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A REVIEW ON STABILITY TESTING OF HERBAL DRUGS: CHALLENGES, REGULATORY COMPLIANCE AND PERSPECTIVES

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Abstract : Pharmaceutical items must be consistent in quality in order to provide the desired therapeutic benefits. It's difficult to achieve consistent quality in herbal goods because of their physical and chemical complexity and their inherent diversity. Regulations or guidelines for the stability test parameters and test methodologies of herbal products stored under suggested settings have been established by regulatory bodies all over the world. The test parameters and methods for these herbal products are contained in the guidelines and regulations of five global authorities and eight countries/regions, namely the Association of Southeast Asian Nations (ASEAN), the Eurasian Economic Commission (EEC), the European Medicines Agency (EMA), the International Coordinating Committee for Technical Requirements for Human Medicines (ICH), the World Health Organization (WHO), Australia, Canada, China, India, Japan, Switzerland, and Zambia.

The test parameters (temperature and relative humidity) for long-term, expedited, or intermediate tests have been included in the guidelinesand regulations, and the physical, chemical, and biological stability tests between different dosage forms have been compared.The drug approval process is the regulatory process by which a person/organization/sponsor/ innovator obtains clearance to launch a medicine on the market. In general, there are four parts to the drug approval process: the application to conduct clinical trials, the clinical trials themselves, theapplication for marketing authorisation of the drug, and post-marketing research. Every country has its own regulatory authority, which is in charge of enforcing rules and regulations as well as issuing guidelines to govern medication marketing.

***Keywords*: Stability, herbal drugs, organization, regulations.**

1.0 INTRODUCTION

To sustain therapeutic efficacy, it is critical to maintain the quality of herbal products during storage. Stability tests are used to determine how herbal products retain their qualities under specified storage circumstances such as heat, humidity, light, oxygen, and other physical elements and physical and chemical changes (such as vibration or freezing) and container parameters. Herbal medications come in a variety ofdosage forms (tablets, powders, or liquids for oral administration, or topical creams), hence dosage form stability testing is necessary. Different mechanisms necessitate different approaches. Physical (sensory qualities, physical state, particle size, etc.), chemical (active ingredient test, pH properties, identification, etc.), microbiological, and toxicological properties can all be tested to verify the stability of herbal products.

Because all of these attributes can alter the quality, safety, or efficacy of herbal products, stability testing should be used to evaluate their shelf life. In the context of herbal medicine development, global harmonisation of stability testing has recently been stressed, although acceptance of worldwide standards can only be done through sharing international information and experience. Family. As a result, we describe the parameters and stability testing methodologies utilised for herbal products in various dosage forms in this study and the guidelines. Guidelines and regulations are issued by international organisations such as the Association of Southeast Asian Nations (ASEAN), the EurasianEconomic Commission (EEC), the European Medicines Agency (EMA), the International Council on Harmonization of Technical Requirements for

Medicines for Human Use (ICH), and the World Organization (WHO), as well as national governments such as Australia, Canada, China, India, Japan, Switzerland, and others.

2.0 PURPOSE AND OBJECTIVE [1,2]

To assure the intended therapeutic efficacy and achieve uniform drug quality, consistency in the quality of medicinal products is critical.Herbal products are difficult to work with because of their inherent variability and physicochemical complexity. Regulations or guidelines onstability test parameters and test techniques for herbal products stored under recommended circumstances have been established by regulatorybodies around the world.

The parameters and procedures for evaluating herbal products are outlined in recommendations and regulations produced by five worldwide and eight national authorities, including the Association of Eastern Nations. South Asia (ASEAN), the Eurasian Economic Commission (EEC), the European Medicines Agency (EMA), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the World Organization (WHO), Australia, Canada, China, India, Japan, Switzerland and Zambia areamong the countries represented. Physical, chemical, and biological stability tests are compared between various dosage forms and test circumstances (temperature and relative humidity) utilised for accelerated long-term or intermediate testing that are currently included in guidelines and regulations.

