A Review on Quality Control in Herbal Medicine Formulations

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Abstract:

This study aims to summarize the essential quality measures for herbal formulations, covering their parameters and standards. It emphasizes the importance of adhering to strict quality assurance criteria throughout the manufacturing process and beyond, ensuring the efficacy, stability, and longevity of the finished products. Additionally, the review explores the historical background of herbal formulations, distinguishes between quality assurance and quality control, and discusses methods like macroscopic and microscopic characterization in ensuring the quality of herbal products.

Keywords: Herbal formulations, Quality assurance, GMP, Manufacturing process

INTRODUCTION

Since antiquity, herbal medications have been used to treat a wide range of diseases, and they constitute an important part of modern healthcare. Even with the amazing developments in contemporary medicine, medicinal herbs are still very important to healthcare. (Calixto, 2000, pp. 179-189) Therapeutic herbs have drawn a lot of interest lately because of their well-known immunomodulatory, adaptogenic, and antimutagenic activities. About 25% of all current medications are thought to come either directly or indirectly from higher plants.

The World Health Organisation (WHO) estimates that between 65 and 80 percent of the world's population living in underdeveloped nations depends mostly on plants for basic healthcare because of their poverty and lack of access to contemporary medication. Because synthetic medications are overused and have greater rates of adverse drug responses, natural therapies are becoming more popular as safer substitutes. India comes in ninth place worldwide with about 47,000 plant species, more than 7,500 of which have therapeutic qualities. Apparently, 800 species are exploited, with 120 species being used significantly.

Major pharmaceutical corporations are currently displaying rekindled interest in generating standardized phytotherapeutic medicines with demonstrated efficacy, safety, and quality as well as in searching higher plants for new lead molecules. Because natural product libraries show a wider range of molecular properties than synthetic and combinatorial equivalents, including molecular mass, octanol-water coefficient, and diversity in ring systems, it is becoming more widely acknowledged that screening natural products may be more effective in discovering new chemical entities.

Safety, quality, and efficacy of herbal medications have come under question as their use worldwide increases. The approval of herbal medications and formulations within contemporary medical systems must be justified by strict quality control. One major problem the sector faces is the absence of rigorous evaluation criteria and quality control requirements for herbal products. (Solescki, 1975. *Neanderthal Flower Burial of Northern Iraq*. *Science*, 4th edition.)

HISTORY:

The first kind of healthcare in history worldwide, traditional medicine, has mostly depended on herbs, especially spices, which have been essential to the development of civilizations. Ever since antiquity, spices have been used for everything from food and clothing to shelter and medicine. Natural pharmacopoeias are standardized natural pharmacopoeias that resulted from experiments and observations of animals on the therapeutic application of plants.

Many medications now come from natural sources; in the US, active components from plants make up about 25% of prescribed medications. Some drugs use synthetic reproductions of particular plant chemicals or plant extracts. History supports the continued usage of these plants, as seen by the finding of marshmallow root, hyacinth, and yarrow among the remains of a Stone Age man in Iraq.

First published in 1820, the first U.S. Pharmacopoeia offered a thorough list of herbal medications together with information on their applications, dosages, and efficacy. But when Western medicine evolved in the eighteenth century from an artisanal to a scientific field, herbal knowledge became less accessible. A more informal and maybe less standardized use of herbs resulted from pharmaceutical research centers replacing traditional herbal vendors as the main makers of medications. (Bensky, 1993)

The Upanishads, Buddhism, and other Indian philosophy all arose in East India alongside the development of Ayurvedic medicine. Ayurvedic treatment heavily relied on spices; the Charaka Samhita, the first book on internal medicine, lists 582 herbs. (Bedi et al., 1989)

QUALITY ASSURANCE:

Given the possible hazards to patients' lives and health, regulatory bodies in the modern pharmaceutical sector give particular weight to the idea of quality. Many rules have been created to guarantee a high standard of quality; these go beyond rigorous compliance and verification of quantifiable requirements to include a well thought-out and directed procedure. Today, quality is the responsibility of the whole staff and cannot be left to a centralized quality department. (World Health Organization, 2002, p. 15)

