD
- CAPILLARY ELECTROPHORISIS
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

CONCLUSIONS

EFFICIENT STANDARDISATION AND QUALITY CONTROL OF MULTIHERBAL FORMULATIONS CAN BE ACHIEVED BY ADOPTING A 6 POINT PROTOCOL CONSISTING OF:

I) STANDARDISATION AND AUTHENTIFICATION OF INGREDIENTS
II) SOP DEVELOPMENT FOR MANUFACTURING PROCESS OF FORMULATIONS
III) TRIPLE ‘P’ BASED SCREENING COUPLED WITH RESIDUAL ANALYSIS OF FORMULATIONS
IV) STABILITY (SHELF LIFE) STUDIES
V) EFFICACY
VI) SAFETY
MULTIHERBAL FORMULATIONS
STANDARDISATION & QUALITY CONTROL

CONCLUSIONS

- Marker compounds are highly useful for quality control.
- Markers of ingredients may not be the markers of formulations.
- Various process steps have been correlated with chemical transformations.
- Markers of formulations can be re-classified.
- Markers specific to formulations need to be isolated.
- Identified various chromatographic and spectroscopic techniques.
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