3.0 REGULATORY BASIS OF HERBAL DRUG STABILITY TESTING [3]

Drug regulatory bodies such as the European Medicines Agency (CPMP, 2003a, 2012, 2011a, 2011b; EMEA, 2008a, 2008b, 2010), the International Conference on Harmonization (ICH, 2003), and the World Health Organization (WHO, 2009) all require stability data before approving a drug product. If an expiry date is indicated for a herbal material or herbal preparation, some stability evidence that supports the planned shelf life under the specified storage conditions should be available, according to WHO's Supplementary guidelines for the manufacturing of herbal medicines, section 17.4. To support the shelf-life of finished herbal products, stability data is always required (WHO, 2006). EMEA has also issued a specific set of guidelines on the quality of HMPs, which clearly states that Since the herbal substance or herbal preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. The stability of other substances present in the herbal substance or in the herbal preparation, should, as far as possible, also be demonstrated, e.g., by means of appropriate fingerprint chromatograms. It should also be demonstrated that their proportional content remains comparable to the initial fingerprint (CPMP, 2011b). Current Good Manufacturing Practice USFDA states that Nevertheless, if you use an expiration date on a product, you should have data to support that date. You should have a written testing program designed to assess the stability characteristics of the dietary supplement, and you should use the results of the stability testing to determine appropriate storage conditions and expiration dates (USFDA, 2003). Kruse and Sultan (2010) examined the legal requirements for quality control and stability studies on HMPs and suggested some special features. It is clear from these extracts that drug regulatory bodies require that the shelf life of a herbal product be evaluated and suggested based on properly developed stability data. Tests of markers (active or analytical), biological assays, and/or chromatographic chemoprofiling or fingerprinting of control and stability samples of a product under various stability circumstances are some of the methods used to determine shelf life. These parameters are largely agreed upon in many worldwide and country-specific quality guidelines for herbal medications and goods.

4.0 CURRENT SCENARIO IN STABILITY TESTING OF HERBAL DRUGS AND PRODUCTS[3]

For the past decade, many study reports on stability studies on herbal medications and items have appeared in the literature. A close examination of these studies found that the circumstances used, the duration of stability testing, and the factors used to determine shelf life areall very variable. In order to compile this study, we looked at a number of reports on herbal drugs and goods.

1. Compile their stability data;
2. Recognise the challenges in their stability testing;
3. Discuss the extent of compliance with the stability testing conditions recommended in drug regulatory guidelines; and
4. Propose approaches for generating comprehensive stability data for these drugs and products.

5.0 CHALLENGES IN STABILITY TESTING OF HERBAL DRUGS/PRODUCTS [3]

Stability testing aids in the establishment of storage conditions for a drug product's QSE to be maintained throughout its shelf life. However, ensuring QSE for a herbal product under the effect of diverse storage circumstances is far more difficult than it is for a synthetic drug product. Chemical complexity, diversity in biochemical makeup of raw material, selection of marker(s) for stability testing, and impactsof enzymes present in it are some of the primary obstacles that make stability testing of a herbal drug/product a herculean work. Complexity in chemistry An herbal medication is a chemical composition that is exceedingly complicated and diverse. These can be extremely polar or non-polar, hydrophilic or lipophilic, acidic or basic, and have a low or high molecular mass. The lack of consistency in chemical compositionis a key impediment to the establishment of a thorough chromatographic fingerprint, which is required by regulatory criteria for determining aherbal product's shelf life. Furthermore, the amount of these various ingredients per unit mass of a herbal medication varies from traces to a few milligrams. As a result, all or most of the ingredients aren't separated or purified enough to be used as active/analytical makers in qualitativeor quantitative drug analysis. Furthermore, distinct ingredients in a herbal medication, whether present in trace or significant levels, elicit multiple pharmacological responses by working independently, synergistically, or antagonistically, which accounts for the herbal drug's diversebiological actions.

5.1 Variability in biochemical composition [3]

Seed selection, growth conditions, fertilisers, pesticides, heavy metal concentration, microbial contamination, and harvesting, drying, andpost-harvest processing processes all influence the content and character of phytoconstituents in a herbal raw material, either directly or indirectly. It means that a specific herbal medication obtained from various sources is likely to have varied biochemical makeup. As a result, the biochemical compositions of herbal medicinal items obtained from various sources and developed by various manufacturers tend to differ.

5.2 Role of markers[5]

Markers are chemically known substances that are used to calculate the quantity of herbal medicinal components in herbal medicinal products. They may or may not have a therapeutic effect. It is necessary to justify the marker selection. For HMP stability testing, finding the"correct" analytical marker is critical. Typical sources for finding markers are:

1. Drafts and monographs (EDQM Pharm Europa).
2. Experience and knowledge gained from other plants/constituents.
3. Conduct literature research on known ingredients.
4. 4 Scientific investigation.

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
Quantified	Defined range	Activer marker (contributing to thetherapeutic activity,)
Other	Related to the Validated analytical range	Analytical marker for analytical purposes.

5.3 Analytical methods for Herbal products [5]

Herbal medicines are typically analysed using high performance liquid chromatography (HPLC), gas chromatography (GC), thin layer chromatography (TLC), quantitative UV visible spectroscopy, or a combination of these technologies. During one analysis, HPLC and GC procedures can be employed for identification and purity testing, as well as the detection of single chemicals for assay. The procedures of LC and GC mass coupling can also be used for determination, but they are more complex and expensive.