Meeting all legal and experience requirements at every stage of the production of high-quality herbal medical goods—from the selection and procurement of raw herbal materials through processing, intermediate stages, and final production steps to the finished product—defines quality in the manufacturing of these products. To guarantee adherence to the many standards relevant to the pharmaceutical sector, quality assurance is therefore an administrative job that comprises control and documentation procedures. (World Health Organization, 2002, p. 15)

Quality assurance of the product depends on more than just appropriate sample and acceptable checking out of many ingredients and the finished dosage form. The producing section bears primary responsibility for maintaining high-satisfactory product throughout manufacturing. Errors in packaging or filling, such as product contamination, mislabelling, or poor packaging; and non-conformance to product registration can result from the removal of the responsibility from production for producing a high-satisfactory product.Employees providing quality warranty should establish management or checkpoints to monitor the product's quality during processing and after the manufacturer's crowning splendor.These begin with raw materials and the factor checking out and include batch auditing, balance monitoring, packing, labeling, and finished product checking out. (World Health Organization, 2002)

Excellent warranty may be portrayed in relation to pharmaceutical company as:

Quality Assurance = GAP + GHP + GMP + GLP + different measures

GAP = Good agriculture practices.

GHP = Good harvesting practices.

GMP = Good production practices.

GLP = Good laboratory practices.

GAP (Good agriculture practices):

The production and basic processing of these traded and therapeutically used plants is the aim of the Good Agricultural Practices (GAP) for medicinal herbs. Production of all plant materials utilized in the food, feed, pharmaceutical, flavoring, and fragrance sectors is subject to these regulations. Assuring that the plant raw material satisfies both customer demand and the strictest quality requirements is the main goal of GAP.

GHP (Good harvesting practices):

Mostly obtained from the tissues or organs of medicinal plant species, usually in dried form, plant medications are the basis of phytomedicines. The World Health Organisation (WHO) reports that some 21,000 plant species are known to be utilized therapeutically as plant medications. Seventy to ninety percent of these species are gathered from their natural habitats for commercial use. But just between 50 and 100 species are actively grown with methods like Plant Tissue Culture (PTC).(Dr. Mukherjee, 2002)

GMP (Good Manufacturing practices):

Particularly because regulatory requirements have gotten harsher in recent years, the pharmaceutical sector has worked closely with the FDA to guarantee the public receives pure, high-quality life-saving medications. All elements that influence product quality, either separately or in concert, are covered by this all-encompassing strategy. It guarantees that goods satisfies the specifications needed for its intended usage. The system of quality control for pharmaceutical

producers guarantees that:

- Good Manufacturing Practices (GMP) and other pertinent codes such Good Laboratory Practices (GLP) and Good Clinical Practices (GCP) guide the design and development of pharmaceuticals.
- Accurate raw materials and packaging materials are purchased, stored, and used with proper arrangements created.
- For raw materials, intermediate products, bulk goods, and throughout the manufacturing process—including calibration and validation—strict controls are in place.
- As per set processes, the completed goods are efficiently processed and examined. Before authorized staff confirms that every production batch conforms with the label claims and other relevant regulatory provisions pertaining to manufacturing, control, and release, pharmaceutical items are not released for sale. (Malik, 1940, 7th edition, p. 407)

QUALITY ASSURANCE OF HERBAL DRUGS:

Good Manufacturing Practices (GMP) compliance and appropriate control of the botanical ingredients can guarantee the quality of herbal products. A large number of herbal remedies have several botanical components, each in minute amounts. Establishing requirements for completed items can benefit from chemical and chromatographic studies. The producer should decide about shelf life and stability. Quality standards should be same for other pharmaceutical preparations as well as for various dosage forms of herbal treatments, such pills and capsules.

Licensed herbal products in the UK follow the important European Scientific Cooperative on Phytotherapy monographs. Most herbal medicines have been sold in India for a very long time—some even before the 1948 Drugs and Cosmetics Act. Similar regulations govern the manufacture and sale of herbal products in other non-industrialized nations as they do in the UK. Improving financial opportunities for herbal therapies, boosting customer confidence, and establishing scientific credibility all depend on the quality, safety, and efficacy of herbal medications. (Dr. Mukherjee, 2002)

Confusion between Quality assurance and quality control

Activities to guarantee the development or maintenance procedures are sufficient to achieve system goals are known as quality assurance (QA). Its main concern is making sure that the proper procedures are defined and carried out accurately. Examples are improving standards and creating methodologies. A quality assurance review evaluates process components, such the proper level of definition of requirements.

Conversely, efforts for assessing created work outputs make up Quality Control (QC). To be confident that particular outputs satisfy the specified criteria, it seeks to find flaws in them. Although testing is a standard quality control task, it also covers various kinds of inspection. Quality control depends on the product and is concerned with confirming that what has been done has met expectations.

Though they are sometimes used synonymously, "quality assurance" and "quality control" are not the same thing. To make sure final goods, packaging components, and raw materials fulfill specified requirements, quality control is mostly concerned with their analysis. Quality assurance is related to quality control but also include policies, staff training, record-keeping, facility design and monitoring. Developing quality into the product is stressed in the quality assurance philosophy as opposed to depending only on evaluating the finished product to find flaws.

GENERAL CONCEPT:

Specification development and setting heavily rely on the following broad ideas. All of them should be taken into account in particular circumstances even when they are not all relevant.

[1]. Characterization:

Only by a precise and stringent definition of the initial plant components can consistent quality for herbal products be ensured. Establishing thorough and pertinent requirements hence calls for characterizing a herbal substance, preparation, or herbal medical product.

A. Macroscopic and microscopic characterization: Macroscopic characterization uses the size, color, texture, fracture, and appearance of medicinal plant material.

a) Size:

The raw material thickness, width, and length are crucial factors in assessing a crude medication. An inch graduated ruler will work well for this measurement.

b) Colour:

The colour is useful in indicating the general origin of the drug; for example, material derived from the aerial part of the plant isusually green, whereas material derived from the underground part of the plant is usually devoid of green colour

c) Odour and Taste:

Taste and smell of a raw material are very subjective standards. After determining the odour strength—weak, distinct, or strong—the odor sensation—musty, mouldy, rotten, fruity, fragrant, and so on—is ascertained.

d) Surface characteristic:

Examining the texture best involves rubbing a tiny bit of material between your thumb and forefinger; it is usually described as "smooth," "rough," or "gritty." Contact between two materials defines their hardness or softness. Sample brittleness and appearance of the fractured plane as fibrous, smooth, rough, granular, and so on are revealed by bending and breaking the sample. The general form of material and the presence of several components can be determined with the help of all these properties.

Plant elements including leaves, roots, bulbs, fruits, seeds, barks, woodlands, underground drugs, complete species, and unorganised drugs are primarily used in the microscopic characterisation of plants. (Kokate et al., 2003, pp. 100-104)

e) Leaf Constants:

- **Palisade Ratio**: This refers to the average number of palisade cells beneath each epidermal cell. It can be assessed using powdered plant material.
- **Number of Veins and Islets**: This indicates the density of veins and vein terminations per square millimeter of leaf surface between the midrib and the edge. In 1929, Levin quantified this characteristic in numerous dicot leaves.
- **Vein-Termination Number**: This measures the density of vein endings per square millimeter of leaf surface between the midrib and the margin.
- **Stomatal Number**: This represents the total count of stomata per square millimeter on the leaf's epidermis.
- **Stomatal Index**: This ratio compares the number of stomata to the total number of epidermal cells, considering each stoma as equivalent to one cell. It is calculated using the following formula: -

$$\textbf{S.I. = S / E + S x 100}$$

Where, S.I. = Stomatal index

S = Number of stomata per unit area

E = Number of epidermal cells in the same unit area (Kokate et al., 2003)

f) Trichomes:

These are other vital diagnostic characteristics that support drug identification and adulterant detection. Trichomes are glandular or tubular elongated epidermal cell outgrowths (fig. 1). Other names for trichomes were plant hairs. The structure and quantity of cells of trichomes determine their grade as follows: (Kokate et al., 2003)

- Covering trichomes, non-globular trichomes and Clothing trichomes
- Glandular trichomes
- Hydathodes or special type of trichomes.