5.4 Shelf-life [2,3,5]

Herbal medicinal medicine products have the same shelf life as chemically specified APIs, but the unique nature of herbal medications must be taken into account. In the event of a herbal medical product including a natural product or a herbal medication preparation having elements with recognised therapeutic efficacy, it is recommended that the variation in component during the proposed shelf-life should not exceed ± 5% of the initial assay value, unless justified to widen the range up to ±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- 160per cent of the marker's expected content in the extract and/or product. During stability testing, the completed product's limits are set at 10% due to the presence of matrix effects (placebo), a lack of accuracy and selectivity (combination products), and low analyte concentrations. Given that the marker content cannot be defined to a specific level, the relative changes from the starting value (95-105 percent or 90-110 percent from the original value) are supplied.

5.5 Enzymatic activities during shelf life [3]

Plant secondary metabolites are the chemical constituents of a herbal medication. Their levels in plants are controlled by the coordinatedactions of numerous enzymes classified as oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Interconversion processes, conjugation reactions, oxidative polymerization, and degradative reactions are all catalysed by these enzymes (Bayindirli, 2010). Barz and Koster (1981) gave a detailed collection of the degradation of several phytoconstituents under the effect of various enzymes. Enzyme activity is regulated by feedback mechanisms during the pre-harvest period. The enzyme activity after harvesting are determined by the conditions used for processing and/or storing the plant material/produce. A substantial amount of research has been conducted on the post-harvest behaviour and stability of enzymes in edible plant products such as fruits and vegetables.. These post-harvest active enzymes, which mostly

comprise catalase, peroxidase, lipoxygenase, chlorophyllase, pectin, esterase, ascorbate oxidase, polygalactouronase, galactolipase, and phospholipase, continue to work throughout plant product storage and induce chemical composition changes. Color, texture, consistency, and taste all vary as a result of these alterations. Edible plant produce can be utilised for both nutritional and medicinal purposes. Garlic, zinger, blackberries, olive, Indian blackberry (black plum, jamun), Indian gooseberry (Amla), and many more, for example, are utilised as both herbal medications and food products. Their post-harvest procedures, however, differ depending on their intended purpose.

The edible items are stored at low temperatures and high humidity and have a shelf life of a few days to a few months (Aked, 2000). In afew days, these products undergo significant changes in colour, texture/consistency, and taste, which are due to the catalytic activities of phenylperoxidase (PPO), polygalactouronase, and lipoxygenase, respectively (Toivonen and Brunnell, 2008). In contrast, products designed for use as herbal medications are often dried in a controlled environment that hinders/decreases the deterioration caused by microorganisms, enzymes, and hydrolytic processes.Peroxidase and catalase (CAT) can continue to function after being exposed to temperatures as high as 60 °C, whereas the other enzymes are inactivated (Gökmen, 2010; Sukrasno, 2014). This total or partial inactivation of enzymes results in a series of events that vary depending on the enzyme. Heat treatment of red ginseng, for example, results in the inactivation of catabolic enzymes responsible for the metabolism of antioxidant constituents, the hydrolysis of saponins to ginsenosides Rh2, Rh4, Rs3, Rs4, and Rg5 with anticancer properties, and the production of 20(S)-ginsenoside Rg3 with antimetastatic, vasorelaxant, and antiplatlet aggregation properties.However, when it is steam processed, the production of two ginsenosides, Rg3 and Rg5, increases, and panaxytriol is created, resulting in an increase in the herb's anticancer action (Wang et al., 2007). Another example is sinigrin, which is a key component (glucosinolate) in many cruciferous vegetables. Myrosinase, an enzyme found in plants and gut microbiota, hydrolyzes it to allyl isothiocyanate. However, when heated, myrosinase is inactivated, and so the anticancer ability of allyl isothiocyanate is lost (Patel et al., 2012). The most prevalent observable alteration in herbal products is post-harvest browning.The culprits for this change are PPO, peroxidase (POD) and/or Phenylalanine ammonia lyase (PAL) that oxidize a phenolic compound to a quinone, which imparts brown appearance to the product (Fig. 2).

Quinone is a highly reactive species that may combine with other elements to produce complicated compounds. In a herbal product, phenolic compounds can be present as such or produced in situ by glycosidases from terpenoidal/flavonoidal glycosides. Browning in apples, for example, is begun by glycosidase-catalyzed hydrolysis of quercetin glycoside to produce quercetin, which is then transformed to proanthocyanidin through flavan-3,4-diol. Finally, quinones are produced by the PPO-catalyzed oxidation of proanthocyanidine. Browning is also caused by amine oxidases, oxalate oxidases, and superoxide dismutases found in mitochondria, chloroplasts, and peroxisomes (Adams, 2010).Based on these many findings on enzyme post-harvest activities, it can be concluded that enzymes can play a key role in determining the shelf life of a herbal product. Nonetheless, there are some reasons against post-harvest degradative actions of enzymes in plant material intended for therapeutic application. These are the following:

1. Almost all herbal medications, with the exception of those necessary for the isolation/extraction of essential or volatile oils, are exposed to a variety of procedures in order to preserve their physical, chemical, organoleptic, and pharmacological properties.These treatments primarily try to remove water by drying it out in the sun or by artificial methods such as freeze drying, heat drying, microwave drying, far infrared drying, vacuum drying, and spray drying. During these treatments, the moisture content of plant material decreases from 60–80% to 5–12%, and weight decreases by 15–80% depending on the kind of plant organ (Silva Jnior et al.,2011). The removal of water, as well as the exposure to heat, inactivates the majority of the enzymes.

2. To form HMPs, several fresh or dried plant materials are extracted with organic solvents. The enzymes are either denatured not extracted in these solvents, or their activity is drastically diminished. As a result, the plant extracts are either enzyme-free or contain inactive enzymes. These considerations do not allow us to be certain that no enzyme is active during shelf life.

As a result, in order to analyse the influence of enzyme activity on the shelf life of a herbal product, it is advised that suitable enzyme tests be used to identify enzymes that have a high likelihood of being active post-harvesting. Furthermore, their biochemical functions and levels during shelf life should be tracked using particular enzyme assays and/or the levels of specific substrate(s) or product(s) during shelf life.

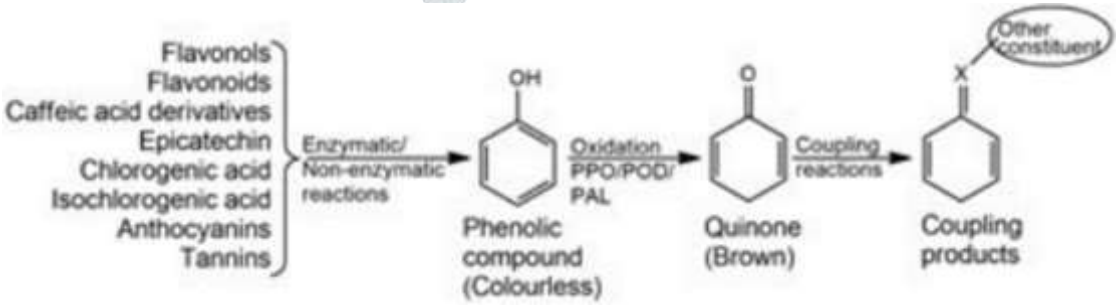

figure 2. degradation of constituents leading to browning and other products.

6.0 STABILITY TESTING PARAMETERS [1,4]

6.1 ASEAN

ASEAN provides stability testing recommendations to assure the quality of finished herbal products (traditional medicines) in their appropriate packaging adhere to storage circumstances and durations. The dosage forms' parameters are as follows: Capsules (sensory, laboratory features, solubility, disintegration, content, and microbiological content); Oral powder (sensory, laboratory characteristics, strength, and microbial content); Soft capsules (sensory features, laboratory properties, solubility, disintegration, and microbiological content); Tabletsand tablets (coated and uncoated; organoleptic, laboratory properties, hardness, friability, solubility, disintegration, content, and microbiological content); Suspension (sensory, laboratory properties, viscosity, pH, microbial content, particle or particle size fluctuation, andreliance on again); Solution (sensory, laboratory characteristics, viscosity, pH, and microbial content); Emulsion (sensory, laboratory characteristics, viscosity, pH, and microbial content); Semisolid preparations (ointments, creams, gels, lotions, and pastes; organoleptic, laboratory characteristics, viscosity, pH, and microbial content); Plaster (sensory, laboratory characteristics, microbial content, and adhesion);Lozenges and herbal infusion sachets (sensory, laboratory features, content, and microbiological content); and herbal sachets (sensory, laboratory characteristics, content, and microbial content) (sensory, laboratory, and microbial content).

6.2 EEC

The EEC mandates the recording of stability studies during the storage of herbal medicines in compliance with drug substance and drug rules. The physical, chemical, biological, and microbiological parameters, as well as the presence of preservatives (such as antioxidants and antimicrobial preservatives), and the operation of the delivery mechanism, are all determined during stability testing (such as a dose delivery system). All pharmaceuticals must be evaluated for their appearance, active components, breakdown products, preservatives, and antioxidant content, according to regulations.Furthermore, EEC laws need the following testing for dosage forms: Pills (pill dissolution, disintegration, content, and abrasion resistance); hard gelatin capsules (brittleness, solubility, disintegration, content, and microbial purity); tablets (pill dissolution, disintegration, content, and abrasion resistance); tablets (pill dissolution, disintegration, content, and abrasion resistance); tablets (pill dissolution, disintegration, content, and Soft gelatin capsules (dissolution, disintegration, microbial purity, pH, tightness, and adhesion); oral emulsions, suspensions, and solutions (sludge formation, pH, viscosity, extractables, and microbial purity); and solutions (dissolution, disintegration, microbial purity, pH, tightness, and adhesion) (transparency), Suspension (dispersion, rheological characteristics, average particle size/distribution, polymorphic transformation, and polymorphic mutual transformation) and emulsion (phase separation and average size and distribution of dispersed spheres) needed additional test parameters.Powders and granules for oral solutions or suspensions (content and recovery); metered-dose inhalers (dose uniformity, valve activation times, aerodynamic particle size distribution, microscopic evaluation, content, airtightness, microbial contamination, Valve delivery or injection weight, weight loss, pump management, foreign mechanical inclusions, and substances removal and discharge from the plastic and elastic parts of the container, cover, and pump); suspended aeros (content and recovery); suspended aeros (content and recovery);foreign mechanics of inclusions, as well as removal and discharge of materials from the plastic and elasticity of the container, closure, and pump Parts); dosage forms for topical (external use), eye, and ear applications, including topical ointments, creams, pastes, gels, solutions, eye drops, and sprays (transparency, uniformity, pH, wash Resuspension, thickness, viscosity, particle size distribution) suspension, microbial purity, and weight loss Asterisks indicate test settings that are optional.