(a)

(b)

Fig.1 Trichomes

g) Stomata:

Transpiration is stomata's secondary function; gas exchange is their primary and most important one. Conversely, dicot leaves are often seen to have a profusion of stomata. The following categories of dicotyledon stomata are distinguished by the configuration and form of subsidiary cells.

- Paracytic or rubiaceos or parallel- celled stomata
- Diacytic or caryophyllaceous or cross-celled stomata
- Anisocytic or cruciferous or unequal-celled stomata
- Anomocytic or ranunculaceous or irregular-celled stomata

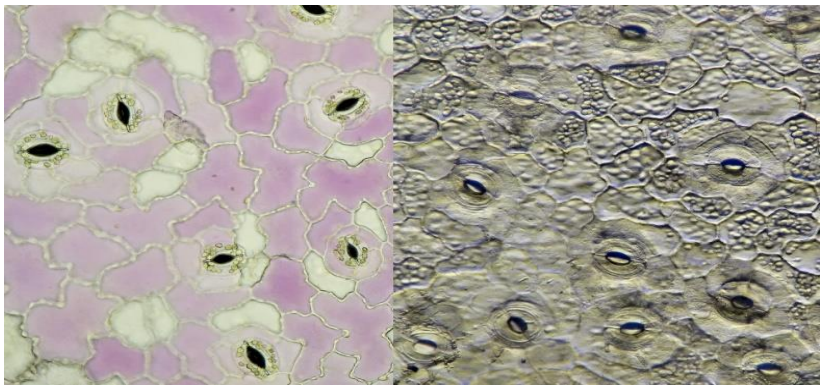

Fig. 2 Stomata

B. Phytochemical characterization:

Chromatographic fingerprinting is utilized to gather analytical data on constituents, encompassing those with confirmed therapeutic effects and compounds suitable as active or analytical markers. This method produces a profile that shows the qualitative and quantitative assessment of diverse components found in complex plant extracts, even when their precise identities are unknown. Among chromatographic techniques, thin layer chromatography (TLC) stands out as the simplest and most cost-effective, providing detailed insights into the composition of medicinal plant materials and their formulations, making it ideal for confirming raw materials.

High-Performance Thin Layer Chromatography (HPTLC) combines sensitivity and selectivity, offering stability indicators. Non-chromatographic assays such as gravimetric, titrimetric, and spectrophotometric methods offer simpler analyses that provide a broader view of compound groups present in herbs or polyherbal products. After this initial analytical procedure, the customer may choose to conduct further tests at another accredited laboratory of their preference. (Dr. Mukherjee, 2002)

C. Impurities:

Impurities can be categorized into two main types:

- Impurities originating from starting materials (including active ingredients and excipients) and containers.
- Process impurities that arise during the production process.

Pollutants are substances that can be radioactive as well as come from outside sources such heavy metals, pesticides, mycotoxins, fumigants, and biological waste.

The special character of herbal medicinal products makes degradation products, especially toxicologically associated pollutants resulting from the breakdown of herbal compounds or preparations, and should be avoided.

Important factors to consider are also residual solvents and industrial activity by-products.

[2]. Design and development considerations:

The foundation of creating specifications should be the information and statistics obtained during the manufacture of a herbal preparation, substance, or medical product. In general, only characteristics pertinent to the dose form and the particular herbal component or preparation present should be the focus of quality testing of herbal medicinal products. For example, under the following situations it could be reasonable to think about removing or lowering some tests:

- If the herbal medicine is grown organically without the use of pesticides or other chemicals and any contamination from nearby plantations has been reduced, then fewer pesticide residue tests may be necessary.

- Scientific data supports the exclusion or reduction of microbial limit tests in herbal medicines such as extracts or tinctures according to the ethanol concentration.