6.3 EMA

According to the "Guidelines for New Medicinal Substances and Product Stability Testing" (CPMP / ICH / 2736/99) and "Stability Guidelines," EMA requires certain storage stability testing for herbal products to ensure quality. "Guidelines for Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02 and EMEA/CVMP/846/99)" and "Testing of Veterinary Drugs and Substances (CVMP/VICH/899/99)". According to EMA regulations, all herbs must be tested to verify they meet requirements such as instructions, identification, analysis, contaminants, and microbiological restrictions. Furthermore, the following test parameters are specified:Tablets (coated and uncoated) and hard capsules (dissolution, disintegration, hardness, friability, quality uniformity, content, and microbial limit); oral suspension (quality uniformity, pH, microbial limit, antibacterial preservative content, antioxidant preservative content, extractable,alcohol content, dissolution (for oral suspension) and resuspension (for dry powder products), particle size distribution, dispersibility (loss ondrying, identification, purity, Quality uniformity or average quality of the coating, determination, particle size, and microbiological quality ormicrobial limit test). foreign mechanics of inclusions, as well as removal and discharge of materials from the plastic and elasticity of the container, closure, and pump Parts); dosage forms for topical (external use), eye, and ear applications, including topical ointments, creams, pastes, gels, solutions, eye drops, and sprays (transparency, uniformity, pH, wash Resuspension, thickness, viscosity, particle size distribution)suspension, microbial purity, and weight loss Asterisks indicate test settings that are optional.

6.4 ICH

The ICH recommendations cover the description, identification, analysis, and impurity content of chemicals, as well as basic guidelinesfor verifying the storage stability of new pharmaceutical products. However, we feel that the ICH standards apply to herbal products because international papers controlled by the EMA, Australia, Japan, or Switzerland are based on the ICH guidelines. Tablets (coated and uncoated) and hard capsules (dissolution, disintegration, hardness, friability, uniformity of dosage unit, moisture content, and microbial limit) are the specific dosage form stability test parameters; oral liquid (uniformity of dosage unit, pH value, microbial limit, content of antibacterial preservatives and antioxidants, extractables, alcohol content, dissolution, particle size distribution of oral suspension, dispersibility of oral suspension). The content of the rheological properties, the reconstitution time, and the rheological properties); parenteral medications (uniformity of dosage unit, pH value, sterility, endotoxin, pyrogen, particulate matter, content, antibacterial and antiseptic) The presence of agents and antioxidants, extractables, and drug delivery system functional tests (including pre-filled syringes, auto-injector barrels, or their equivalents, osmotic pressure, particle size distribution of the injectable suspension, dispersibility, and reconstitution time).

6.5 WHO

A technical report on pharmaceutical preparations and guidelines on appropriate herbal processing procedures (Annex 1), as well as guidelines on active pharmaceutical components and stability testing of completed pharmaceuticals, are published by the WHO Expert Committee (Annex 10). The look, determination, and degradation of goods, as well as the amount of preservatives and antioxidants, are all general requirements for the stability of completed pharmaceuticals.. Specific characteristics are also supplied based on the product's dosing type (ie, liquid, solid, or other forms). Liquid herbal dosage forms include liquid extracts, decoctions, infusions, tinctures, syrups, and oral solutions that have all been examined for precipitation, clarity, pH, viscosity, extractables, and microbiological contamination. Precipitation formation, clarity, pH, viscosity, extractables, amount of microbial contamination, dispersibility, rheological characteristics, average particle size or distribution, and polymorphic transformation should all be tested in the oral suspension. In an oral emulsion, look for precipitation formation, transparency, pH, viscosity, extractables, microbiological contamination level, phase separation, and average bead size or distribution. The quantity and time required to reconstitute perfumes, powders, or granules used in oral solutions or suspensions must be calculated. Solid herbal dose forms include herbal bags, plant powders, dry extract powders, granules, pills, hard gelatin capsules, soft gelatincapsules, tablets, and lozenges. Friability, dissolution, disintegration, content, and microbiological contamination levels in hard gelatin capsuleshave all been investigated. The dissolving, disintegration, microbiological contamination level, pH, leakage, and film build of softgel capsuleshave all been investigated. Tablet dissolution, disintegration, content, hardness, and friability should all be tested. Ointments, creams, and ointments are examples of other dose forms. Transparency, homogeneity, pH, suspending ability (for emulsions), consistency, viscosity, particle size distribution (for suspensions), microbiological contamination levels, sterility, and weight loss of these ointments subjected to testing Sterility, particle matter, and extractives have been examined in ophthalmic and otological products (such as creams, ointments, solutions, and suspensions).The uniformity of the inhaler's dose content, the number of labelled drug applications per container that meet the established dose delivery, streamlined particle size distribution, microscopic evaluation, content, leakage rate, level of microbial contamination,valve delivery or injection weight, extractable or available Weight loss, pump delivery, extractable or leachable plastic foreign particles, and elastic components of containers, closures, and pumps are all subject to examination. The dressings and patches were tested for in vitro releaserate, leakage, microbiological contamination level, sterility, peel strength, and adherence. Other dosage forms also contain therapeutic oil, butno test parameters are provided.

7.0 COUNTRY-LEVEL REGULATORY ORGANIZATION [1,4]:

7.1 Australia

The Australian government mandates the stability testing of auxiliary drugs in the following dosage forms: solutions, suspensions, creams, ointments, tablets (direct compression production), tablets (granulation production), capsules (two tablets, produced by dry blending),capsules (two tablets, produced by granulation), soft capsules containing solutions (soft gels), soft capsules containing suspensions, and soft capsules containing powder mixtures (soft gels). The EMA guideline "Guidelines for Stability Testing of Existing Active Substances and Related Finished Products (CPMP / QWP / 122/02 rev 1 corr.)"

7.2 Canada

Shelf-life testing of natural and non-prescription medical devices is required by the Canadian government to determine the shelf life afterpacking and storage conditions. Purity, physical qualities, quantities of therapeutic substances, amount per dosage unit, and efficacy are all part of these examinations. Physical test parameters for different dosage forms are defined by the Canadian government as follows: immediate-release tablets, lozenges, and capsules (description, disintegration, and weight change or average weight); fast-dissolving tablets (description,dissolution, and weight or average weight) Changes; extended-release, combined-release, and timed-release tablets and capsules (changes in dosage unit description, dissolution, weight, or average weight).topical preparations (description and preservative effect); transdermal patches(description, uniformity, and adhesion of the dosage unit or Peel force); and metered dosage form (the number of discharges per container andthe uniformity of the administered dose).

7.3 China

To maintain the shelf life and suitable storage conditions of herbal goods, the Chinese government demands rapid and long-term stability testing.The stability test parameters of different dosage forms of Chinese herbal medicine products stipulated in the Chinese Pharmacopoeia are as follows, according to the Anhui Food and Drug Administration (China): pills (description, identification, disintegration, content, microbiological determination and limit); powder (Description, identification, uniformity of appearance, content, particle size, measurement, and sterile powder for topical treatment of wounds or burns or external use and microbial limits); particles (description includes moisture softening, identification, content, solubility, particle size, Test and microbial limit); tablets (description, identification, hardness, disintegration, foamability, testing and microbial limit); concentrated decoction (description includes sucrose crystallisation and phase separation, identification, relative density, insoluble content, Testing and microbial limit); colloid (description, identification, content, test and microbial limit); syrup (description, identification, relative density, pH, test and microbial limit); transdermal (description, identification, gypsum quality extraction, Heat resistance, excipient properties, adhesion and microbial limit); liquid mixture (description including transparency, identification, relative density, pH, content and microbial limit); drop pill (description, identification, disintegration, test and microbial limit) Limit); soft capsule (description, identification, disintegration, content, test and microbial limit); medicinal liquor (description, identification, ethanol content, methanol content, total solids, test and microbial limit); tincture (description, identification, ethanol Content, test and microbial limit); liquid extract (description, identification, ethanol content, test and microbial limit); extract (description, identification, test and microbial limit); plaster (description, identification, softening point and test); Gel (description, identification, pH, viscosity, test and microbial limit); ointment (description including rancidity, odor, color, phase separation, identification, particle size, sterility used to treat burns or wounds, and microbial limit); fragrance Family solution (description, identification, pH, test and microbial limit); bag (description, identification, content, solubility, test and microbial limit); liniment, lotion and smear (description, identification, relative density, pH, Ethanol content, refractive

index and microbial limit); suppositories (description, identification, disintegration, testing and microbial limit); nasal preparations (description, identification, pH, determination, sterility and microbial limit); ophthalmic preparations (description, Identification, pH, visible foreign matter, particle size, foreign metal content, sterility and microbial limit); aerosol (description, identification, transfer rate, total spray volume, total number of transfers per container, emissions per transfer, Active ingredient content per transfer, particle size, sterility and microbial limit); and spray (description including precipitation and phase separation trend, identification, particle size, spray test, determination, sterility and microbial limit).