[3]. Pharmacopoeial examinations and acceptance standards:

Important criteria for several analytical methods and approval conditions relevant to herbal compounds, herbal preparations, and herbal therapeutic products are included in the Indian Herbal Pharmacopoeia. If pharmacopoeial methods are suitable, they should be applied.

Drying of Plant Drugs

A raw medicine is dried to eliminate enough moisture to improve its consistency and stop microbial growth. The drug's ultimate quality is considerably influenced by the drying stage. It is best to dry medications slowly at moderate temperatures if they need enzymatic action. On the other hand, it is advised to dry medications right after selection if they do not require enzymatic action. pharmaceuticals containing volatile oils can become odorless if not quickly dried or distilled, and wet pharmaceuticals can sprout mold. Since many fresh drugs have a high water content, drying equipment and stills should ideally be situated close to the plants to reduce shipping expenses. Hours to weeks can pass during the drying process, which is mostly influenced by the weather while drying outside. Artificial heat drying, accomplished by means of continuous belt driers, open flames, stoves, or hot-water pipes, is quicker in areas with high humidity. Important elements of the drying process are making sure there is enough air circulation and at least 15 cm between trays in drying sheds. (Sivarajah & Belachandra, 1994; Maurice, 1963; Iyengar & Nayak, 2004)

HERBAL SUBSTANCES:

These are mostly complete, broken, or chopped plants, plant parts, algae, fungus, and lichen in their natural state—usually dried but occasionally fresh. Herbal compounds also include exudates that have not undergone particular processing. Under the binomial nomenclature system—which comprises the genus, species, variety, and author—herbal substances are appropriately identified by their botanical name.

Among the botanical materials that are examples of herbal compounds are leaves, flowers, roots, bulbs, seeds, and bark. Even in cases when a herbal ingredient is the foundation of a herbal preparation, it needs a thorough description. Unless there is a good reason, fatty or essential oils employed as active components in herbal medical formulations require a specification for the herbal substance. (United States, 2002. *USP 25/NF 20*, First Asian Edition. U.S. Pharmacopeia Convention, Inc.)

Tests for Identification:

1. Foreign matter:

In herbal goods, foreign matter can refer to any unnamed organism, element, or product that is not limited in any way. Examples are mineral admixtures like dust, stones, and dirt that do not conform to the therapeutic plant content. Content of medicinal plants should be free of obvious contamination indications.

Sampling:

Because most of the foreign material is stacked on top of the naturally non-uniform medicinal plant content, preparing a pooled sample for herbal medications is challenging. The sample size must so be big enough to be regarded as representative. Depending on the kind of drug, a weighted sample of the entire substance (50–500gm) is taken.

Procedure:

A thin layer of the plant material specified below is put over a layer of paper. Foreign material must be identified and the proportion recorded after it has been seen or with 6x or 10x magnifying lenses examined. To remove dust—which is regarded as a mineral addition—the remaining herbal medicine sample is sieved at 250 mesh. Every category should have its foreign matter count expressed in grammes per 100 grammes of air-dried sample.

The WHO describes the following numbers of samples as necessary to classify the foreign matter of any herbal medicine, unless otherwise stated:

- Leaves, flowers, seeds and fruits - 250 gm
- Roots, rhizomes and barks - 500 gm
- Cut medicinal plant material - 50 gm

2. Total ash:

We call this process of the product's constituents oxidizing "ashing." When a crude medicine is prepared for marketing, a high ash value suggests contamination, substitution, adulteration, or negligence. The whole amount of material produced after the ground drug is completely burned at a low temperature (around 450°C) to remove all carbons is measured using total ash. At higher temperatures, the alkali chloride may turn volatile, in which case this method might be employed to remove it. Total ash, which comprises both physiological ash formed from plant tissue and non-physiological ash—which results from debris like sand and dirt adhering to the plant surface—commonly contains carbonates, phosphates, silicates, and silica.

3. Acid Insoluble ash:

After boiling all of the ash for 5 minutes in 25 millilitres of diluted hydrochloric acid, collect the insoluble material in ash less filter paper, rinse with hot water, and ignite to constant weight. Utilising the air-dried medication as a guide, determine the amount of acid insoluble ash.

4. Water Soluble Ash:

After boiling the ash for 5 minutes 25 millilitres of water, gather the insoluble material in an ashless filter paper or silica crucible, wash it under hot water, and burn it for fifteen minutes at 450°C. Take the weight of the ash less the weight of the insoluble material; the water-soluble ash is represented by the weight difference. Determine the air dry to water-soluble ash ratio.

5. Assay:

Tests of the composition of herbal compounds including components with recognized therapeutic activity or active indicators are needed, as are specifics of the analytical procedures. Finding out the content of the herbal material should, whenever feasible, be part of a specific, stability-demonstrating process. If it makes sense to use non-specific assays, other supporting analytical procedures might be applied to get overall specificity.

6. Foaming Index:

High molecular weight phytoconstituents having detergent action are found in saponins. Mostly, the capacity of saponins to foam sets them apart. Medical plants of many families contain saponins, but those from the families Caryophyllaceae, Araliaceae, Sapindaceae, Primulaceae, and Dioscoreaceae are especially rich in them.

Recommended procedures for foaming index determination

One gram of plant material needs to be ground into a coarse powder (using a sieve with a size of 1250), weighed precisely, and then placed to a 500 ml conical flask that holds 100 ml of boiling water. Keep the mixture at a full boil for half an hour. After cooling and filtering into a 100 ml volumetric flask, dilute the mixture with water until it passes through the filter. Ten 16cm-high by 16mm-diameter test tubes with stoppers should be filled with the infusion in incremental amounts of 1 ml, 2 ml, and 3 ml. The liquid volume in each tube should be adjusted to 10 ml with water. Close the tubes and give them a 15-second lengthwise shake at a pace of two shakes per second. enables you to gauge the foam's height by standing for fifteen minutes.

The following formula can be used to get the foaming index: -

$$1000 / A$$

Where **A** is the milliliters (mL) of the decoction used to prepare the dilution in the capping tube where 1 cm of foaming is seen.

HERBAL PREPARATIONS:

- Herbal medications can be extracted, distilled, expressed, fractionated, purified, concentrated, or fermented to acquire them.
  These include, but are not limited to, tinctures, extracts, essential oils, liquid juices, distilled excludes, and ground or powdered herbal materials.

Tests for identification:

- Microbial LimitsWater content
- Residual solvents
- Inorganic contaminants, hazardous metals
- Mycotoxins
- Water content

- Assay
- Pesticides, Fumigation agents, etc

PHYSICAL QUALITY ASSURANCE:

Chemical and physiological elements have typically been the focus of quality assurance for phytopharmaceutical products. For both growers and processors, however, the physical quality of plant extracts is equally important. Due to the characteristics of many plant extracts, additional processing is either difficult or impossible without the inclusion of appropriate adjuvant chemicals. For example, it is not possible to effectively dry extracts from plants such as Crataegus fruits, Curcuma, and others into manageable dry goods using techniques like roller, belt, or spray drying. Male fern extract, which is made as a thin extract without the use of solvents, is one example. In spite of this, producers are obligated to reveal the processing techniques employed, and the proportion of active ingredients to matching plant elements stays constant.

CONCLUSION

Good Manufacturing Practices (GMP) compliance and careful inspection of herbal ingredients preserve the quality of herbal products. Quality assurance provides a framework for monitoring and reporting in the pharmaceutical sector by guaranteeing that processes are performed accurately and in compliance with rules. However, the efficacy and dependability of formulations cannot be guaranteed in the absence of strong quality control procedures. This discrepancy emphasizes the necessity of structured quality control procedures designed especially for herbal medicines.

As a result, medication combinations are being added to pharmaceutical formulations more and more frequently to address a variety of symptoms in one formulation. Because of this tendency, analytical chemists must create reliable drug analysis techniques that are specific to these kinds of formulations.

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