7.4 India

The Government of India establishes the following quality inspection criteria for herbal products used in Ayurveda, Siddha, and Unani systems, depending on dose forms: Tablets (description, labelling, weight uniformity, uniformity diameter, disintegration tests, and testing); capsules (description, identification, weight uniformity, uniformity diameter, disintegration test, and determination); and parental preparations(clarity, pH, identification, container volume, sterility, pyrogen test, toxicity test, and determination).

7.5 Japan

The Pharmaceutical Safety and Environmental (Ministry of Labor and Welfare) specifies the following quality requirements for Kampo formulations: Uncoated and filmcoated tablets (content, description, identification, loss on drying, uniformity, disintegration, and content); sugarcoated tablets (content, description, identification, loss on drying, uniformity, disintegration, and content); and hard and soft capsules (content, description, identification, loss on drying, uniformity, disintegration, and determination) . It should be mentioned that the stability test process must be followed in accordance with the ICH recommendations.

7.6 Switzerland

Swiss institutes recommend: Bulk and finished pharmaceuticals in capsule or tablet form incorporating herbal preparations or granules need special drug formulation test conditions (eg disintegration time and average weight). ICH international guidelines should be followed while performing stability tests, which include test criteria such as description, identification, loss on drying, determination, and microbiological purity.

7.7 Zambia

To comply with its herbal registration criteria, the Zambian government demands final product specifications and test methodologies for all dosage forms, including description, identification, analysis, and contaminants (degradation products and microbial limits of active ingredients). The guide also provides other tests for specific dosage forms, as follows: coated and uncoated gelatin capsules and tablets (dissolution, disintegration, hardness, friability, uniformity of dosage units, and content); oral liquids (content uniformity, pH value, limit microbes, the content of antimicrobial preservatives and antioxidants, extractable from containers or closed systems, alcohol content, the solubility of suspensions and powders, dispersibility of suspensions, suspension Viscosity and specific gravity of the liquid or viscous solution. Taking into account global standards and guidelines, the test parameters for oral or topical dosage forms generally specified in more than two global guidelines are divided into three groups:

1. Physical parameters, e.g. description, purity, transparency, hardness, friability, content, unit dosage uniformity, weight change, particle size change, viscosity, relative density, and resuspension;
2. Chemical parameters, such as tests, identification (in most cases, by chromatographic fingerprinting), dissolution, disintegration, pH, and ethanol content; and
3. Biological parameters, such as microbial limit, sterility tests, and irritation.

8.0 STABILTY TESTINGS [8]

8.1 Accelerated Testing

In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input requiredto cause product failure is determined. This is done to subject the product to a condition that accelerates degradation.

2) This information is then projected to predict shelf life or used to compare the relative stability of alternative formulations. This usually provides an early indication of the product shelf life and thus shortening the development schedule.

3) In addition to temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package. In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed simultaneously. Because the duration of the analysis is short, the likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing.

4) Further, in accelerated stability testing, comparison of the unstressed product with stressed material is made within the same assay and the stressed sample recovery is expressed as per cent of unstressed sample recovery.

5)For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures.

8.2 Real Time (Long-Term) Testing

Real-time stability testing is normally performed for longer duration of the test period in order to allow significant product degradation underrecommended storage conditions.

2) The period of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs and must permit one to distinguish degradation from inter-assay variation.

3) During the testing, data is collected at an appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity. The reliability of data interpretation can be increased by including a single batch of reference material for which stability characteristics have already been established.

4) Stability of the reference material also includes the stability of reagents as well as consistency of the performance of the instrument to be used throughout the period of stability testing.

5) However, system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation must be monitored.

8.3 Retained Sample Testing

This is a usual practice for every marketed product for which stability data are required. In this study, stability samples, for retained storage for at least one batch a year are selected.

2) If the number of batches marketed exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage.

3) In this study, the stability samples are tested at predetermined intervals i.e. if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12.18, 24, 36, 48, and 60 months.

4) This conventional method of obtaining stability data on retained storage samples is known as constant interval method.

5) Stability testing by evaluation of market samples is a modified method which involves taking samples already in the market place and evaluating stability attributes.

6) This type of testing inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions.

9.0 Factors influencing product stability[1,6,7]

Drug components (raw ingredients and excipients) occur in varying degrees of microscopic physical states. The pace of conversion is determined by the chemical potential, which corresponds to the difference in free energy between states, as well as the energy barrier that must be crossed for conversion to occur (such as the energy barrier of a chemical reaction). According to the facts presented, a greater temperature can have a negative impact on the physical stability of the formulation.

91. Chemical stability: Chemical degradation of active components in medicines, for example, hydrolysis of -lactams, often results in effectiveness loss. The most prevalent chemical processes that contribute to the degradation of APIs and excipients are oxidation and hydrolysis. At times, many reactions might occur at the same moment. Exposure to adverse temperatures, light, humidity, oxygen, and carbon dioxide are the key environmental conditions that might impair stability. The key dosage form parameters that impact drug stability include particle size (particularly in emulsions and suspensions), pH, solvent system composition (ie, proportion of "free" and overall polarity), anions and cations compatibility, and ionic solutions. Concentration, main packaging, particular chemical additives, and drug and excipient molecular binding and diffusion

9.2 Hydrolysis: The ester and beta-lactam chemical linkages are the most likely to hydrolyze in the presence of In the presence of, for example, the acetyl ester in aspirin hydrolyzes to acetic acid and salicylic acid, but in a dry environment, aspirin hydrolysis is insignificant. The rate of aspirin hydrolysis is related to the vapour pressure in the atmosphere.

9.3. Epimerization: When the dissolved medication is exposed to a moderate pH value (more than 3), this reaction proceeds quickly and results in an example of the spatial organisation of the tetracycline family's dimethylamino groups.

9.4. Decarboxylation: When heated, some dissolved carboxylic acids, such as p-aminosalicylic acid, lose carbon dioxide from the carboxyl group. The resultant product's pharmacological action is diminished.

9.5 Dehydration : Dehydration is caused by acid catalysed dehydration, which produces a molecule with little antibacterial action and is hazardous.

9.6 Oxidation: Oxidation A hydroxyl group directly connected to aromatic rings, conjugated dienes, heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes are the most probable molecular structures to be oxidised. Visual detection of oxidation, such as the transition from colourless adrenaline to its amber derivative, may be impaired in specific dilutions or by certain eyes.

9.7 Photochemical degradation : UV radiation primarily causes the oxidation (photo oxidation) and breakage (photolysis) of covalent bonds. For example, nifedipine riboflavin is very photosensitive.

9.8 Ionic strength: The impact of ionic strength on the attraction between ions is what causes the total concentration of dissolved electrolyte to affect the rate of the hydrolysis process. Inorganic salts' high ionic strength can also impair the solubility of several other medications.

9. The influence of pH : Many medications degrade in solution exponentially when the pH increases or drops within a specified pH range. The pharmacological solution or suspension may be stable in its original formulation for days, weeks, or even years, but when combined with another liquid with a different pH, it degrades in minutes or days. A single unit shift in pH, such as from 4 to 3 or 8 to 9, can affect medication stability by a factor of 10 or more.

10. Ionic compatibility: Compatibility of ions The compatibility or solubility of oppositely charged ions is primarily determined by the amount of charges per ion and the ion's molecular size.

9.0 PERSPECTIVES [1,3]

Despite the considerable contribution of herbal pharmaceuticals to developing country healthcare systems, their quality is not checked by drug regulatory authorities such as the WHO, EMEA, and USFDA. Due to the chemical complexity of the product, extrapolation of physicaland/or chemical stabilities of a herbal product in terms of a single marker to its biological activity may not be advised. An examination of theimpact of storage conditions on physicochemical stability, biological activity, toxicity, and microbiological contamination is essential to establish the safety and therapeutic efficacy of a herbal medicinal product. As a result, during systematic stability studies, physical and chemicalstability, as well as major biological activity(ies), of a herbal drug/product, must be evaluated. The recommendations should also be changed,and the herb's therapeutic activity should be given equal weight in the guidelines. Enzymes that are suspected of remaining active after harvesting and surviving exposure to herbal drug/product processing techniques should also be identified. Their assay and/or monitoring of their activities could become a crucial part of the stability testing processes. Furthermore, research efforts should be focused on identifying indicators in a drug/product whose levels can be extrapolated to or associated with the drug/intended product's therapeutic use(s).

10.0 CONCLUSION:

Although the stability test for herbal products with a known chemical composition is the same as for chemically defined API, the majorityof herbal products are complex. The fundamental research on herbal and chemically determined goods is identical. Herbal medications includethe following distinct characteristics:

- Three batches of medicines and two batches of raw ingredients
- At 30° C and 65 percent relative humidity, there are no three-month test points for medicines.
- Materials Herbal raw materials are only tested at 25° C/60% RH, hence no intermediate/accelerated tests are required. are only at 25 ° C / 60% RH, No need for intermediate/accelerated tests
- Selection of analytical methods, a combination of methods and fingerprints for labeling substances from extracts "quantitative" and "other" Instead of stated values, such as the percentage of standardized extracts and chemical APIs,

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